

JOURNAL OF CROHN'S AND COLITIS

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Official Journal of the European Crohn's and Colitis Organisation

Editor-in-Chief
Laurence J. Egan (Ireland)

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The Journal of Crohn's and Colitis is the official journal of the European Crohn's and Colitis Organisation (ECCO) and is concerned with the dissemination of knowledge on clinical, basic science and innovative methods related to Inflammatory Bowel Diseases. The journal publishes original articles, review papers, editorials, leading articles, ECCO Guidelines, viewpoints, short reports and letters to the editor. All submitted material is subject to a peer-review process.

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Oral presentations

OP001

Whole genome sequencing and imputation in inflammatory bowel disease identifies 26 novel loci and offers therapeutically-relevant mechanistic insights

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Background: Most of the 215 risk loci associated with inflammatory bowel diseases (IBD) to date were discovered by genotyping arrays and are driven by common variants. Such assays, however, do not adequately capture lower frequency variation. Thus, the role of these variants in IBD pathogenesis is unclear.

Methods: To comprehensively interrogate the role of lower frequency variation, we whole-genome sequenced (WGS) 4280 IBD patients and compared them to 3652 population controls. To increase power to detect association, we imputed into new and existing GWAS cohorts totalling over 35000 individuals, using a reference panel augmented with our sequence data. Finally, we combined our data with publicly available summary statistics and conducted meta-analyses in ~60,000 individuals.

Results: Rare variants: We identified an excess burden of rare, damaging missense variants in genes previously implicated in IBD, suggesting that rare variants are likely contributors to IBD pathogenesis. However, no such excess burden was confidently detected in any single gene and much larger sample sizes will be required for their identification.

Low frequency variants: Analysis of imputed data identified a missense (Asp439Glu) variant in *ADCY7* with 0.6% frequency in the general population, which doubles risk of ulcerative colitis. Despite good power to detect associations of this type, this was the only variant we detected, suggesting a minimal contribution to disease susceptibility by low frequency variants.

Common variants: Our meta-analysis identified 24 novel risk loci, including three which contain integrin genes (*ITGA4*, *ITGAV*, *ITGB8*). At two of these, as well as at the previously associated *ITGAL* and *ICAM1* loci, we found strong evidence that the IBD

risk-increasing variant increases expression of the respective integrin gene in activated monocytes. This hints at a mechanism linking non-coding genetic associations to targets of existing therapeutics. We also identified likely causal missense variants in *PLCG2*, mutations in which are known to cause a primary immunodeficiency, and *SLAMF8*, a negative regulator of inflammatory responses.

Conclusions: We conducted a large, multi-faceted study to explore the genetic architecture of IBD across the entire allele frequency spectrum. Our results highlight the continued value of GWAS and their potentially pivotal role in understanding aspects of disease biology through the integration of genomic and functional datasets in specific cells and contexts. We found minimal evidence for strong effects from low frequency variants, despite good power, while the effects of rare variants will require larger sample sizes to be more thoroughly investigated.

OP002

Epigenetic biomarkers to detect ulcerative colitis-associated neoplasia: results from phase I of the ENDCAP-C study

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Background: Chronic inflammation caused by Ulcerative Colitis (UC) causes a pro-neoplastic drive in the inflamed colon, leading to a markedly greater risk of invasive malignancy compared to the general population. Despite colonoscopic surveillance protocols, 50% of cases proceed to invasive cancer before neoplasia is detected. We and others have previously shown an association between epigenetic change, in the form of methylation, specifically in Wnt-signalling associated genes (*sFRP1*, *sFRP2*, *WIF-1* and others) and neoplasia within colons in patients affected by UC.

The Enhanced Neoplasia Detection and Cancer Prevention in Chronic Colitis (ENDCaP-C) trial is an observational, multi-centre test accuracy study, consisting of two phases. The initial phase aimed to measure the accuracy of a panel of markers on a retrospective cohort of patients with ulcerative colitis in order to ascertain their utility in phase 2, a prospective clinical study.

Methods: Patients were identified from retrospective sample collections with the West Midlands area from patients undergoing colonoscopic surveillance for ulcerative colitis.

These were classified as either having “neoplasia”, defined as any of adenocarcinoma, high-grade or low-grade dysplasia; “non-

neoplastic” defined as matched normal mucosal biopsies taken downstream from areas of neoplasia or “control” defined as normal mucosa from patients either with or without chronic inflammation who had been screened for neoplasia without it being found. DNA from biopsy samples then underwent bisulphite pyrosequencing of a 11 marker gene panel (*SFRP1*, *SFRP2*, *SRP4*, *SRP5*, *WIF1*, *TUBB6*, *SOX7*, *APC1A*, *APC2*, *MINT1*, *RUNX3*). Percentage methylation was log transformed and the three groups compared by t-testing and multivariate logistic regression to predict accuracy.

Results: In total, 569 blocks from patients undergoing surveillance were retrieved, consisting of 113 neoplastic, 113 non-neoplastic and 343 control blocks. Of the neoplastic samples, 35/113 were adenocarcinoma and 78/113 were dysplastic. All markers had a success rate of >90% apart from *SFRP1*, *MINT1* and *RUNX3* which were not taken forward to further analysis. In univariate analysis, five markers accurately detected both dysplasia ($p < 0.0001$) and neoplasia ($p < 0.0001$) – *SFRP2*, *SFRP4*, *WIF1*, *APC1A* and *APC2*. A multivariate logistic regression analysis and ROC analysis demonstrated the model using the five marker panel had excellent diagnostic accuracy (AUC=0.87, 95% CI: 0.82–0.92, model $p < 0.0001$).

Conclusions: A five marker methylation marker panel accurately predicts ulcerative colitis associated dysplasia and neoplasia in this population. This panel is being taken forward to prospective validation and in enabling enhanced surveillance in phase two of the study.

OP003

Increased risk of acute arterial events in young patients with severely active inflammatory bowel disease: a nationwide French cohort study

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Background: Magnitude and independent drivers of the risk of acute arterial events in inflammatory bowel disease (IBD) are still unclear. We addressed this question in IBD patients compared to the general population at a nationwide level.

Methods: Using the French National Hospital Discharge Database from 2008 to 2013, all patients aged 15 years or older and diagnosed with IBD were identified and followed up until 31 December 2013. Occurrence of acute arterial events, cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, obesity, smoking behavior, and alcohol use disorder), surgical procedures, and hospitalizations related to IBD were assessed. Acute arterial events included ischemic heart disease, cerebrovascular disease and peripheral artery disease excluding acute mesenteric ischemia. Incidence of first acute arterial event in patients with IBD and expected incidence for each region-, sex-, and 5-year age-specific stratum based on observed incidence in the French general population were calculated. The impact of severe disease activity marker (recent hospitalization for uncontrolled IBD) was assessed among IBD patients by survival analysis adjusted for cardiovascular risk factors.

Results: A total of 210,162 individuals with IBD (Crohn’s dis-

ease [CD], n=97,708; ulcerative colitis [UC], n=112,454) were included. During 595,202 person-years of follow-up, 5554 IBD patients were diagnosed with incident acute arterial events, including 3177 ischemic heart diseases (57.2%), 1715 cerebrovascular diseases (30.9%) and 662 peripheral artery diseases (11.9%). Patients with CD (Standardized incidence ratio (SIR), 1.35; 95% CI, 1.30–1.41) and UC (SIR, 1.10; 95% CI, 1.06–1.13) had an increased risk of acute arterial events overall (Table). Higher values were observed in patients aged less than 35 years, both in CD (SIR, 1.42; 95% CI: 1.09–1.75) and UC (SIR, 1.65; 95% CI, 1.20–2.10). During follow-up, 22% and 13% of CD and UC patients were hospitalized for IBD-related symptoms. After adjustment for general cardiovascular risk factors, the 3-month periods before and after IBD-related hospitalization were associated with an increased risk of acute arterial events compared with other periods in patients with CD and UC (Hazard ratio, 1.77; 95% CI, 1.47–2.12 and 1.87; 95% CI, 1.58–2.22).

Table 1. Standardized Incidence Ratios (SIRs) of acute arterial events, by IBD subtype

	Reported cases	Expected cases	SIR (95% CI)	p value
Crohn’s disease (287,134 person-years)				
All acute arterial events	2244	1658	1.35 (1.30–1.41)	<0.0001
Ischemic heart disease	1253	956	1.31 (1.24–1.38)	<0.0001
Cerebrovascular disease	694	523	1.33 (1.23–1.43)	<0.0001
Peripheral artery disease	297	180	1.65 (1.46–1.83)	<0.0001
Ulcerative colitis (308,068 person-years)				
All acute arterial events	3310	3021	1.10 (1.06–1.13)	<0.0001
Ischemic heart disease	1924	1750	1.10 (1.05–1.15)	<0.0001
Cerebrovascular disease	1021	923	1.11 (1.04–1.17)	<0.01
Peripheral artery disease	365	341	1.07 (0.96–1.18)	0.21

Conclusions: Patients with IBD are at increased risk of acute arterial events, with the highest risk in young patients. Disease activity may also have an independent impact on the risk and, in addition to smoking status, may partly account for differences in CD and UC.

OP004

Resetting of the mucosal T cell repertoire after hematopoietic stem cell transplantation in refractory Crohn’s disease

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Background: Autologous hematopoietic stem cell transplantation (HSCT) is a therapeutic option for Crohn’s disease (CD) patients with severe disease, refractory to immunosuppressants and biologics, after consideration of all therapeutic options including surgery. Several mechanism of action may be involved, including a resetting of the adaptive immune system. The role of T cells in CD pathophysiology is well established although no specific antigen nor T cell TCR have been associated with CD.

The aim our study was to analyze the impact of HSCT on the T cell repertoire in the inflamed intestinal mucosa.

Methods: Intestinal mucosal samples (ileal or colonic biopsies) were collected at baseline (pre-mobilization) and after HSCT (6 months and/or 1 year post transplant), in 16 CD patients recruited in the ASTIC trial or in the Barcelona Center. Endoscopic severity was evaluated by segment using SES-CD. T cell repertoire analysis was performed on DNA extracted from biopsies by next generation sequencing of the TCR β locus (Adaptive Biotechnology Inc., Seattle, Washington, USA). TCR diversity of each sample was studied by quantification of the size taken in the repertoire by significantly expanded clones, and correlated with clinical outcome and endoscopic response (global and by segment) at one year. T cell clones were tracked and the repertoire similarities were quantified between different time points by the Morisita-Horn index (M-H; range 0–1).

Results: Monoclonal expansions in the T cell compartment were present at baseline in the mucosa of CD patients prior to HSCT procedure, expanded clones represented from 5 to 30 per cent of the total repertoire. The T cell repertoire appeared more polyclonal than previously anticipated (from 1000 to 20 000 unique TCR sequences, diversity index 0.02 to 0.1). Importantly, no shared public TCR sequences were found in the mucosa of different patients. After HSCT, TCR clonality was significantly increased in the mucosa of patients. Although around 20 per cent of specific TCR sequences persisted between baseline and after HSCT, the similarity index comparing the TCR repertoire was low (mean M-H=0.17), indicating a profound resetting of the TCR repertoire. In contrast, a high degree of similarity (mean M-H=0.7) was observed between mucosal samples collected at different time points after the procedure in the same patient.

Conclusions: Clonal expansions are present in the mucosa of refractory CD patients. HSCT induces dramatic changes and a significant resetting in the mucosal T cell repertoire.

OP005

The PROSIT cohort of infliximab biosimilar in IBD: a prolonged follow-up on the efficacy and safety across Italy

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Background: The Infliximab biosimilar CT-P13 has been used since March 2015 in Italy. We report here a prolonged follow-up of a prospective, nationwide, multicentre, observational cohort (PROSIT) evaluating the safety, and clinical/endoscopic efficacy.

Methods: A structured data base has been used to record relevant serious adverse events (SAEs), clinical efficacy (partial Mayo [PM] and Harvey-Bradshaw Index [HBI]), inflammatory markers (CRP and calprotectin [calpro]) and endoscopic findings (endoscopic Mayo [EM] and Simple Endoscopic Score for Crohn's Disease [SES-CD]).

Results: Results 680 consecutive patients (373 CD, 307 UC) have been included from academic (n=13) and non-academic (n=12) referral centers. Age at the disease onset was 30.5±13.9 years in CD and 33.7±13.3 years for UC. 400 patients were naïve to anti-TNF α (192 CD, 208 UC), 171 patients (115 CD, 56 UC) had a previous exposure to one or more biologics, whereas the remaining 109 patients (66 CD, 43 UC) were switched after a mean of 18±10 previous infusions of infliximab (range 3–72). All patients were included in the safety evaluation. A total number of over 4,000 infusions were recorded; 92 SAEs (13.5%) were reported, leading to stop biosimilar in 73 patients (10.7%). IRs were 46, leading to stop biosimilar in 38 subjects (5.6%), and were significantly more frequent in patients pre-exposed to anti-TNF α (p<0.02).

Primary failure was recorded in 55/680 patients (8.1%). The efficacy of therapy was calculated following the induction regimen or at least two infusions after switching in 601 patients with a mean follow-up of 32 weeks (range 8–83). As a whole 274 patients were in remission (45.6%), 186 were considered responders (30.9%) and 62 lost the response (10.3%). The remaining patients were failure or stopped the therapy. 377 patients (222 CD) and 150 patients (89 CD) completed the follow-up of 6 and 12 months, respectively. After 1 year of CT-P13 therapy, HBI, SES-CD, CRP, and Calpro significantly (p<0.01) dropped in CD patients (7.1±3.4 vs 3.2±2; 10.1±42 vs 3±2.6; 1.9±1.7 mg/dl vs 0.9±0.8; 565±485 mg/kg vs 126±133 respectively), compared to baseline. Similarly, in UC patients PM, EM, CRP, and Calpro (6.1±2.3 vs 1.9±1.8; 2.1±0.6 vs 1.3±0.8; 3±2 mg/dl vs 0.9±0.7; 759±516 mg/kg vs 72±65, respectively) were significantly reduced (p<0.001). A deep remission was achieved in 57% and 50% of CD and UC patients in whom all information were available, respectively.

Conclusions: This is one of the largest prospective cohort of patients with IBD treated with CT-P13. After a more prolonged follow-up, no further signals of difference in safety and clinical efficacy has been observed.

OP006

Correlation of durability of response, serum trough concentrations and outcome parameters: long-term follow-up of the Trough Concentration Adapted Infliximab Treatment (TAXIT) trial

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Background: The Trough Concentration Adapted Infliximab Treatment (TAXIT) randomized controlled trial [1] showed that targeting patients' infliximab trough concentrations in a 3–7 µg/mL window resulted in a more efficient use of the drug in patients with inflammatory bowel disease (IBD). However, following dose optimization, continued concentration-based dosing was not superior to clinically-based dosing for achieving a co-primary endpoint of clinical and biological remission after 1 year.

Methods: This was a retrospective analysis of the long-term outcome of all 226 patients who completed the TAXIT maintenance phase. Durability of response to infliximab was correlated with serum trough concentrations and important quality of care outcome parameters, including need for IBD-related hospitalization, need for abdominal surgery and steroid use.

Results: With a median follow-up of 41 months after the completion of the TAXIT trial, 167/215 (78%) patients were still on continued treatment with infliximab, and 48/215 (22%) patients needed to stop (11 patients were lost to follow-up). Among the 48 patients who discontinued infliximab, 10/27 (37%) randomized previously to the clinically-based dosing arm did so within 1 year, compared to 2/21 (10%) patients randomized to the concentration-based dosing arm ($p < 0.05$).

Among the 167 patients who continued infliximab, the dosing scheme was intensified in 56 patients and de-intensified in 27 patients, compared to the end of the TAXIT maintenance phase. Median trough concentrations of infliximab at the end of follow-up were 4.73 µg/mL (IQR=3.3–6.42). Five patients developed immunogenicity within 1 year after TAXIT and all had been randomized to the clinically-based dosing arm. In patients continuing on infliximab, the rates of IBD-related hospitalization (16/167 patients or 9.6%), abdominal surgery (4/167 patients or 2.4%) and steroid use (6/167 patients or 3.6%) during the entire follow-up period were very low and significantly better than in patients who had to discontinue infliximab.

Table 1. Outcome parameters in patients who continued infliximab vs. patients who discontinued infliximab

	Continuation of infliximab (n=167)	Discontinuation of infliximab (n=48)	p-value
Hospitalization	16 (9.6%)	16 (33.3%)	<0.001
Abdominal surgery	4 (2.4%)	10 (20.8%)	<0.001
Steroid use	6 (3.6%)	16 (33.3%)	<0.001

Conclusions: In this long-term follow-up of the TAXIT trial, infliximab discontinuation occurred earlier in patients treated in the clinically-based dosing arm than in patients treated in the concentration-based dosing arm. Targeting infliximab trough concentrations to a therapeutic window led to a highly durable treatment response, and was associated with very good outcomes including very low (<5%) surgical rates and steroid use.

References:

- [1] Vande Casteele et al, (2015), Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease, Gastroenterology

OP007

A multi-centre double blind randomised placebo-controlled study of the use of rectal tacrolimus in the treatment of resistant ulcerative proctitis

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Background: Resistant ulcerative proctitis can be extremely difficult to manage. Topically administered tacrolimus, however, may be effective in difficult-to-treat proctitis

Methods: This was randomized, double-blind, placebo-controlled induction trial of rectal tacrolimus in patients with active ulcerative colitis funded by the Broad Medical Research Program (Clinicaltrials.gov registration: NCT01418131). Eleven patients received rectal tacrolimus (0.5mg/ml), and 10 placebo, for 8 weeks. The primary endpoint was clinical response by using the Mayo clinic score.

Results: An interim analysis after 20 patients had completed the study demonstrated highly significant differences between the groups and the study was closed due to ethical considerations with patients already recruited allowed to complete the study. The primary endpoint was met in 8/11 (73%) patients receiving rectal tacrolimus and 1/10 patients receiving placebo (10%; $p=0.004$). Of the secondary endpoints, 5 (45%) rectal tacrolimus patients achieved clinical remission compared to none receiving placebo ($p=0.015$). Mucosal healing at week 8 was achieved in 8 (73%) patients receiving rectal tacrolimus compared to 1 (10%) receiving placebo ($p=0.004$). The IBDQ increased ≥ 16 points over baseline in 5 (45%) of the

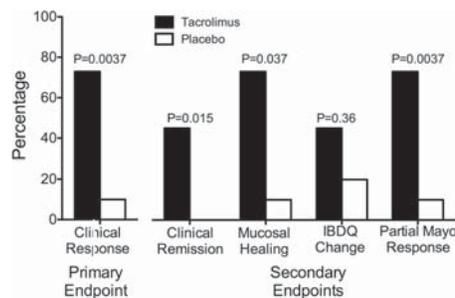


Figure 1. Primary and secondary endpoints.

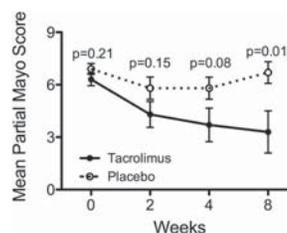


Figure 2. Mean partial Mayo score.

tacrolimus and 2 (20%) of the placebo patients ($p=0.36$). Finally, the average partial Mayo score was numerically lower in the tacrolimus-treated group compared to placebo at week 2 (4.3 ± 0.74 vs. 5.8 ± 0.64 ; $p=0.15$) and week 4 (3.7 ± 0.96 vs. 5.8 ± 0.6 ; $p=0.08$) but was significantly lower at week 8 (3.3 ± 1.2 vs. 6.7 ± 0.62 ; $p=0.01$). There were no safety issues identified with rectal tacrolimus use.

Conclusions: Rectal tacrolimus was more effective than placebo for induction of a clinical response, clinical remission and mucosal healing in resistant ulcerative proctitis

OP008

An innovative treatment for refractory perianal fistulas in Crohn's disease: local micro reinjection of autologous fat and adipose derived stromal vascular fraction

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Background: Mesenchymal cell therapy is promising for the treatment of perianal Crohn's fistulas refractory to conventional therapy. Autologous adipose-derived stromal vascular fraction (ADSVF) is recognized as an easily accessible source of cells with angiogenic, anti-inflammatory, immunomodulatory and regenerative properties. ADICROHN pilot study is based on the innovative hypothesis that combined action of ADSVF associated with trophic characteristics of microfat graft could be beneficial to Crohn patients with refractory perianal fistulas.

Methods: This is a prospective, open, non-comparative, single center, phase I-II clinical trial. Eligible patients are aged >18 years and diagnosed with complex perianal fistula associated with Crohn's disease at least for 6 months with controlled luminal disease (CDAI<220). Fistula(s) had to be refractory to conventional treatment. It was planned to enroll 10 patients. Patients are first subjected to an exam under anaesthesia with drainage by seton placement if indicated, followed at least one week later on the same day by adipose tissue extraction, ADSVF and microfat preparation then injected into the fistula. Patients are monitored at baseline and at 1, 2, 6, 12, 16 and 48 weeks after injection for safety and efficacy analysis. Safety analysis includes at every visits clinical assessment of adverse events. Efficacy analysis includes at every visit clinical evaluation of fistula closure, evaluation of disease activity by PDAI/CDAI scores, and assesment of quality of life by SIBDQ. Fistula closure is also evaluated via radiological assessment with MRI (confirmation of absence of collections >2 cm of the treated perianal fistula) at week 12 and 48.

Results: Since October 2015, 9 patients were treated by this innovative local treatment (among 10 cc of microfat and about 30 millions of ADSVF viable cells subsequently injected into the soft tissue around the fistulas). No serious adverse events have been described. The only side effect were moderate pain on lipoaspiration site. Preliminary efficacy datas at week 12 for the first 7 treated patients showed 71% of response and 28% of complete healing, significant reduction of discharge ($p<0.001$), significant reduction of severity of perianal disease ($p=0.045$) and significant improvement of quality of life ($p=0.039$).

Conclusions: This first study evaluating co-local administration of ADSVF in association with fat graft appears to be a simple, safe and efficient surgical regenerative therapy for perianal Crohn's fistula refractory to conventional therapy.

ClinicalTrials.gov NCT02520843, Eudract: 2013-002602-31.

OP009

Long-term efficacy and safety of Cx601, allogeneic expanded adipose-derived mesenchymal stem cells, for complex perianal fistulas in Crohn's disease: 52-week results of a phase III randomised controlled trial

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Background: Existing therapies for perianal fistulas in Crohn's disease (CD) are associated with a high failure rate and few have been evaluated in randomised controlled trials (RCTs) using hard endpoints. The 24-week results of a RCT showed that Cx601 added onto standard of care was safe and effective for treatment-refractory complex perianal fistulas with a significantly greater proportion of patients achieving clinical and radiological combined remission (CR) compared with placebo+standard of care. We aimed to determine whether this efficacy and safety was maintained over the long-term (52 weeks) (NCT01541579).

Methods: Patients with inactive or mildly active luminal CD and treatment-refractory, draining, complex perianal fistulas were randomised (1:1) to Cx601 (single injection of 120 million eASC to all tracts+standard of care) or control (placebo+standard of care) in this phase III, double-blind, parallel-group multicentre study. An unblinded surgeon administered the treatment and a blinded gastroenterologist evaluated the therapeutic effect. Efficacy was evaluated in the mITT (randomised, treated and ≥ 1 post-baseline efficacy assessment) population at week 52. Pre-specified endpoints included CR (closure of all treated external openings [EOs] that were draining at baseline assessed clinically, and absence of collections >2 cm in the area of the treated perianal fistulas by blinded central MRI reading) and clinical remission (closure of all treated EOs). Sustained CR at week 52 was also evaluated.

Results: 212 patients were randomised to Cx601 (n=107) or control (n=105); 61.8% completed the 52-week follow-up (Cx601, n=70; control=61). The beneficial effect observed at week 24 (CR in Cx601 51.5%, control 35.6%; $p=0.021$) was sustained at week 52; a significantly greater proportion of patients receiving Cx601 vs control achieved CR (56.3% vs 38.6%; $p=0.010$), and clinical remission (59.2% vs 41.6%; $p=0.013$) at week 52. Of patients with CR at week 24, a greater proportion of those treated with Cx601 vs control had no relapse at week 52 (75.0% vs 55.9%). Rates and types of treatment related adverse events were similar in both groups (20.4%, Cx601 vs 26.5%, control).

Conclusions: The efficacy of Cx601 in treatment-refractory complex perianal fistulas of CD patients was sustained for up to 1 year after a single administration. The results also support the favourable tolerability of Cx601 over the long-term.

J. Panes Lancet 2016; 388
 Sustained remission 75% vs 56%

OP010

Long term efficacy and safety of Ustekinumab for Crohn's disease: results from IM-UNITI long-term extension through 2 years

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Background: Ustekinumab (UST) is a fully human IGG1 mAb to human IL 12/23p40 approved for treatment of moderate to severe active Crohn's disease (CD). The ongoing IM-UNITI long-term extension (LTE) evaluates efficacy & safety of subcutaneous (SC) UST through approximately 5 years of treatment, with results through wk96 reported herein.

Methods: 1281 patients (pts) entered the maintenance study, including 397 UST induction responders in the primary population (randomized to SC placebo (PBO); n=133, UST 90mg q12w (q12w); n=132, or UST 90mg q8w (q8w); n=132). A one-time dose adjustment to 90mg q8w occurred in pts in the randomized group who met loss of response criteria between wks8 & 32. Non-randomized pts included: PBO induction responders who continued on PBO, non-responders to PBO induction who received a single UST 130mg IV dose then UST 90mg SC q12w if in clinical response at wk8, & non-responders to UST induction who received UST 90mg SC & if in clinical response at wk8 continued on UST 90 mg q8w. All pts com-

pleting wk44 were eligible to enter LTE continuing on the treatment they were on at wk44. This included 567 UST treated pts of which 237 were from the primary population. Pts receiving PBO were discontinued following the unblinding of the entire study, which occurred after the Week 44 DBL.

Results: Table 1 presents analyses for randomized pts where pts with missing data or who discontinued are assumed not to be in response or remission at wk92, with 72.6% of q12w pts & 74.4% of q8w pts (non-dose adjusted) achieving remission at wk92. **Based on observed data analyses, among randomized pts who continued to receive UST through wk96, 79.2% of q12w & 87.1% of q8w pts (non-dose adjusted) were in remission & 90.9% & 94.3% were in response at wk92, respectively.** Among all UST treated pts who continued to receive UST through wk96, remission & response rates at wk92 were 70.7% & 84.7%.

Safety events (per hundred subject years) were not higher among all UST treated pts compared to PBO from wk44 through wk96, including overall AE's (82.9 vs 91), SAE's (14.16 vs 18.2), & serious infections (3.73 vs 4.33), with 536.8 subject years of follow-up among UST treated pts & 115.4 subject years among PBO pts. Among all UST treated pts, there were 2 deaths (sudden death, asphyxia). There were two non-NMSC malignancies reported between wks44 & 96, a seminoma (UST) & a papillary thyroid cancer (PBO only).

Conclusions: **SC** UST maintained clinical response & remission through two years. No new safety signals were observed.

OP011

Etolizumab treatment leads to early improvement in symptoms and inflammatory biomarkers in anti-TNF-refractory patients in the open-label induction cohort of the phase 3 HICKORY study

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Abstract OP010

	Continuous 90 mg UST Q12 wks N=84	Continuous 90 mg UST Q8wks N=82	Subjects with Prior dose-adjustment ^b N=71	All Ustekinumab treated N=237
Clinical Remission (%)	72.6	74.4	53.5	67.5
Clinical Response (%)	83.3	80.5	67.6	77.6
Clinical Remission and not receiving corticosteroids at Week 92 (%)	67.9	63.4	42.3	58.6
Clinical Remission in patients refractory or intolerant to TNF-antagonists	19/32 (59.4%)	19/27 (70.4%)	15/32 (46.9%)	53/91 (58.2%)
Clinical Remission in patients naive to TNF-antagonists	29/38 (76.3%)	29/39 (74.4%)	18/28 (64.3%)	76/105 (72.4%)
Median change in CDAI from maintenance baseline	-34.0	-40.0	-24.0	-36.0

^aPatients who had insufficient data at the designated analysis time point are considered not to be in clinical remission or response.

^bPatients who were in clinical response to ustekinumab induction dosing, were randomized, met loss of clinical response criteria from Week 8 through Week 32, and received ustekinumab 90 mg SC Q8w.

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Background: Etrolizumab, an anti-β7 mAb targeting integrins α4β7 and αEβ7, showed significantly greater clinical remission at wk 10 vs placebo (PBO) in the phase 2 EUCALYPTUS trial. We assessed changes in symptoms and inflammatory biomarkers in a TNF refractory or intolerant (aTNF-IR) pts treated in a non-pivotal open-label induction (OLI) cohort of a phase 3 study.

Methods: HICKORY is a multicentre, randomised, double-blind, PBO-controlled phase 3 study (NCT02100696) evaluating the safety and efficacy of etrolizumab during induction and maintenance in a TNF-IR pts with moderate-to-severe UC. The study includes a non-pivotal OLI cohort that treated 130 pts with etrolizumab 105 mg every 4 wk for 14 wk. Symptomatic improvement in this cohort was assessed based on the change in weekly mean rectal bleeding (RB) and stool frequency (SF) scores (each scored on a scale of 0–3), derived from pts' daily eDiary entries. SF remission was defined as a weekly mean score of ≤1 (rounded to the nearest integer) with ≥1 point reduction from baseline (BL). RB remission was defined as a weekly mean score of 0 (rounded to the nearest integer) with ≥0.5 point reduction from BL. Faecal calprotectin (FC) and C-reactive protein (CRP) were measured at BL and wk 14 or early termination. Changes in SF, RB, PRO score (SF + RB), FC and CRP were assessed descriptively.

Results: Of 130 treated pts, 97% received all induction doses, 80% had a BL Mayo Clinic endoscopic score of 3, and 45% had received ≥2 prior aTNFs. RB remission rates improved from BL to wk 4 (~30%) and 14 (~50%). SF remission rates improved from BL to wk 4 (~10%) and 14 (~25%). PRO scores improved regardless of disease severity and irrespective of prior treatment with 1 or ≥2 aTNFs. The mean (± SE) decrease in PRO was 22% (±3%) at wk 4 and 36% (±3%) at wk 14; this decrease mirrored mean reductions in FC and CRP. Overall, FC and CRP levels decreased at wk 14 by a mean (95% CI) of 57% (42 to 69) and 33% (15 to 47), respectively. Mean decrease in CRP in pts with CRP levels >2.87 mg/L (ULN) at BL was 47%. Mean decreases in FC and CRP levels at wk 14 were greater in pts in SF remission (FC, 83%; CRP, 54%) and in pts in RB remission (FC, 69%; CRP, 49%). Etrolizumab demonstrated favourable safety and tolerability.

Conclusions: aTNF-IR pts with moderate-to-severe UC reported symptom improvement as early as wk 4 during OLI treatment with etrolizumab. Clinically meaningful improvement in disease activity

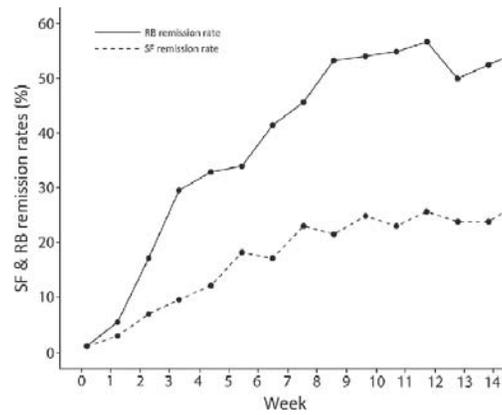


Figure 1

was observed in pt-reported SF and RB scores, serum CRP and FC by wk 14.

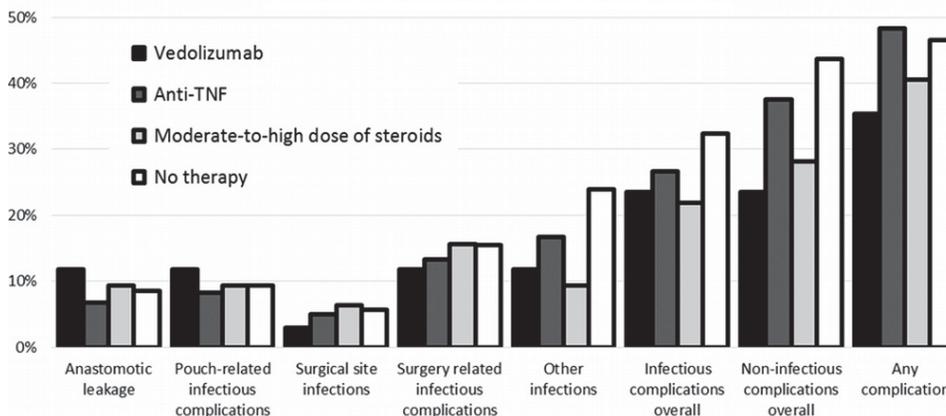
OP012 Perioperative use of vedolizumab is not associated with short-term postoperative infectious complications in patients with ulcerative colitis undergoing (procto)colectomy with ileal pouch-anal anastomosis

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Background: Vedolizumab (VDZ), a bowel focused anti-adhesion molecule, is effectively used in patients with ulcerative colitis (UC). Preoperative use of VDZ has recently been associated with increased risk of short-term postoperative infectious complications. We assessed this risk in a single-center cohort of patients with UC undergoing (procto)colectomy with ileal pouch-anal anastomosis (IPAA).

Methods: A chart review was performed in all patients undergoing (procto)colectomy with IPAA between 2006 and September 2016. Patients receiving a permanent ileostomy were excluded. Short-term postoperative infectious complications were evaluated within 30 days after (procto)colectomy and included pouch related complications, surgical site and other infections. The comprehensive compli-

Short-term postoperative complications



Abstract OP012 – Short-term postoperative complications.

cation index (CCI) was calculated based on all complications reported within 30 days of (procto)colectomy.

Results: We identified 170 patients undergoing (procto)colectomy (46% female, median age 38 years, median disease duration 6 years). Thirty-four patients (20%) received VDZ within 14 weeks, 60 (35%) received anti-TNF within 8 weeks, 32 (19%) received a moderate-to-high dose (≥ 20 mg/day) of prednisone, and 71 (42%) received no therapy at time of (procto)colectomy. Surgery was laparoscopy-assisted in 131 patients (77%). Pouch construction was performed at first stage in 47 patients (28%), more frequent in patients with dysplasia/cancer (85% vs. 13%, $p < 0.001$), and less frequent in patients under VDZ (9% vs. 32%, $p = 0.005$), anti-TNF (15% vs. 35%, $p = 0.006$), or steroids (0% vs. 34%, $p < 0.001$). Pouch construction at first stage was the only independent risk factor for short-term postoperative infectious [Odds ratio 2.40 (95% CI: 1.18–4.90), $p = 0.016$] and overall complications [3.11 (1.52–6.40), $p = 0.002$]. As shown in Figure 1, no significant difference could be observed between different treatment categories and development of short-term postoperative complications. The CCI and postoperative hospitalization stay were comparable between each treatment category, and only elevated in patients undergoing pouch construction at first stage [20.9 (0.0–30.8) vs. 0.0 (0.0–20.9), $p = 0.001$, and 11 (9–17) vs. 7 (5–10) days, $p < 0.001$, respectively].

Conclusions: In this large single-center cohort of patient with UC undergoing IPAA surgery, perioperative use of vedolizumab was not associated with short-term postoperative (infectious) complications. However, in patients under biological therapy or moderate-to-high dose of steroids pouch construction should be postponed to a second stage of surgery.

OP013

Disease management and outcomes of patients with Crohn's disease at high risk of recurrence. Results from PRACTICROHN study

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Background: Surgery in Crohn disease (CD) is associated with poor prognosis and higher rate of clinical and surgical recurrence. The aim of our study was to compare the characteristics and management of CD patients that have undergone one surgery with patients that have undergone more than one surgery.

Methods: PRACTICROHN was an observational study that included patients aged ≥ 18 years-old from 26 Spanish hospitals who underwent CD-related resection with ileocolonic or ileorectal anastomosis between January 2007 and December 2010. Patient data were retrospectively collected from medical records. Categorical variables were compared with the χ^2 test or Fisher's exact test. Kaplan-Meier method was used to assess time to clinical recurrence and a log-rank test to obtain statistical significance.

Results: 314 patients were analyzed, 262 (83%) were included in the

first surgery (50% males) and 52 (16%) referred previous surgeries (36% males). Mean age at diagnosis was similar in the first surgery group (FSG) (33 ± 14 years) vs second surgery group (SSG) (43 ± 12 years), $p = 0.021$. Age at index surgery was 39 ± 13 years in FSG vs 43 ± 12 in SSG, $p = 0.021$. Smoking habit was higher in FSG vs SSG (41% vs 34%, $p = 0.47$). Montreal classification in the two groups were similar except for behavior, with higher proportion of patients with B1 in FSG vs SSG (124 (48%) vs 13 (28%)) and higher proportion of B2 and B3 in SSG (74 (29%) B2 in FSG vs 21 (46%) in SSG and 57 (22%) B3 in FSG vs 12 (26%) in SSG), $p = 0.027$. Regarding treatment, 33 (13%) patients in the FSG received steroids previous to surgery vs 13 (27%) patients in the SSG. $p = 0.029$. No difference in IMM and biological treatment previous to surgery was found between the two groups. After surgery, a higher proportion of patients received prophylactic treatment with IMM in the SSG compared with FSG $p = 0.012$. No difference in the rate of colonoscopies performed during first year after surgery was found between the two groups as well as in the findings at the colonoscopies. Hospitalizations and postoperative complications were also similar. There was no difference in clinical recurrence in SSG in patients receiving or not prophylaxis ($p = 0.5$) whereas in FSG clinical recurrence-free survival was greater in patients with prophylactic treatment ($p = 0.03$) (Fig. 1).

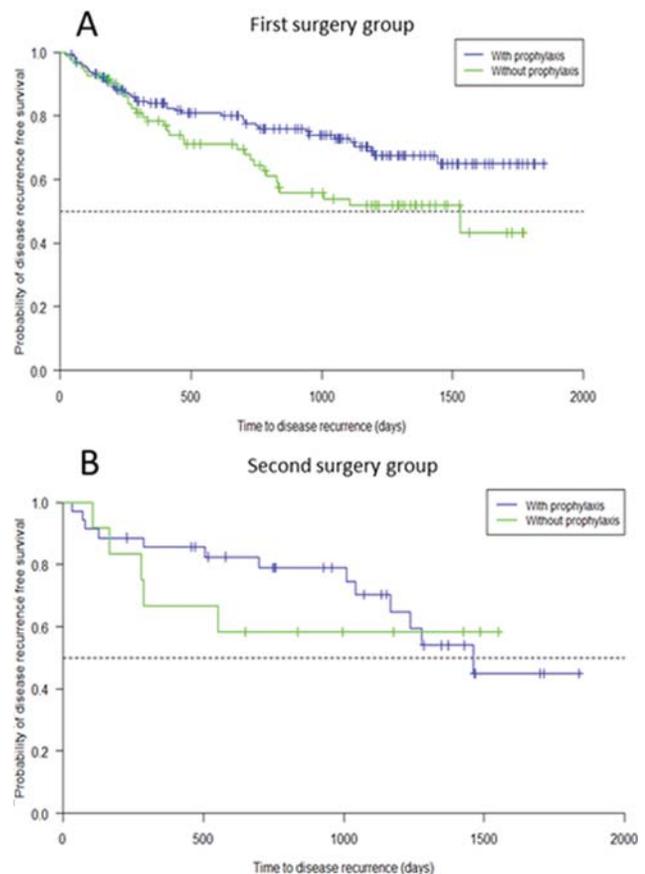


Figure 1. Time to disease recurrence in FSG vs SSG.

Conclusions: In our sample, although patients in SSG were less smokers and received more prophylaxis with IMM and similar post surgery follow-up, they presented more clinical recurrence. This confirms that undergoing a second surgery is a main factor of poor prognosis.

OP014

Histological remission is predictive of improved clinical outcomes in patients with ulcerative colitis: results from the TOUCHSTONE open-label extension

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Background: Histological remission (HR) has been reported as a positive prognostic indicator of clinical activity in ulcerative colitis (UC). The TOUCHSTONE open-label extension (OLE) is an opportunity to examine the impact of histologic remission on UC activity during a long-term evaluation of efficacy and safety of ozanimod 1 mg. TOUCHSTONE was a randomized, double-blind, placebo-controlled phase 2 trial designed to assess the efficacy and safety of ozanimod 0.5 mg and 1 mg versus placebo during induction and maintenance in patients with moderate to severe UC [1], and established that ozanimod induced and maintained clinical response, clinical remission (CR), endoscopic mucosal healing, and HR through weeks 8 and 32.

Methods: A total of 197 patients were randomized (1:1:1) and treated with daily ozanimod at 0.5 mg, 1 mg, or placebo in TOUCHSTONE. Of the initial 197 patients randomized, 170 (86%) entered OLE and received daily ozanimod 1 mg, and 131 (77%) and 105 (62%) completed assessments at weeks 44 and 80. In this analysis, HR was defined as a Geboes score <2 and CR was defined as rectal bleeding score =0 and stool frequency score ≤1.

Results: Of the patients who entered OLE, 27% showed histologic remission at the time of OLE entry and 34% were in CR. Clinical remission increased to 62% at OLE week 32, with 62%, and 55% in CR at OLE weeks 44 and 80. At OLE weeks 44 and 80, CR was seen in 83% and 80% of those in HR at OLE entry compared to 55% and 46% of those not in HR at OLE entry.

The proportion of patients in CR increased throughout OLE while receiving 1 mg of ozanimod, regardless of prior treatment in the TOUCHSTONE study or HR status at OLE entry. The highest rates of CR were seen in patients in HR at OLE entry who had received ozanimod for 32 weeks prior to OLE entry, with CR rates at OLE weeks 4 and 8, with over 90% in CR. The lowest CR rates were seen in patients naïve to ozanimod and not in HR at OLE entry, with CR increasing from 13% at entry to 50% at OLE week 8, reaching a peak of 56% at OLE week 32. Overall, treatment with ozanimod for 32 to 36 weeks resulted in CR in 80% of patients.

Most common adverse events seen in OLE were UC flare, back pain, URTI, anemia, and nasopharyngitis. Transient asymptomatic elevations in ALT or AST >3× ULN were seen in 3% of patients.

Conclusions: Histological remission is predictive of CR in patients with UC receiving ozanimod 1 mg in OLE. All patients, whether naïve to or having received ozanimod in TOUCHSTONE, showed additional improvements in CR upon continued treatment with ozanimod 1 mg in OLE. Patients naïve to ozanimod had a rapid improvement in CR over the first 8 weeks of treatment with ozanimod 1 mg in OLE.

References:

- [1] Sandborn WJ, Feagan BG, Wolf DC, et al. (2016), Ozanimod induction and maintenance treatment for ulcerative colitis. *N Engl J Med*, 1754–62

OP015

Cost-effectiveness of laparoscopic ileocecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIRIC TRIAL

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Background: The optimal therapeutic approach to ileocecal Crohn's disease (CD) remains unclear. The objective of the study was to compare infliximab with laparoscopic ileocecal resection in patients with thiopurine or steroid refractory recurrent CD of the terminal ileum, with respect to quality of life (QoL) and cost-effectiveness.

Methods: A multicentre randomised controlled, open-label trial was performed in 33 centres in The Netherlands and the UK. Adult patients with CD of the terminal ileum who failed >3 months of thiopurine treatment or steroids without signs of a critical stricture were randomly allocated to either infliximab or laparoscopic ileocecal resection. Patients with a prior ileocecal resection, a diseased length >40 cm, abdominal abscesses or fluid collections or an American Society of Anaesthesiologists (ASA) score of III or IV were excluded. Primary outcomes were QoL measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) and costs per QALY at one year follow-up. The economic evaluation estimated the marginal direct medical, non-medical and time costs, costs per quality adjusted life year (QALY) and cost-utility ratio according to intention-to-treat analysis one year after initiation of treatment. Dutch Trial Registry NTR1150.

Results: Between May 2008 and October 2015, 143 patients were included (33% male) with a median age of 27 years (interquartile range 22–40). Eventually, 65 patients started with infliximab and 70 patients were operated. At time of submission, 98.6% of the patients have completed follow-up. At baseline, the mean difference (MD) in IBDQ score was 4.9 points in favour of the resection group. After correction for the baseline difference, the MD at one year was 5.8 points in favour of resection (95% confidence interval (CI) –4.7 to 16.3, p=0.28). A significant difference in favour of the resection group in QoL was observed with the SF-36 general health questionnaire, on the physical scale (MD 3.2, p=0.035) and the mental scale (MD 4.1, p=0.036). Mean direct total costs per patient at one year were €19,655 in the infliximab and €10,724 in the resection group (MD €–8,931, 95% CI: €–12,087 to €–5,097). One QALY gained in the resection group was associated with a societal costs reduction of €77,221. In the sensitivity analysis, 95% of CE-pairs were located in the south-east quadrant, confirming that laparoscopic ileocecal resection was on average less costly and more effective than infliximab.

Conclusions: Although QoL at one year was not significantly better with the IBDQ, laparoscopic ileocecal resection can be considered an acceptable alternative for infliximab. Surgery improved general quality of life and was associated with a reduction in costs compared to infliximab induction and maintenance therapy.

OP016

Potential role of bile acid receptor FXR in microscopic colitis

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Background: Microscopic colitis (MC) is a chronic inflammatory bowel disease and includes two distinct histological forms: lymphocytic colitis (LyC) and collagenous colitis (CC). The etiology of MC is probably multifactorial, secondary to an abnormal immune reaction in predisposed individuals, triggered by luminal factors (such as infection, drugs or bile acids). Bile acid (BA) malabsorption has been described in approximately 44% of MC patients, which often respond to cholestyramine, a BA-binding resin. Farnesoid X receptor (FXR) is the main BA receptor and is expressed at high levels in the intestine, especially in the terminal ileum (TI) and proximal colon. FXR-mediated mechanisms prevent the noxious effects of BA accumulation, preserving the integrity of the intestinal epithelial barrier and preventing chemically induced intestinal inflammation. Reduced FXR activation has been implicated in the pathophysiology of inflammatory bowel disease. Our aim was to explore the expression of FXR in patients with MC.

Methods: Archival formalin-fixed paraffin-embedded (FFPE) samples (from the TI, right colon-RC and left colon-LC) were obtained from patients with MC and age and gender-matched healthy controls. Immunohistochemistry was performed using a mouse anti-human FXR monoclonal antibody (Perseus Proteomics, Tokyo, Japan). Nuclear FXR expression was scored in a semi-quantitative way by one experienced gastrointestinal pathologist, who was blinded to the clinicopathological information and biopsy location.

Results: 140 FFPE samples (24 from the TI, 54 from the RC and 62 from the LC) from 34 patients with MC (26 LyC and 8 CC) and 31 controls were retrieved. There was a non-significant reduction of FXR expression in the ileum of patients with MC versus controls (moderate-high FXR expression: 76.9% vs 90.9%; p=NS). There was a significant reduction of FXR expression in patients with MC versus controls both in the right colon (moderate-high FXR expression: 23.1% vs 64.3%; p=0.003) and left colon (moderate-high FXR expression: 12.1% vs 44.8%; p=0.027). We found no difference in FXR expression between the two types of MC.

Conclusions: Patients with MC present a significantly lower expression of FXR in the colon. This could render colonic epithelial cells more susceptible to the deleterious effects of BA, contributing to disease pathogenesis and symptoms in MC. These results open the possibility of exploring FXR agonists in the treatment of steroid-refractory MC.

OP017

Telemedicine enables a safe shift from examination room based care to personalised care for inflammatory bowel disease: a pragmatic randomised multicenter trial with myIBDcoach

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Background: Inflammatory bowel disease (IBD) is a group of chronic diseases with a heterogenic disease course and therapy response. Tight and personalised control of disease activity, with attention for all aspects influencing activity, is warranted to prevent long-term complications and improve quality of life (QoL). This is challenging given the increasing economic pressure on health systems, moreover since the incidence of IBD is rising. We developed myIBDcoach: the first telemedicine system for IBD patients, regardless of phenotype, severity or treatment. We aimed to evaluate the effect of myIBDcoach on number of outpatient visits, patient-reported quality of care (PRQoC) and health outcomes in a pragmatic, randomised trial. **Methods:** From September 2014 to May 2015, all consecutive IBD outpatients in 2 academic and 2 non-academic hospitals in The Netherlands, aged 18 to 75 years, with internet-access and Dutch proficiency, were eligible for inclusion. Patients were randomised (1:1) to use of myIBDcoach (intervention group) or standard care (control group) and followed for 12 months. Patients using myIBDcoach were invited to visit the outpatient clinic at least once a year, or on demand. Data on outpatient visits, flares, corticosteroid use, hospitalisations, emergency visits and IBD-related surgery were collected from the hospital electronic patient record and analysed using multivariate linear regression analysis. At baseline and 12 months, patients were requested to fill out a questionnaire including PRQoC, QoL (SIBDQ), adherence (MMAS-8) and self-efficacy (IBD-SES). Questionnaire data were analysed using linear mixed models.

Results: In total, 465 patients used myIBDcoach and 444 continued standard care. The mean number of outpatient visits during follow up was lower in the intervention group compared to the control group (1.55±1.50 and 2.34±1.64; p<0.001). After 12 months, both groups reported high scores on PRQoC on a VAS-scale, respectively 8.16±1.37 and 8.27±1.28 (p=0.411). The mean number of hospitalisations was lower in the intervention group compared to the control group (0.05±0.28 and 0.10±0.54; p<0.001). No differences were observed in flares, corticosteroid use, emergency visits or surgeries. Patients using myIBDcoach reported higher medication adherence rates

($p < 0.001$), higher, but not significant, QoL ($p = 0.057$) and similar self-efficacy scores ($p = 0.572$).

Conclusions: This pragmatic trial showed that telemedicine through myIBDcoach was safe, reduced outpatient visits and hospitalisations and improved medication adherence with equal PRQoC compared to standard care. MyIBDcoach monitors disease activity, patient reported outcomes and drug side-effects and may therefore be used to reorganise IBD-care enabling value based healthcare.

OP018

Optimal anti-TNF stop week during pregnancy depends on anti-TNF type

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Background: The ECCO pregnancy guideline provides recommendations regarding anti-TNF treatment during pregnancy that apply to all anti-TNF types. However, in our prospective cohort we found that women using adalimumab (ADA) had lower anti-TNF drug levels in cord blood than women using infliximab (IFX). We aimed to develop a stopping model for women using anti-TNF during pregnancy that can be used in clinical practice.

Methods: Women with IBD were prospectively enrolled at our pre-conception outpatient clinic from Dec '08 until Jul '16 and were counseled according to the ECCO pregnancy guideline. During bimonthly visits, information on disease activity, medication use, weight gain and complications were recorded. If patients were in remission 6 months before conception until gestational week 20; anti-TNF treatment was stopped at week 22–24. At birth, anti-TNF was measured in cord blood and considered of low risk for the newborn when below 3 $\mu\text{g/mL}$. A multiple linear regression was performed to determine independent predictors of the anti-TNF level in cord blood. In addition, a linear model was developed to predict anti-TNF cord blood drug level at birth.

Results: In total, 320 live births were documented of which 131 were exposed *in utero* to anti-TNF (73 IFX/58 ADA) born to 103 women (84 (82%) CD, 18 (17%) UC, 1 (1%) IBDU). Concomitant treatment with thiopurines was more often used with IFX ($n = 29; 40\%$) than with ADA ($n = 5; 9\%$) ($p = 0.0001$). Median anti-TNF stop week was the same for IFX and ADA: respectively 23.0 (IQR 21.0–31.5) and 23.0 (IQR 22.0–37.0) ($p = 0.56$). There was a trend towards more

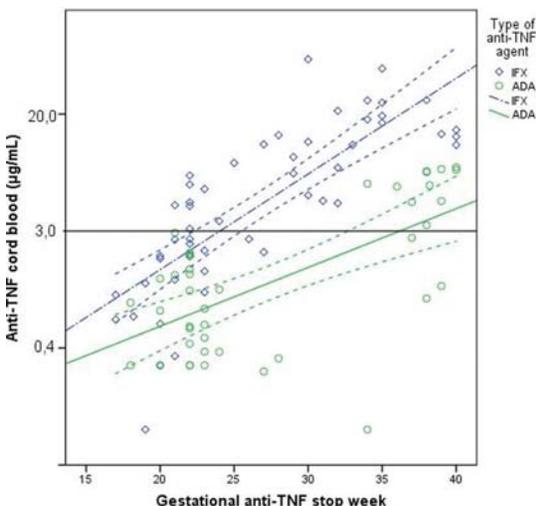


Figure 1

relapses during pregnancy in the ADA group compared to the IFX group, however, this difference was not statistically significant. There were 94 cord blood samples obtained (52IFX, 42ADA). At birth, median anti-TNF cord blood was significantly higher in IFX users (4.9 $\mu\text{g/mL}$ (IQR 1.9–14.7)) than ADA users (1.1 $\mu\text{g/mL}$ (IQR 0.4–37.0)) ($p = 0.0001$) and the median maternal anti-TNF was higher in IFX users (1.7 $\mu\text{g/mL}$ (IQR 0.4–6.9)) than ADA users (0.6 $\mu\text{g/mL}$ (IQR 0.3–3.6)) ($p = 0.05$). The multiple linear regression model demonstrated that 2 variables had a significant influence on anti-TNF cord blood level, namely: type of anti-TNF and gestational anti-TNF stop week. In the final model, the optimal time to stop anti-TNF, defined as gestational anti-TNF stop week leading to a cord blood level of 3 $\mu\text{g/mL}$, was 24,6 weeks for IFX and 36,8 weeks for ADA (Fig. 1).

Conclusions: These results suggest that the continuation of ADA up till the first half of the 3rd trimester does not lead to high anti-TNF cord blood levels.

OP019

Correlation of clinical and endoscopic outcomes in patients with active Crohn's disease treated with mongsersen (GED-0301)

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Background: Mongsersen (GED-0301), an antisense oligodeoxynucleotide complementary to the sequence of Smad7 mRNA, is being evaluated for the treatment (tx) of patients (pts) with active Crohn's disease (CD) (Monteleone et al. N Engl J Med 2015;372:1104–13). It is formulated as a gastro-resistant, delayed-release, pH-dependent tablet that delivers active substance to the distal GI tract with negligible systemic exposure. We explored the correlation between clinical and endoscopic indices in a phase 1b study.

Methods: Pts with active CD (CD Activity Index score [CDAI] = 220–450, total simple endoscopic score for CD [SES-CD] ≥ 7 , or ileal disease SES-CD ≥ 4) were randomised to 4, 8, or 12 wks of oral mongsersen 160 mg daily, followed by an observation period without study drug. Centrally read endoscopic assessments were performed at baseline (BL) and Wk 12. Daily electronic diary records were used to collect CD symptoms; a clinical evaluation, including CDAI determination, occurred at monthly visits through Wk 12.

Results: 63 pts were enrolled; at BL, mean age was 41.5 yrs, mean SES-CD was 11.2, mean CDAI was 294, and mean CD duration was 11.6 yrs; 46% had prior TNF- α exposure, and 33% had prior CD surgery. Improvement in clinical outcomes occurred as early as wk 2 in the 4-, 8-, and 12-wk tx groups: clinical response (CDAI decrease ≥ 100), 21%, 26%, and 29%; clinical remission (CDAI < 150), 16%, 17%, and 19%; and mean change from BL in CDAI, -77.9, -77.2, and -78.6. These improvements were maintained across all 3 tx groups over 12 wks of tx, with the highest rates observed in the 12-wk tx group: clinical response, 53%, 44%, and 67%; clinical remission, 32%, 35%, and 48%; and mean change from BL CDAI, -124, -113, and -133. In all, 52 pts had evaluable endoscopies at Wk 12; of these, 37% had endoscopic response ($\geq 25\%$ reduction in SES-CD from BL to Wk 12), with no meaningful difference across tx groups. Among pts with SES-CD > 12 , 63% had $\geq 25\%$ and 31% had $\geq 50\%$ reduction in CDAI. Change in SES-CD (adjusted for BL CDAI, SES-CD, and tx group) showed a moderate correlation with change in CDAI ($r = 0.37$; $p = 0.01$). SES-CD was developed in pts with

intact GI anatomy. Examining this relationship in the 32 pts without prior CD surgery showed an improved correlation ($r=0.48$; $p=0.01$). Adverse event (AE) rates and serious AE rates were low and similar across tx groups. Mongsersen was generally safe and well tolerated. **Conclusions:** Mongsersen showed clinical and endoscopic improvements at Wk 12 for pts with active CD. A moderate correlation was seen between clinical and endoscopic benefit. This correlation improved when the analysis was confined to pts without prior CD surgery. No new safety signals were identified.

OP020

Recent anti-TNF exposure predicts lower vedolizumab trough concentrations in patients with Crohn's disease

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Background: Vedolizumab (VDZ) inhibits interaction of the $\alpha_4\beta_7$ integrin with mucosal addressin cell adhesion molecule (MAdCAM)-1. We have previously shown that anti-TNF treatment influences MAdCAM-1 expression in gut biopsies. We studied the impact of recent anti-TNF exposure on VDZ trough concentrations (TC) and response in patients with Crohn's disease (CD) and ulcerative colitis (UC).

Methods: From 75 patients (46 CD, 29 UC) starting VDZ therapy in a tertiary referral center, VDZ and anti-TNF serum concentrations (median [IQR]) were measured at trough during VDZ therapy at w2, w6, w10 (CD only), w14 and w22 using in-house developed ELISAs. Clinical response was evaluated by clinical symptoms and physician global assessment. Biological response and remission (based on CRP) were assessed at w6 and w22 in patients with CD who had baseline CRP >5 mg/L (n=25). Twenty-eight patients with CD underwent endoscopy after w22 to assess mucosal healing (MH) and all patients with UC received sigmoidoscopy at w10 (MH defined as Mayo endoscopic sub-score of 0/1).

Results: Clinical response was achieved in 46% (21/46) and 66% (19/29) of the patients with CD and UC. Only in patients with UC, an exposure-response relation was found between VDZ TC up to w22 and clinical response (data not shown, $p<0.0001$). At w22, 48% (12/25) and 32% (8/25) of the patients with CD were in biological response and remission. Patients in biological remission had higher VDZ TC at w6, w10 and w22 (data not shown, $p=0.02$, $p=0.04$ and $p=0.01$). MH was achieved in 18% (5/28) of the patients with CD and in 66% (19/29) of the patients with UC. Patients with UC with MH had higher VDZ TC up to w22 compared to patients with no MH ($p=0.02$, $p=0.006$, $p=0.03$ and $p=0.04$ for w2, w6, w14 and w22). Patients with CD with MH had higher VDZ TC at w6 and w10 ($p=0.006$, $p=0.03$).

Most patients (70/75) were previously exposed to anti-TNF. Of these, 30 had still detectable anti-TNF concentrations at the first VDZ infusion. Patients with CD who were recently exposed to anti-TNF (<16 weeks before the start of VDZ therapy, n=38) had lower VDZ TC at all time points, compared to patients with no recent anti-TNF exposure (e.g., w6: 16.8 $\mu\text{g/mL}$ [12.5], n=18 vs. 28.5 $\mu\text{g/mL}$ [18.2], n=28, $p=0.006$ and w22: 6.8 $\mu\text{g/mL}$ [8.0], n=16 vs. 15.5 $\mu\text{g/mL}$ [12.4], n=27, $p=0.005$). We observed numerical though non-

significant lower response rates in patients with recent anti-TNF exposure (data not shown, $p>0.1$).

Conclusions: An exposure-response relation was observed as early as w2 and up to w22, with impact of higher VDZ TC on meaningful outcomes. The inverse association between recent anti-TNF exposure and VDZ TC in patients with CD is intriguing and might be explained by a residual effect of anti-TNF treatment on MAdCAM-1 expression.

OP021

Hyperbaric oxygen therapy is safe and effective for hospitalized ulcerative colitis patients suffering from moderate-severe flares: a multi-center, randomized, double-blind, sham-controlled trial

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Background: A dysregulated tissue hypoxia response is central to ulcerative colitis (UC) pathogenesis. Hyperbaric oxygen therapy (HBOT) markedly increases tissue oxygen delivery and case series suggest a potential therapeutic benefit in UC. Hospitalized UC patients often require 2nd line therapy (colectomy or biologics) for non-responsiveness to steroids. We investigated the therapeutic potential of HBOT as an adjunct to steroids for UC patients hospitalized for moderate-severe flares.

Methods: UC patients hospitalized for moderate-severe flares (Mayo score ≥ 6 , endoscopic sub-score ≥ 2) were block randomized across 3 sites in a 1:1 fashion to either steroids + daily HBOT (2.4 ATA @ 100% oxygen, 90 minute, 10 sessions) or steroids + daily sham hyperbaric air (1.2 ATA @ 21% oxygen, 90 minutes, 10 sessions). Sham patients were pressurized to 1.34 ATA to mimic pressure changes observed with HBOT, and then decompressed to 1.2 ATA for the remainder of the treatment. Patient blinding was maintained by covering all consoles and valves, and the hyperbaric teams followed an a priori established script to ensure similarity when treating both groups. The treating medical team, gastroenterologist, and surgeon were blinded to study assignment. Clinical assessments were performed by a blinded gastroenterologist. The primary outcome was the clinical remission rate at study day 5 (partial Mayo score ≤ 2 with no sub-score >1). Secondary outcomes were: clinical response (reduction in partial Mayo score ≥ 2 , rectal bleeding sub-score of 0-1) and progression to 2nd line therapy (colectomy, anti-TNF therapy, cyclosporine).

Results: A total of 18 patients (10 HBOT, 8 Sham) were randomized and treated. HBOT patients had a higher median baseline CRP level (81 vs. 10, $p=0.07$) with comparable mean baseline Mayo scores (9.9 vs. 10.9, $p=0.14$). The study met its primary end-point of clinical remission at study day 5 for HBOT vs sham (50% vs. 0%, $p=0.04$). Response to HBOT was observed as early as day 3 (60% vs. 13%, $p=0.07$), and a significantly higher proportion of HBOT patients achieved day 10 response (80% vs. 25%, $p=0.05$) and remission (50% vs. 0%, $p=0.04$). HBOT patients less often required progression to 2nd line therapy (10% vs. 63%, $p=0.04$) or colectomy specifically (0% vs. 38%, $p=0.07$) while hospitalized. There were no adverse events.

Conclusions: The use of HBOT as an adjunct to steroids for hospitalized UC patients suffering from moderate-severe flares resulted in higher rates of response and remission, and a reduction in rates of colectomy or progression to anti-TNF therapy while hospitalized. HBOT is safe and well tolerated, and further randomized trials are needed to confirm our findings. #NCT02144350.

OP022

Proximity extension assay based proteins show immune cell specificity and can diagnose and predict outcomes in inflammatory bowel diseases: IBD Character study

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Background: Proximity extension assays (PEA) can compare concentrations of multiple proteins across biological samples and utilises the specificity of antibody proximity and the sensitivity of polymerase chain reaction to detect proteins of interests. As part of IBD Character, we performed high-throughput prospective case-control serum profiling to identify proteins that can predict Inflammatory Bowel Disease (IBD) and its disease course.

Methods: Serum profiling was performed in treatment naïve newly diagnosed IBD and Non-IBD (symptomatic and healthy controls) using PEA panels (Olink Proteomics). Phenotypic data were obtained for all patients and follow up outcome data were captured for the Edinburgh and Oslo IBD cohorts. Treatment escalation was defined as the need for surgery and/or biologic therapies after initial induction of remission. Linear models were created for each protein including age and sex as covariates. Statistical analysis was performed using R. **Results:** Protein profiles were available in 635 patients (152 CD, 159 UC, 26 IBD-U, 298 non-IBD). 61 protein markers were significantly associated with IBD including MMP12 (Holm-adjusted $p=4.1 \times 10^{-26}$). Mapping the top markers to the cell-specific FANTOM 5 [1], several differentially expressed proteins originate from innate and adaptive immune cells such as dendritic cells.

As diagnostic markers, 5 proteins differentiate UC from CD including MMP-12 ($p=4.6 \times 10^{-4}$)

Follow up data were available for 206 patients. A total of 25 (32%), 21 (18%) and 2 (18%) patients required treatment escalation in the CD, UC and IBDU respectively. The data were randomly split into a testing ($n=124$) and a validation cohort ($n=82$). Using multivariable analyses with age, sex and follow up time as covariates, 9 proteins survived Holm adjustment and 8 of these proteins significantly predicted escalation in the validation cohort.

1000 iterations of unsupervised linear discriminant consensus clus-

tering were performed using 7 randomly selected top protein probes. This identified 2 patients groups that had significantly different disease courses: logrank $p=2.2 \times 10^{-10}$, HR 5.6 (2.0–15.6), outperforming conventional biomarkers in predicting treatment escalation (hsCRP >4 mg/L, HR 3.2 (1.7–5.8), logrank $p=0.0003$ and Alb <36 g/L, HR 2.7 (1.4–5.2), $p=0.0004$).

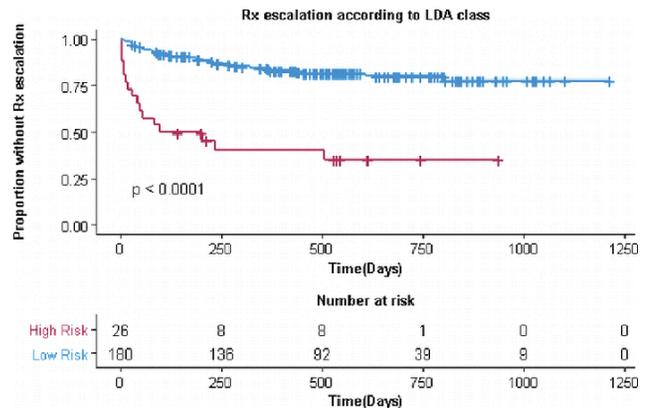


Figure 1

Conclusions: We have identified immune cell-specific PEA-based serum proteins that can diagnose IBD and predict disease course. These data demonstrate the translational potential of a PEA based technology in IBD

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OP023

Maintenance of clinical effect in patients with moderate-to-severe Crohn's disease treated with filgotinib, a selective JAK1 inhibitor: exploratory 20-week data analysis of the phase 2 FITZROY study

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Background: Filgotinib is an oral, selective Janus kinase 1 (JAK1) inhibitor, which demonstrated efficacy in patients with rheumatoid arthritis. This 20-week Phase 2 study evaluated the efficacy and safety of filgotinib in patients with moderate-to-severely ac-

tive Crohn's disease (CD). The primary endpoint (CDAI remission at Week 10) was met with an acceptable safety profile. Here, efficacy data from the exploratory Week 10–20 period as well as overall safety data are presented.

Methods: 174 patients with moderate-to-severely active CD (CDAI: 220 to 450) and ulcerations confirmed by centrally read endoscopy were randomized 3:1 to receive 200mg filgotinib (FIL) or placebo (PBO) QD for 10 weeks. Immunosuppressants were to be discontinued prior to treatment initiation but corticosteroid-treated patients remained on stable doses until Week 10. Based on clinical response at Week 10 (CDAI decrease from baseline ≥ 100 , as calculated by the investigator), patients were assigned to FIL (200mg or 100mg QD) or PBO for an additional 10 weeks. Patients assessed as clinical responders underwent mandatory corticosteroid tapering after Week 10. The second part of the study was exploratory.

Results: Baseline characteristics were similar in both initial treatment groups, including mean disease duration (8.3 y), mean CDAI score (293), mean CRP (15.6 mg/L, 41% >10mg/L), oral corticosteroids (51%, mean daily dose 20.8 mg/day).

At Week 20, 50–71% of initial FIL 200mg responders showed clinical remission and 67–79% showed clinical response, depending on their assignment to FIL 200mg QD, FIL 100mg QD or PBO. The FIL initial responders also maintained their gains in quality of life, as revealed by an IBDQ score at Week 20 that was at least 38.1 points higher than baseline. 59% (13/22) of patients not responding to PBO after 10 weeks showed clinical response at Week 20 upon being switched to FIL 100mg QD, and 32% (7/22) showed clinical remission.

The proportion of patients experiencing at least one TEAE was 75% with FIL (all periods of FIL exposure) and 67% with PBO (all periods of PBO exposure). Serious TEAEs occurred in 9% of FIL patients and 4% of PBO patients. TEAEs leading to discontinuation occurred in

18% for FIL and 9% for PBO. Serious infections were reported in 3% of FIL patients, and none in the PBO group.

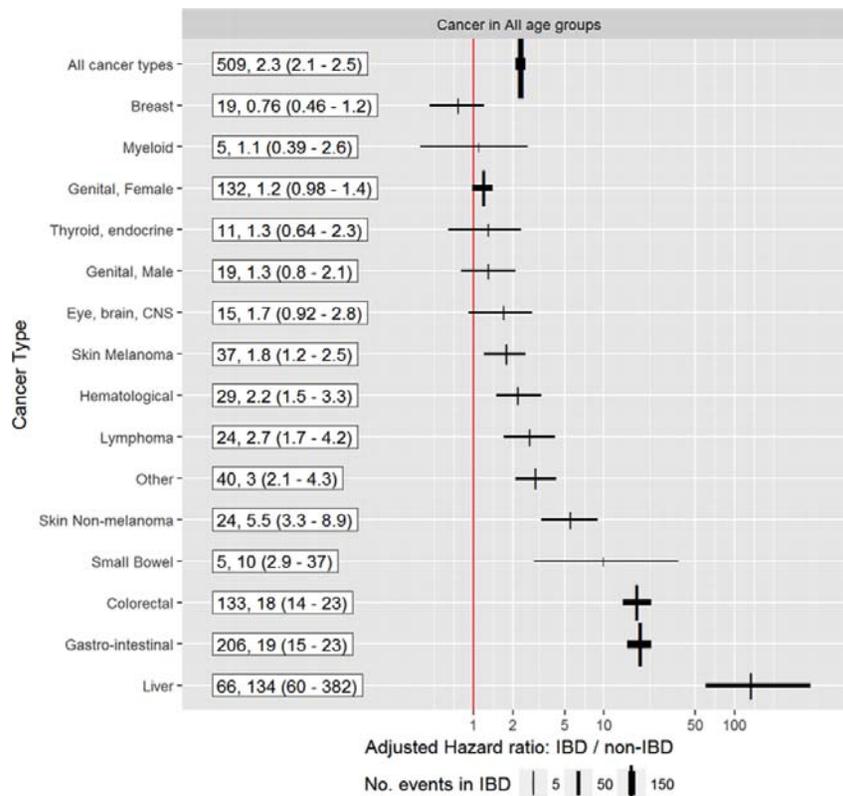
Conclusions: Clinical efficacy, induced with filgotinib after 10 weeks of treatment, as well as IBDQ improvements were sustained through Week 20 despite mandatory steroid tapering. 100mg filgotinib also showed efficacy, however this needs to be further evaluated. The efficacy and safety data of filgotinib suggest a favourable risk/benefit profile.

OP024
Childhood-onset inflammatory bowel disease and risk of cancer – a Swedish nationwide cohort study 1964–2014

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Background: Inflammatory bowel disease (IBD) with onset in adult age has been linked to an increased risk of cancer, especially colorectal cancer, but risk assessments in childhood-onset IBD are scarce.



Abstract OP024 – Figure 1. Hazard ratio of cancer in childhood-onset IBD, as compared to matched general population reference individuals 1964–2014. Numbers next to the forest plot represent the number of cancers in IBD-patients, Hazard ratio (95% confidence interval).

Methods: We used Cox regression to estimate hazard ratios (HRs) for cancer in 9,341 individuals with childhood-onset IBD (<18 years) (ulcerative colitis (UC): n=3,380; Crohn's disease (CD): n=3,046; IBD-unclassified (IBD-U): n=2,915) compared to 92,224 general population comparators matched for sex, age, year, and place of residence. Data on incident cases of IBD 1964–2014 were obtained from the National Swedish Patient Register comprising both inpatient and non-primary outpatient care, while cancer data were obtained through the Swedish Cancer Register. Medication data was obtained from the National Prescribed Drug Register for incident cases of childhood onset IBD since 2005 (n=3,386).

Results: There were 509 (3.46/1000 person-years) first cancers in patients with childhood-onset IBD compared to 2,237 (1.52/1000 person-years) in the general population comparators during follow-up, corresponding to a HR of 2.30 (95% confidence Interval (CI)=2.09–2.53). HRs for any cancer were 3.19 in UC and 1.76 in CD. While the relative risk was highest the first year of follow-up (HR=6.03), it remained elevated also after ≥5 years of follow-up (HR=2.29; 95% CI: 2.07–2.53). Patients with childhood-onset IBD also had an increased risk of cancer before their 18th birthday (HR=3.54; 95% CI: 2.22–5.46, n=26 cancers in IBD). Gastrointestinal cancers were associated with the highest relative risks (<18th birthday: HR=40 (95% CI: 13–175, n=12 cancers in IBD); ≥18th birthday: HR=18 (95% CI: 14–23, n=194 cancers in IBD)), but the absolute risks were low.

Patients with exposure to thiopurines (HR=4.23; 95% CI: 2.14–7.91) did not have a significantly more increased risk of cancer than patients never exposed to thiopurines (HR=3.59; 95% CI: 1.5–7.71).

Conclusions: Childhood-onset IBD is associated with an increased risk of cancer, both during childhood and later in life, especially gastrointestinal cancer. Thiopurine treatment in children is unlikely to be a major risk factor for cancer development in IBD in this age group

OP025

Evaluation of adalimumab effectiveness in anti-tumor necrosis factor-naïve pediatric patients with Crohn's disease in clinical practice

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Background: Adalimumab is an anti-tumor necrosis factor (ATNF) agent approved for the treatment of Crohn's disease in children since September 2014. We assessed the duration and effectiveness of adalimumab treatment in pediatric Crohn's disease patients in clinical practice without prior ATNF therapy.

Methods: In a retrospective cohort study using registry data from clinical care visits at 43 centers in the USA in the ImproveCareNow Network, ATNF-naïve patients induced with adalimumab prior to 18 years old with at least one post-induction visit were identified. We assessed the duration of treatment and the clinical effectiveness of adalimumab based on steroid-free clinical remission using Physician Global Assessment (PGA, inactive) and Short Pediatric Crohn's Disease Activity Index (sPCDAI, ≤10), as well as steroid-free clinical response using PGA (inactive or mild) and sPCDAI (≤25). Clinical care and frequency of visits were decided by the patient, parent and clinician. Data from clinical care visits were assessed every 3±1.5 months for 1 year, then every 6±3 months through 3 years. Descriptive statistics, Fisher's Exact Test and multivariable logistic regression analyses were performed.

Results: There were 174 patients (57% male, 25% <13 years old at induction) treated with adalimumab from August 2008 to December 2015. The number of patients followed post-induction for 3, 6, 12, 24 and 36 months was: 174, 174, 154, 71 and 39; the percentage of followed patients remaining on adalimumab was: 100%, 95%, 94%, 97% and 80%.

Of patients on adalimumab at 3, 6, 12, 24 and 36 months: 69%, 75%, 79%, 94% and 81% were in steroid-free clinical remission by PGA; and 71%, 77%, 80%, 91% and 86% by sPCDAI. Of patients on adalimumab at 3, 6, 12, 24 and 36 months: 88%, 91%, 93%, 99% and 94% had a steroid-free clinical response by PGA; and 83%, 85%, 91%, 98% and 100% by sPCDAI. Concomitant immunomodulator therapy did not appear to improve outcomes.

Conclusions: In the largest series with the longest follow-up, adalimumab was durable and effective as initial ATNF therapy for pediatric Crohn's disease in clinical practice. Of patients followed for 24 months, 97% remained on adalimumab. Steroid-free clinical remission was achieved in 91%–94%, and steroid-free clinical response in 98%–99%, of patients who remained on adalimumab for

Abstract OP025

	Baseline	3 Months	6 Months	12 Months	24 Months	36 Months
Patients being followed for this duration post-induction	174	174	174	154	71	39
Patients remaining on adalimumab [n, (%)]	174 (100%)	174 (100%)	166 (95%)	145 (94%)	69 (97%)	31 (80%)
Steroid free remission-PGA						
Yes	25 (15%)	110 (69%)	120 (75%)	112 (79%)	64 (94%)	25 (81%)
No	145 (85%)	49 (31%)	40 (25%)	30 (21%)	4 (6%)	6 (19%)
Steroid free remission-sPCDAI						
Yes	39 (32%)	97 (71%)	106 (77%)	91 (80%)	42 (91%)	19 (86%)
No	85 (68%)	39 (29%)	32 (23%)	23 (20%)	4 (9%)	3 (14%)
Steroid free response-PGA						
Yes	82 (48%)	140 (88%)	146 (91%)	132 (93%)	67 (99%)	29 (94%)
No	88 (52%)	19 (12%)	14 (9%)	10 (7%)	1 (1%)	2 (6%)
Steroid free response-sPCDAI						
Yes	55 (44%)	113 (83%)	117 (85%)	104 (91%)	45 (98%)	22 (100%)
No	69 (56%)	23 (17%)	21 (15%)	10 (9%)	1 (2%)	0 (0%)

24 months. The effect of dosage on outcomes is being investigated. These findings are important for patients, parents and clinicians considering ATNF therapy.

OP026

Zero diagnostic yield of dysplasia in polyp adjacent biopsies for patients with inflammatory bowel disease

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Background: Patients with inflammatory bowel disease (IBD) undergoing colonoscopic polypectomy are recommended by current guidelines (ECCO, 2013 [1]; AGA & ASGE 2015 [SCENIC] [2]) to have biopsies taken from the area immediately adjacent to the resected polyp to determine whether there is adjacent dysplasia present. With improvements in endoscopic imaging technology and use of pancolonic dye spray, as recommended by the same guidelines, it is possible to characterise colonic lesions with higher levels of confidence than previously.

We reviewed the diagnostic yield of such adjacent biopsies over a recent five year period.

Methods: A systematic search of our histopathology database revealed cases where polyps had been endoscopically resected or biopsied in patients with IBD between January 2010 and December 2015. Endoscopy reports and medical records were reviewed and patient demographic and disease specific details were recorded, along with details of polyp characteristics and histopathology outcomes.

Results: Over a five year period, 302 polyps were biopsied or resected in 131 patients undergoing 178 colonoscopic examinations. Median patient age was 60 (range 17–82), with 43% female. One hundred and twenty three patients (92%) had ulcerative colitis, 6 Crohn's colitis and 2 IBD-unclassified. Thirty patients (23%) had PSC. Median disease duration was 20 years (range 1–58 years). The majority of patients were on ASA based monotherapy. On a per-procedure analysis, 71 patients (40%) underwent chromoendoscopy, while 49 (28%) had their examinations with a high-definition colonoscope. On a per polyp analysis, median size was 4mm (range 1–45) and the predominant morphology was Paris 0-Is (sessile, n=98, 32%). Histology was tubular adenoma in 76 (25%), tubulovillous adenoma in 14 (5%), hyperplastic in 112 (37%), post-inflammatory in 32 (11%), sessile serrated polyp in 31 (10%), traditional serrated adenoma in 2 (0.7%), high-grade dysplasia or cancer in 2 (0.7%) and other in 33 (11%). Inflammation in adjacent biopsies was present in 34 patients (11%). Dysplasia in adjacent biopsies was detected in 2 patients (0.7%) and was endoscopically visible in both cases. Therefore the proportion of endoscopically unsuspected dysplasia revealed by adjacent biopsies was 0/300 (0%, 95% CI: 0–1.6%)

Conclusions: The diagnostic yield for polyp adjacent biopsies in patients with IBD is negligible. We suggest that with contemporary use of high definition technology and chromoendoscopy it is no longer necessary to biopsy endoscopically normal adjacent tissue to detect invisible dysplasia.

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- [2] Laine et al. (2015). SCENIC international consensus statement

on surveillance and management of dysplasia in inflammatory bowel disease, Gastroenterology

OP027

IL-33/ST2 axis sustains gut mucosal wound healing and cancerogenesis in colitis-associated colorectal cancer

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Background: IL-33/ST2 axis is important in IBD. Emerging evidence suggests its role in epithelial proliferation and contribution to inflammation-driven tumorigenesis. Our aim was to characterize its contribution in the DSS and AOM/DSS model of colitis.

Methods: C57/BL6 wild-type (WT), IL-33 KO and ST2 KO mice were given one dose of AOM followed by two cycles of 3% DSS for 7d. WT mice, injected with vehicle and given drinking water were used as controls (CT). At 8 wks post AOM injection mice were sacrificed. IHC, immunofluorescence (IF) and qPCR were done. FACS analysis was performed on resected, isolated polyps. 3% DSS was administered for 5d to WT, IL-33 KO and ST2 KO mice. DSS was replaced with drinking water for 2 wks (recovery period). Another group of WT mice received DSS for 5d and IL-33 or vehicle (VEH) every other day during the recovery period. Mice were sacrificed either after DSS challenge or after 1 or 2 wks of recovery.

Results: In AOM/DSS model IL-33, ST2L, and sST2 mRNA transcripts were dramatically elevated in WT vs. CT mice. IHC of treated WT mice revealed localization of ST2 to the intestinal epithelium in tissues immediately adjacent to tumors, while within the tumors themselves, ST2+ cells displayed a spindle/fibroblast-like morphology with a unique distribution throughout the polyps. Little to no staining for ST2 was present in CT. Using IF, ST2 co-localized with α SMA in polyps; ST2 was not exclusive for α SMA+ cells. At FACS analysis ST2 was mainly expressed by CD3/CD8+ cytotoxic T cells, and CD11b+CD11c- and CD11b+CD11c+ myeloid cells. Non-hematopoietic cells (CD45-) also expressed ST2. At 5 weeks post AOM injection WT had already pre-tumorous lesions, while IL-33 KO and ST2 KO mice showed their absence with a more impressive mucosal inflammation, likely due to reduced epithelial proliferation and repair caused by the absence of IL-33 signaling. At sacrifice, increased number and size of polyps were observed in WT vs. IL-33KO and ST2KO mice. More severe colitis was observed following DSS+1wk recovery vs. after 5d of DSS, which decreased after DSS+2wks recovery. ST2 staining was more evident during the recovery phase following DSS, localized to subepithelial myofibroblasts in proximity to areas of re-epithelialization. Both IL-33 and ST2 KO mice showed increased colonic inflammation after 2 wks recovery compared to after 5d DSS and vs WT. IL-33 treatment resulted in increased body weight, reduced DAI, and decreased colonic inflammation after 2 wks recovery vs. VEH.

Conclusions: Our results suggest that activation of the IL-33/ST2 axis sustains mucosal healing and tumorigenesis in the murine model of colitis-associated CRC.

OP028

Gut specific regulatory T cells – a new frontier for Crohn's disease therapy

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Background: We have recently shown that Tregs isolated from the peripheral blood of patients with Crohn's Disease (CD) play a critical role in controlling both phenotype and expansion of auto-reactive T cells (1). This is a critical step to developing cell based therapy for Crohn's disease, where where primary and secondary non response rates to biologics remain unacceptably high. The immune system used retinoic acid (ATRA) to induce a4b7 and thus prime Tregs to home to the gut. We sought use ATRA *in-vitro* in order to engineer gut specific Tregs for our Phase 1 trial in Crohn's Disease. We then validated our findings *in-vitro* and *in-vivo*.

Methods: Tregs were isolated from peripheral blood of CD patients. ATRA supplementation was tested in standard culture conditions. The expression of a4b7 was assessed by flow cytometry. Suppression assays were performed using autologous effector T cells (Teff). An ibidi flow chamber system coated with recombinant human MAdCAM-1 was used for *in-vitro* trafficking experiments. SCID mice xenografted with foetal intestinal small bowel were used for *in-vivo* experiments. Parametric and non-parametric data were calculated as the mean \pm s.d. and median (IQR). For comparison of parametric and non-parametric data, t-test, or ANOVA were used.

Results: *Ex-vivo* expansion of Tregs in the presence of ATRA significantly induced the expression of a4b7 compared to Rapamycin alone (5.57% \pm 3.12 vs 82.8% \pm 9.5, p=0.0057) Cells treated with Rapa+ATRA maintained their superior suppressive ability compared to Rapamycin treated Tregs (95.8% \pm 3.5% vs 91.15% \pm 10.1% p=ns; at Treg:Teff 1:1 ratio). RAPA+ATRA Tregs did not produce IFN γ or IL17 under pro-inflammatory cytokine challenge. When flowed through a MAdCAM-1 coated chamber, significantly higher numbers of Rapa+ATRA treated cells were observed to roll (Rapa 0.83 \pm 0.40 vs Rapa+ATRA 10.17 \pm 2.54 p=0.005), crawl (Rapa 0 vs Rapa+ATRA 4 \pm 0.89 p=0.001) and firmly adhere (Rapa 0.33 \pm 0.21 vs Rapa+ATRA 36.8 \pm 1.78, p<0.001) than those treated with Rapa alone. When Tregs were transferred into mice, a higher proportion of Tregs were found in xenografts of animals treated with Rapa+ATRA Tregs compared Rapa Tregs (12.10 (7.54–22.83) vs 4.97 (1.72–7.63), p=0.0056). Importantly there was a higher proportion of Tregs in inflamed xenografts of animals treated with Rapa+ATRA Tregs compared to those treated with Rapa Tregs (18.35 (12.95–28.63) vs 6.78 (2.65–9.61), p=0.0095).

Conclusions: The addition of ATRA to Treg culture *in-vitro* confers a gut homing phenotype. This is functionally relevant *in-vitro* and *in-vivo*. The treatment maintains the highly suppressive and pheno-

typically stable phenotype of these cells. These gut specific Tregs will be implemented in our first in man trial Treg therapy for Crohn's disease.

OP029

Hypoacetylation of histone-3 is a hallmark of intestinal fibrosis in Crohn's disease

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Background: Recurrent cycles of intestinal inflammation and repair drive fibrosis and stricture formation in patients with Crohn's disease (CD). Histone acetylation is an important epigenetic mechanism that impacts gene transcription and is controlled by the histone deacetylase enzymes (HDACs). This pathway can be pharmacologically manipulated by HDAC inhibitors such as valproic acid (VPA), which protects against experimentally induced colitis and reduces fibrosis in non-intestinal models of disease. In this study we investigate the relationship between histone-3 acetylation levels and inflammation and fibrosis in CD and test the ability of VPA to modulate synthesis of collagen I.

Methods: Histone-3 acetylation was assessed by immunohistochemistry in FFPE tissue from healthy controls (n=12), CD patients with: quiescent (n=8); inflammatory (n=7); and fibrotic disease (n=6). The effects of VPA (5mM) on collagen I synthesis, measured by qPCR, immunofluorescence and ELISA, were tested in *ex-vivo* CD gut cultures, a novel 3D organotypic model of the gut and a human intestinal fibroblasts cells line (CCD18co cells). An Illumina HT12 array was also performed on RNA extracted from CCD18c0 cells (n=4) to further elucidate pathways regulated by VPA. The array was analysed using "significance analysis of microarray" package in R, and pathway analysis performed using the Reactome database.

Results: Relative to healthy controls and CD patients with quiescent disease, there was a reduction in histone-3 acetylation in the mucosa overlying both inflamed and strictured gut (p=0.004, ANOVA). Histone-3 acetylation was also lower in strictured gut relative to adjacent non-strictured areas (p=0.015, n=6). *Ex-vivo* cultures of CD biopsies with VPA, which increases histone-3 acetylation, led to a reduction in collagen I RNA expression (COL1A2, p=0.005, n=8). Levels of collagen I protein were also lower in conditioned media taken from an organotypic model of the gut treated with VPA (p=0.016, n=3). Gene expression arrays further identified genes enriched in 24 pathways that were regulated by VPA, including the collagen degradation pathway (p=0.044), with a reduction in collagen I protein confirmed by immunofluorescence (p=0.013, n=4).

Conclusions: Hypoacetylation is a pathological feature of both inflammation and fibrosis in CD. Treatment with VPA increases histone acetylation and suppresses collagen expression in CD patient biopsies and models of intestinal fibrosis, demonstrating a direct link between histone acetylation and collagen production in CD. The data highlight the potential to exploit existing drugs that modulate histone acetylation in the treatment of fibrostenosing CD.

OP030

Identification of disease-relevant bacterial signatures in gnotobiotic IL-10 deficient mice using fecal samples from IBD patients undergoing hematopoietic stem cell transplantation

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Background: Imbalanced microbial composition has been linked to the pathogenesis of inflammatory bowel diseases (IBD). Hematopoietic stem cell transplantation (HSCT) proved to be successful in inducing remission in severe, highly refractory Crohn's disease (CD) patients, possibly by erasing immune responses against gut microbes. Gnotobiotic mouse models colonized with human microbiota brought insights into the mechanistic aspects of host-microbe interactions. The aim of this study was to assess the functional role of microbiota signatures associated with different disease states.

Methods: High-throughput 16S rRNA gene amplicon sequencing was performed on (n=147) fecal samples collected from (n=13) healthy donors and (n=31) HSCT-treated CD patients. Germ-free (GF) wild-type (WT) and IL10^{-/-} mice (129 Sv/Ev; n=12 mice/group) were colonized with fecal microbiota from CD patients before and after HSCT at different disease states. Selection of CD patients for transfer into GF mice was based on clinical and endoscopic disease activity, including paired patient samples collected under remission or relapse following HSCT.

Results: Microbiota profiling showed a significantly reduced microbial diversity in patients compared with healthy controls. Patients in remission showed higher microbial diversity than patients in relapse or at active state of the disease. Patients with fistulating or ileal phenotype had the least diverse ecosystems. High level of inter-individual variation was observed. Despite an incomplete transfer of donor microbiota with a 20–40% loss of species-level taxa, humanized mice reflected the dysbiotic features of their respective human donors, indicated by richness and diversity measures. Histopathological evaluation showed moderate to severe inflammation in colon and cecum of the IL10^{-/-} mice associated with microbiota from patients in relapse. In contrast, IL10^{-/-} mice associated with microbiota from patients in remission remained disease-free. To validate the phenotype transfer, we gavaged the mice three times with donor microbiota during the first week of colonization. Remission-associated mice showed higher species richness but still remained disease-free, while relapse-associated mice developed enhanced inflammation measured at the level of fecal complement C3 concentrations. Endpoint microbial composition remained similar, regardless of the number of inoculations and F1 generation of mice displayed a stable engraftment of human microbiota.

Conclusions: Transfer of patient-derived fecal microbiota mimics the disease phenotype in gnotobiotic IL10^{-/-} mice. Bacterial composition, not the number of species is responsible for disease initiation. Humanized mice represent a potential tool for recapitulating disease phenotypes in IBD.

OP031

Long-term safety and tolerability of oral tofacitinib in patients with Crohn's disease: results from a phase 2 open-label 48-week extension study

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Background: Tofacitinib is an oral, small molecule Janus kinase inhibitor that is being investigated for inflammatory bowel disease. The efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) for inducing and maintaining clinical remission in patients (pts) with moderate to severe Crohn's disease (CD) was investigated in two Phase 2b studies [1,2]. We present data from a follow-up open-label long-term extension (OLE) study.

Methods: This was a Phase 2b, multicentre, 48-week (wk) OLE study (NCT01470599) in pts with CD who completed the maintenance study (NCT01393899) or withdrew due to treatment failure. Pts in clinical remission (CD activity index [CDAI] <150) at Wk 26 of the maintenance study received tofacitinib 5 mg BID; all other pts received 10 mg BID. A single dose adjustment of 5 to 10 mg BID or vice versa was allowed post Wk-8, at the physicians' discretion. The primary objective was to assess safety. All efficacy endpoints were exploratory. Descriptive summaries by initially assigned dose were calculated based on observed data with no imputation of missing data.

Results: 62 pts in remission and 88 pts not in remission at baseline (BL) received tofacitinib 5 and 10 mg BID (Table). 22 and 3 pts in 5 and 10 mg BID switched dose during the 48-wk study. 43 and 45 pts initially assigned 5 and 10 mg BID completed the study. Both groups had similar adverse event (AE) and serious infection rates; Gastrointestinal disorders and Infections were the most common AE system organ classes (SOC). CD, nasopharyngitis and urinary tract infections were the most common AE terms. Serious AEs (SAEs) occurred in 8.1% and 19.3% of 5 and 10 mg BID pts; CD/worsening condition was the most common SAE: 4.8% and 10.2% for 5 and 10 mg BID, respectively. Discontinuations (d/c) due to AEs excluding worsened CD attributed to insufficient clinical response occurred in 4.8% and 11.4% of 5 and 10 mg BID pts, with Infections the most common SOC. One case of basal cell carcinoma occurred with 10 mg BID. At Wk 48, 87.9% and 55.6% of 5 and 10 mg BID pts were in remission, with a mean CDAI change from BL of -4.8 and -121.9, respectively.

Conclusions: Both doses had similar AE rates overall but SAEs and early d/c due to AE rates were higher in 10 mg BID. However, only 10 mg BID pts entered with active disease and some pts switched dose groups post-Wk 8. This study showed no new safety findings from those previously reported.

References:

- [1] Panés J et al, (2016), Efficacy and safety of oral tofacitinib for induction therapy in patients with moderate-to-severe Crohn's disease: results of a Phase 2b randomised placebo-controlled trial, *J Crohns Colitis*, 10: S18
- [2] D'Haens G et al, (2016), Efficacy and Safety of Oral Tofacitinib for Maintenance Therapy in Patients with Moderate to Severe Crohn's Disease: Results of a Phase 2b Randomized Placebo-Controlled Trial, *J Crohns Colitis*, 10: S17

Abstract OP031

Table Summary of safety and efficacy through 48 weeks in the open-label extension study

	Tofacitinib 5 mg BID (N=62)	Tofacitinib 10 mg BID (N=88)
Baseline characteristics* (FAS)		
Female, n (%)	30 (48.4)	41 (46.6)
Age of onset of CD, years (SD)	28.0 (9.8)	26.6 (10.9)
CDAI, mean (SD)	77.1 (43.2)	291 (95.8)
Prior TNFi failure, n (%)	42 (67.7)	69 (78.4)
Discontinuations, n (%)		
All causes	19 (30.6)	43 (48.9)
Due to insufficient clinical response/worsening of CD	6 (9.7)	27 (30.7)
Due to AEs, n (%)	3 (4.8)	10 (11.4)
Infections (SOC)	2 (3.2)	3 (3.4)
Switched dose groups, n (%)		
	22 (35.5)	3 (3.4)
Treatment-emergent adverse events		
AEs, n (%)	49 (79.0)	67 (76.1)
GI (SOC)	32 (51.6)	39 (44.3)
CD worsening	21 (33.9)	17 (19.3)
Infections (SOC)	31 (50.0)	42 (47.7)
Nasopharyngitis	8 (12.9)	7 (8.0)
Urinary tract infections	8 (12.9)	7 (8.0)
Herpes zoster (all)	1 (1.6)	2 (2.3)
Opportunistic infection, n (%)	1 (1.6)	1 (1.1)
AEs of special interest, n (%)		
Intestinal perforation*	0 (0.0)	0 (0.0)
Malignancy	0 (0.0)	1 (1.1) ^b
CV event	0 (0.0)	0 (0.0)
SAEs, n (%)	5 (8.1)	17 (19.3)
CD	3 (4.8)	9 (10.2)
Serious infections, n (%)	2 (3.2)	2 (2.3)
Deaths, n (%)	0 (0.0)	0 (0.0)
Efficacy endpoints at Week 48 (FAS, observed)		
Clinical remission ^c n (%)	29 (87.9)	20 (55.6)
Sustained clinical remission ^d n (%)	24 (75.0)	12 (34.3)
CDAI score, median (min–max)	67.0 (-10–332)	147.5 (49–334)
CDAI change from BL, mean (SD)	-4.8 (60.1)	-121.9 (129.2)
Observed CRP, median (min–max) [mg/L]	2.9 (0.1–53.5)	6.5 (0.2–69.8)
Observed fecal calprotectin, median (min–max) [mg/kg]	148.5 (25.2–1005.0)	224.5 (25.2–1537.0)

All data are presented by dose assigned at randomisation

Unless indicated otherwise, data are based on the FAS population (N=62 and N=88 for tofacitinib 5 and 10 mg BID, respectively)

*Adverse event preferred term

^bRepresents BL characteristic at OLE study entrance

^cAdjudicated malignancy events including one case of basal cell carcinoma

^dRemission was defined as CDAI <150. For this analysis, N=33 and N=36 for tofacitinib 5 and 10 mg BID, respectively

^eSustained clinical remission was defined as being in remission at both Week 24 and Week 48. For this analysis, N=32¹ and N=35 for tofacitinib 5 and 10 mg BID, respectively

AE, adverse event; BID, twice daily; BL, baseline; CD, Crohn's disease; CDAI, Crohn's disease activity index;

CRP, C-reactive protein; CV, cardiovascular; FAS, full analysis set; GI, gastrointestinal; n, number of patients;

SAEs, serious adverse events; SD, standard deviation; SOC, system organ class; TNFi, tumour necrosis factor inhibitor

OP032

Efficacy and safety of oral tofacitinib as maintenance therapy in patients with moderate to severe ulcerative colitis: results from a phase 3 randomised controlled trial

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Background: Tofacitinib is an oral, small molecule Janus kinase inhibitor that is being investigated for ulcerative colitis (UC). Efficacy and safety of tofacitinib 10 mg twice daily (BID) were reported in OCTAVE Induction 1 & 2 [1].

Methods: OCTAVE Sustain (NCT01458574) was a Phase 3, randomised, double-blind, placebo (PBO) -controlled study that enrolled PBO or tofacitinib patients (pts) who completed OCTAVE Induction 1 or 2 with at least clinical response (≥ 3 points and $\geq 30\%$ decrease from baseline (BL) Mayo score plus a decrease in rectal bleeding subscore of ≥ 1 or absolute rectal bleeding subscore ≤ 1). Pts were re-randomised (1:1:1) to maintenance treatment with PBO (N=198), tofacitinib 5 (N=198) or 10 mg BID (N=197) for 52 weeks (wks). The primary endpoint was remission (total Mayo score ≤ 2 , no subscore > 1 , rectal bleeding subscore of 0) at Wk 52. Key secondary endpoints were mucosal healing (Mayo endoscopic subscore

≤1) at Wk 52, and sustained steroid-free remission (remission at Wks 24 and 52; no steroid use ≥4 wks prior to each visit) among pts in remission at BL.

Results: At Wk 52, tofacitinib 5 and 10 mg BID had significantly greater effect vs PBO for the primary endpoint of remission, and secondary endpoints of mucosal healing, clinical response as well as sustained remission, sustained mucosal healing and sustained clinical response (Table; $p < 0.001$ all comparisons). Among pts in remission at BL, both tofacitinib groups had significantly higher proportions of pts with sustained steroid-free remission vs PBO ($p < 0.001$ all comparisons). Adverse event (AE), serious AE and serious infection rates were similar among all groups. Despite more frequent infections with tofacitinib vs PBO, discontinuations due to AEs were numerically lower for tofacitinib vs PBO. A dose dependent increase in herpes zoster (HZ) rate was observed. There were no deaths, malignancies (excluding non-melanoma skin cancer) or intestinal perforation AEs in either tofacitinib group. Changes in lipid and creatine kinase levels were consistent with results from tofacitinib studies in other populations.

Conclusions: Tofacitinib 5 and 10 mg BID were significantly more

effective vs PBO as maintenance therapy over 52 wks in pts with moderately to severely active UC. Despite a dose-dependent increase in HZ, overall, AE rates were similar among both tofacitinib groups. No new safety findings emerged from those previously reported in studies of rheumatoid arthritis.

References:

- [1] Sandborn WJ et al, (2016), Efficacy and safety of oral tofacitinib as induction therapy in patients with moderate-to-severe ulcerative colitis: results from 2 phase 3 randomised controlled trials, *J Crohns Colitis*, 10: S15

OP033

Reduction of tissue pSTAT3 in Crohn's disease patients treated with filgotinib (GLPG0634, GS-6034), a JAK1-selective inhibitor

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Abstract OP032

Table: Summary of efficacy and safety through 52 weeks in OCTAVE Sustain

	Placebo N=198	Tofacitinib 5 mg BID N=198	Difference from placebo (95% CI)	Tofacitinib 10 mg BID N=197	Difference from placebo (95% CI)
Remission at Week 52, n (%)†	22 (11.1)	68 (34.3)***	23.2 (15.3, 31.2)	80 (40.6)***	29.5 (21.4, 37.6)
Sustained remission, n (%)‡	10 (5.1)	44 (22.2)***	17.2 (10.6, 23.7)	50 (25.4)***	20.3 (13.5, 27.1)
Mucosal healing at Week 52, n (%)	26 (13.1)	74 (37.4)***	24.2 (16.0, 32.5)	90 (45.7)***	32.6 (24.2, 41.0)
Sustained mucosal healing, n (%)‡	13 (6.6)	55 (27.8)***	21.2 (14.1, 28.3)	65 (33.0)***	26.4 (19.0, 33.8)
Sustained steroid-free§ remission among remitters at baseline, n/N (%)	3/59 (5.1)	23/65 (35.4)***	30.3 (17.4, 43.2)	26/55 (47.3)***	42.2 (27.9, 56.5)
Clinical response at Week 52, n (%)	40 (20.2)	102 (51.5)***	31.3 (22.4, 40.2)	122 (61.9)***	41.7 (32.9, 50.5)
Sustained clinical response, n (%)‡	38 (19.2)	97 (49.0)***	29.8 (20.9, 38.7)	117 (59.4)***	40.2 (31.4, 49.0)
Treatment-emergent AEs, n (%)	149 (75.3)	143 (72.2)	-	156 (79.6)	-
Treatment-emergent SAEs, n (%)	13 (6.6)	10 (5.1)	-	11 (5.6)	-
Infections, n (%)	48 (24.2)	71 (35.9)	-	78 (39.8)	-
Herpes zoster, n (%)	1 (0.5)	3 (1.5)	-	10 (5.1)	-
Serious infections, n (%)	2 (1.0)	2 (1.0)	-	1 (0.5)	-
Malignancies (excluding NMSC)	1 (0.5)	0 (0.0)	-	0 (0.0)	-
NMSC	1 (0.5)	0 (0.0)	-	3 (1.5)	-
Discontinuations due to AEs, n (%)	37 (18.7)	18 (9.1)	-	19 (9.7)	-

*** $p < 0.001$ vs placebo; †, primary endpoint; ‡, sustained endpoints were defined as achieving response/remission at both Week 24 and Week 52; §, steroid-free was defined as not requiring corticosteroids for ≥4 weeks prior to each visit

Patients entering OCTAVE Sustain could be receiving a maximum of prednisone 25 mg/day or equivalent. Steroid tapering was mandatory at baseline, with all patients steroid-free by Week 7

Binary efficacy data are full analysis set, non-responder imputation and compared using Cochran-Mantel Haenszel chi-square test
AE, adverse event; BID, twice daily; CI, confidence interval; LS, least squares; NMSC, non-melanoma skin cancer; SAE, serious AE

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Background: Janus kinases (JAK) are a family of tyrosine kinases that play a key role in the signalling of more than 60 cytokines and growth factors. Many of these cytokines display pro-inflammatory activity in Crohn's Disease (CD). The selective JAK1 inhibitor filgotinib blocks cytokine signalling through the inhibition of STAT phosphorylation and has shown clinical efficacy in a double-blind, placebo-controlled Phase 2 study in CD (FITZROY). In order to understand the mechanism of action of filgotinib in CD patients, we measured the level of pSTAT3 in gut biopsies from this study.

Methods: CD patients were randomized 3:1 to receive 200mg filgotinib or placebo QD for the first 10 weeks. Two biopsies, one each from the most and least affected mucosa, were collected during screening and at Wk 10 from each of the 6 predefined segments of the lower gastrointestinal tract. Samples from 60 patients with complete set of paired biopsies were selected. pSTAT3 was evaluated by IHC using an antibody specific to phosphorylated Y705. H-Score was quantified using Definiens Tissue Studio software. The mixed effect ANOVA method was used for evaluating the treatment effect and difference between patients achieving clinical remission (defined as CDAI <150) and those who did not.

Results: Basal pSTAT3 level was comparable for the filgotinib and placebo groups. Following filgotinib treatment, pSTAT3 level was significantly reduced in the most affected mucosa from all segments combined: -36% (95% CI: -51%, -17%), whereas reduction in the placebo arm was not significant (although with less subjects): -24% (95% CI: -49%, +14%). In patients with clinical remission at Wk 10, pSTAT3 levels showed a significant reduction from baseline in each group: -62% (95% CI: -83%, -16%) with placebo, and -42% (95% CI: -57%, -21%) with filgotinib. In patients not achieving clinical remission, pSTAT3 from the placebo arm showed an average numerical increase of +12% (95% CI: -21%, +94%) whereas pSTAT3 was on average reduced with filgotinib: -28% (95% CI: -51%, +7%). Similar observations were made in the least affected mucosa of different segments.

Conclusions: Significant reduction of pSTAT3 by filgotinib on inflamed gut of CD patients provides direct evidence of its anti-inflammatory effect. Clinical remission status is associated with a decrease in pSTAT3. In non-remitters, the observed pSTAT3 reduction with filgotinib illustrates its pharmacodynamic effect through JAK1 inhibition. A large phase 3 program in CD and UC is ongoing.

OP034

Efficacy and safety of abrilumab in subjects with moderate to severe ulcerative colitis: results of a phase 2b, randomised, double-blind, multiple-dose, placebo-controlled study

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Background: $\alpha_4\beta_7$ integrin is a validated target in IBD. We studied abrilumab (AMG181/MEDI7183), a fully human monoclonal antibody against $\alpha_4\beta_7$ integrin, in subjects with ulcerative colitis (UC) and inadequate or loss of response to anti-tumor necrosis factors (TNFs) or immunomodulators.

Methods: This phase 2b, multicentre, randomised, double-blind, placebo (PBO)-controlled, parallel-group, multi-dose study enrolled subjects with moderate to severe UC (total Mayo Score 6–12, rectosigmoidoscopy score ≥ 2). Subjects received PBO or abrilumab (7, 21, or 70 mg) subcutaneously (SC) on day 1, weeks 2 and 4, and every 4 weeks or abrilumab 210 mg SC on day 1, stratified by prior anti-TNF exposure and participation in a pharmacokinetic (PK) sub-study. The primary endpoint was remission at week 8 (table); key secondary endpoints were response and mucosal healing at week 8. Endoscopy was centrally read. CD4+ T cell subsets were enumerated and $\alpha_4\beta_7$ receptor occupancy was measured in a subset of subjects.

Results: This study enrolled 354 subjects. The final allocation of 116, 21, 40, 98, and 79 in the PBO, 7, 21, 70, and 210 mg groups, respectively, was due to a systematic misalignment in investigational product; study blind and randomisation were intact. Remission rates were 4.4, 1.6, 2.9, 13.5, and 13.4% in the PBO, 7, 21, 70, and 210 mg groups, respectively; response and mucosal healing rates are listed in the table.

Higher rates of remission, response, and mucosal healing in the prior anti-TNF failure subgroup 210-mg arm were observed: 13.9, 51.9, and 40.6%, respectively. Maximal reduction of free $\alpha_4\beta_7$ on naïve CD4+ T cells in the peripheral blood was sustained through week 8, except for the 7-mg group. Abridumab induced a significant post-dose increase in $\alpha_4\beta_7$ -high central memory CD4+ T cell (Tcm) counts from baseline to week 8. Exposure-response (E-R) modeling of PK data demonstrated that subjects in decile groups with mean trough levels >10 $\mu\text{g/mL}$ showed maximal remission rates. Adverse events were balanced among groups through week 24, with no PML or deaths. No subject developed neutralising antibodies to abrilumab.

Conclusions: Abridumab demonstrated a favorable safety, immunogenicity, PK, pharmacodynamic, and efficacy profile, suitable for fur-

Abstract OP033 – Table 1. Percent reduction of pSTAT3 at Week 10 from most affected area in all segments in CD patients

Treatment	Overall (95% CI) Patient number	Remitters (95% CI) Patient number	Non-remitters (95% CI) Patient number
Filgotinib	-36% (-51%, -17%) n = 42	-42% (-57%, -21%) n = 26	-28% (-51%, +7%) n = 16
Placebo	-24% (-49%, +14%) n = 18	-62% (-83%, -16%) n = 7	+12% (-21%, +94%) n = 11

Abstract OP034 – Table 1. Rates of remission, response, and mucosal healing at week 8 in subjects who received abrilumab.

ALL SUBJECTS					
Characteristic, % (adjusted rates)	Placebo N = 116	Abrilumab			
		7 mg Q4W N = 21	21 mg Q4W N = 40	70 mg Q4W N = 98	210 mg N = 79
Remission rate ¹	4.4	1.6	2.9	13.5*	13.4*
Response rate ²	26.0	12.3	47.2*	49.4*	47.4*
Mucosal healing rate ³	16.8	12.2	13.9	32.2*	29.8*

ANTI-TNF-FAILURE SUBJECTS					
Characteristic, % (adjusted rates)	Placebo N = 70	Abrilumab			
		7 mg Q4W N = 5	21 mg Q4W N = 10	70 mg Q4W N = 50	210 mg N = 38
Remission rate ¹	1.4	11.2	5.5	7.0*	13.9*
Response rate ²	27.1	21.3	31.7	41.1	51.9*
Mucosal healing rate ³	16.0	10.6	13.2	18.8	40.6*

¹ Defined as total Mayo score ≤ 2 and no individual subscore > 1

² Defined as decrease from baseline in total Mayo score ≥ 3 points and $\geq 30\%$, and a decrease in the subscore for rectal bleeding ≥ 1 or an absolute score 0 or 1

³ Defined by an absolute subscore for rectosigmoidoscopy 0 or 1

* Nominal *p*-value < 0.1 vs placebo

Q4W: every four weeks; TNF: tumor necrosis factor

ther testing in subjects with UC. Efficacy did not appear to correlate with peripheral target coverage or changes in $\alpha_4\beta_7$ -high Tcm. E-R modeling suggests that higher abrilumab exposure may result in higher remission and response rates. Disclosure: Amgen and AstraZeneca/MedImmune sponsored this study.

OP035

Efficacy and safety of abrilumab (AMG 181/MEDI 7183) therapy for moderate to severe Crohn's disease

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Abstract OP035

Table. Patient Remission and Response Rates

Total Patient Population				
	Placebo (N=98)	Abrilumab		
		21 mg Q4W (N=26)	70 mg Q4W (N=84)	210 mg (single dose) (N=41)
CDAI Remission, %				
Week 8	12.8	23.1	14.4	21.9
Week 12	17.6	41.7*	27.9	30.8
CDAI Response, %				
Week 8	27.0	32.4	43.2*	29.4
Week 12	29.6	47.4	48.9*	46.6*
CRP change from baseline at week 8, mg/L, mean (SE)	2.93 (2.16)	1.05 (2.41)	-0.45 (2.03)	-1.43 (2.07)
FCP change from baseline at week 8, mg/L, mean (SE)	-104.26 (186.15)	-534.31 (308.98)	-34.14 (135.15)	141.28 (243.14)

Prior Anti-TNF-Failure Patients				
	Placebo (N=79)	Abrilumab		
		21 mg Q4W (N=20)	70 mg Q4W (N=65)	210 mg (single dose) (N=32)
CDAI Remission, %				
Week 8	5.8	7.6	9.6	16.3*
Week 12	8.2	22.9*	17.4*	24.8*
CDAI Response, %				
Week 8	15.1	16.2	39.3*	27.0
Week 12	14.2	30.0	39.4*	37.4*

Anti-TNF-naïve Patients				
	Placebo (N=19)	Abrilumab		
		21 mg Q4W (N=6)	70 mg Q4W (N=18)	210 mg (single dose) (N=9)
CDAI Remission, %				
Week 8	35.3	70.2	19.1	26.5
Week 12	45.8	76.3	40.4	29.2
CDAI Response, %				
Week 8	63.2	75.0	31.0*	27.4
Week 12	67.4	73.8	42.7	50.7

Data are shown as adjusted rates (%) unless noted. **P* < 0.1 vs placebo; all *P*-values are nominal. N = number of patients in the analysis set. CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; FCP, fecal calprotectin.

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Background: Adhesion molecule $\alpha 4\beta 7$ is a validated treatment target in inflammatory bowel diseases. We evaluated abrilumab, a fully human monoclonal antibody against $\alpha 4\beta 7$, in patients with moderate to severe Crohn's disease (CD).

Methods: This phase 2b, randomised, multi-centre, double-blind, placebo (Pbo)-controlled study enrolled patients aged 18–65 years with moderate to severe CD (CDAI score 220–450) and evidence of active inflammation (by endoscopic evaluation, or elevated C-reactive protein or fecal calprotectin). In addition, patients must have had inadequate or loss of response or intolerance to immunosuppressives, TNF antagonists, or corticosteroids. Eligible patients were randomised to receive Pbo or abrilumab (21 or 70 mg) SC on day 1, weeks 2 and 4, and every 4 weeks (Q4W) for up to 24 weeks, or one dose of abrilumab 210 mg SC on day 1. The primary endpoint was CDAI remission (score <150) at week 8. Key secondary endpoints were remission at week 12 and CDAI response (reduction from baseline of ≥ 100) at weeks 8 and 12. CD4+ T cell subsets were enumerated and $\alpha 4\beta 7$ receptor occupancy was measured in a subgroup of patients.

Results: This study enrolled 249 patients. Final randomisation allocation was affected by a systematic misalignment in investigational product, resulting in 98, 26, 84, and 41 patients in the Pbo, 21 mg Q4W, 70 mg Q4W, and 210 mg treatment groups, respectively. The study blind and randomisation were intact. Baseline demographics were similar. Statistically significant improvement was not achieved between the abrilumab 70 mg Q4W and Pbo arms for the primary endpoint ($p=0.76$ vs Pbo) (Table). However, higher rates of remission and response were observed in the active treatment arms at week 12, particularly in patients with prior failure of TNF antagonists assigned to the 210 mg abrilumab group. Maximal reduction of free $\alpha 4\beta 7$ on naïve CD4+ T cells in the peripheral blood was sustained from the first measurement at week 2 to week 8 for all dose groups, and through week 12 for the 21 mg Q4W and 70 mg Q4W groups. Abrilumab induced a significant post-dose increase in $\alpha 4\beta 7$ -high central memory CD4+ T cell counts between baseline and week 8. Adverse events were similar among treatment groups through week 24, with no cases of PML or deaths. No patients developed neutralizing antibodies to abrilumab.

Conclusions: Although the primary endpoint was not met, beneficial effects of abrilumab were observed for remission and response rates. There was no safety imbalance compared with Pbo.

Amgen and AstraZeneca/MedImmune sponsored this study.

OP036

Short duration, low intensity pooled faecal microbiota transplantation induces remission in patients with mild-moderately active ulcerative colitis: a randomised controlled trial

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Background: Faecal microbiota transplantation (FMT) has demonstrated variable efficacy in the treatment of active ulcerative colitis (UC) in three randomised control trials (RCT) to date. Interpretation of FMT RCT evidence is limited by each trial using a different donor stool processing method, placebo control, as well as timing and method of administration. Although the optimal approach is unclear, protocols involving a lower treatment burden may make FMT for UC more accessible.

Methods: A multi-centre randomised, double-blind, placebo-controlled trial of FMT in adults with active UC (total Mayo 3–10 with an endoscopic Mayo sub-score ≥ 2) was performed. Anaerobically prepared donor stool (pooled from 3–4 donors) or autologous FMT (placebo) were stored frozen at -80°C , thawed and then administered via colonoscopy on day 0 followed by 2 enemas by day 7. The primary outcome was steroid-free remission of UC as defined by a total Mayo score of ≤ 2 with an endoscopic Mayo score of ≤ 1 at week 8. Secondary end points included clinical response (≥ 3 point reduction in Mayo score), clinical remission (Simple Clinical Colitis Activity Index ≤ 2), endoscopic remission (Mayo ≤ 1) and safety. A mandatory taper of oral corticosteroids was performed; those patients unable to cease oral corticosteroids were considered FMT non-responders.

Results: 73 patients with UC were randomised; 38 received donor FMT and 35 received autologous FMT. 3 dropped out from the donor group and 1 from the autologous group during the 8 week observation period. In the intention to treat (ITT) analysis, 12/38 (32%) patients who received pooled donor FMT achieved the primary endpoint of steroid-free remission, as compared to 3/35 (9%) who received autologous FMT ($p=0.02$). In the per-protocol analysis, 12/35 (34%) vs 3/34 (9%) achieved the primary endpoint ($p=0.02$). In the ITT analysis, clinical response and clinical remission rates were 55% vs 20% ($p<0.01$) and 50% vs 17% ($p<0.01$) respectively. Steroid-free endoscopic remission occurred in 55% vs 17% ($p<0.01$). UC disease extent and disease duration were not significantly associated with achieving the primary endpoint in the donor FMT group. The frequency of serious adverse events (SAE) was not different between the donor and autologous FMT groups; 3 SAE's were recorded in the donor FMT group (1 worsening colitis, 1 *Clostridium difficile* colitis requiring colectomy, and 1 pneumonia) and 2 SAE's in the autologous FMT group (both worsening colitis).

Conclusions: In active UC, one week of induction therapy with anaerobically prepared pooled donor FMT is more effective than placebo (autologous FMT) in inducing both clinical and endoscopic remission at 8 weeks.

OP037

Infants born to mothers with inflammatory bowel disease exhibit distinct microbiome features that persist up to 3 months of life

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Placebo = autologous stool
Analysis Wk 8

133 eligible
↓
73 included

The MECONIUM study

W

York, United States; ²Icahn School of Medicine at Mount Sinai, Genetics and Genomic Sciences, New York, United States; ³Icahn School of Medicine at Mount Sinai, Department of Pediatrics, New York, United States; ⁴Icahn School of Medicine at Mount Sinai, Obstetrics, Gynecology and Reproductive Science, New York, United States; ⁵Icahn School of Medicine at Mount Sinai, Immunology, New York, United States

Background: Human studies have demonstrated changes in the diversity and abundance of the microbiome during pregnancy coinciding with changes in maternal immune status. Furthermore, accumulating evidence suggests that maternal health may influence the newborn's microbiome development. These balancing acts may be even more complicated in pregnant women with IBD, who exhibit a variety of immunological and gut microbiota alterations. Yet, no data exist on the effect of IBD on the microbiome during pregnancy, and its role on the infant gut microbiota composition.

Methods: The "Exploring MEchanisms Of disease traNsmission In Utero through the Microbiome" (MECONIUM) Study is a prospective study that recruits pregnant women with and without IBD and their offspring. Stool and saliva samples were collected during pregnancy, and placenta was collected at delivery. Serial stool samples were collected from the newborns up to 90 days of life. The microbial composition was surveyed using 16S rRNA sequencing. QIIME was used to compare the overall microbiota diversity, and the LefSe method was used to find differential taxa features.

Results: 125 pregnant women (43 with IBD) and 79 babies (26 born to mothers with IBD) were included; 193 maternal samples (148 stool, 45 placenta) and 245 infant stool samples were analyzed. Among all babies, 35.4% were born via C-section and 96% were full-term. Even though 74% of women with IBD were in remission throughout pregnancy, this group presented lower bacterial diversity ($p=0.001$, ANOVA), and different overall bacterial composition in stool ($p=0.001$; PERMANOVA, unweighted Unifrac), with enrichment in *Gammaproteobacteria* and a decrease in *Bacteroidetes*. Mothers with IBD presented differences in the overall composition of their placental microbiome ($p=0.001$) with a decrease in *Firmicutes*, and expansion in *Alphaproteobacteria* and *Actinobacteria*. Babies born to IBD mothers showed a different stool bacterial composition

($p=0.001$), that persisted over time, with expansion of *Gammaproteobacteria* and a reduction in *Actinobacteria* taxa, differences that were independent of mode of delivery (Figure).

Conclusions: IBD women maintain dysbiosis in their gut microbiota during pregnancy, and present with different placental microbiome. Babies born to mothers with IBD demonstrate different gut microbiome composition that persists for up to 3 months of life, and is independent of mode of delivery. These findings suggest that maternal IBD status affects the gut microbiome composition in offspring, which could contribute to future disease risk.

OP038

Impact of ileocecal resection in Crohn's disease patients on mucosal microbiota

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Background: Mucosa-associated bacteria are believed to play a more prominent role in the pathogenesis of Crohn's disease (CD) as they are in closer contact to the gut immune system. Our aim was to study temporal changes of the microbiota in CD patients undergoing ileocecal resection and to identify the predictive value of recurrence-related microbiota.

Methods: A total of 204 samples from CD patients undergoing ileocecal resection were prospectively collected: biopsies were taken from the resected intestine (histologically inflamed (N=63) and non-inflamed ileum (N=56)) and from the neoterminal ileum (N=85) during postoperative endoscopy at month 6. Postoperative endoscopic recurrence (POR) was defined by a Rutgeerts score ≥ 2 . The microbiota was evaluated by 16S rDNA sequencing using an Illumina MiSeq platform. Calculation of alpha and beta diversity and statistical analysis were performed in QIIME.

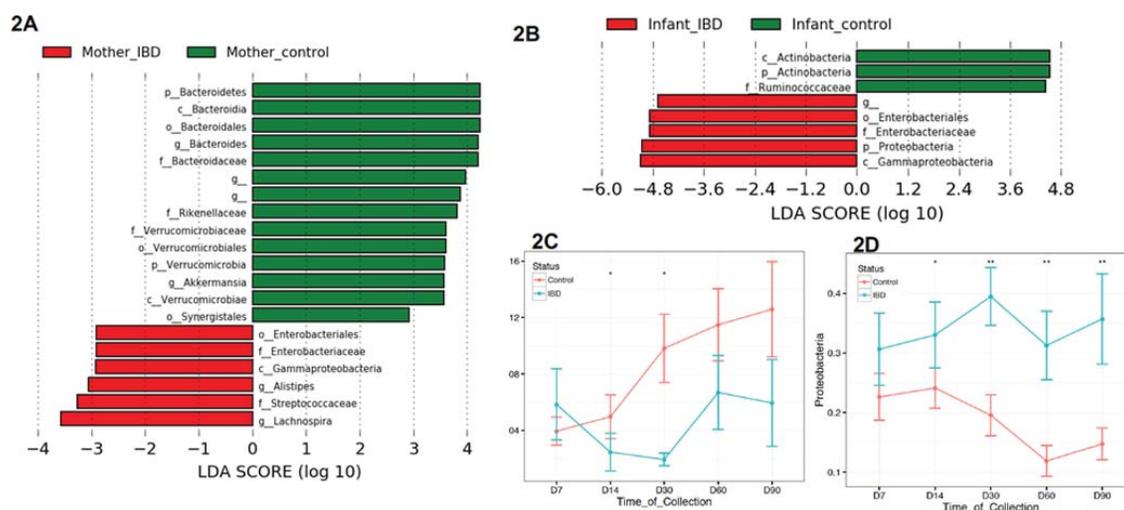


Figure 2 - 2A. Top discriminative bacteria as determined by LefSe analysis. Pregnant IBD women present an enrichment in bacteria from the *Gammaproteobacteria* class, and a decrease in bacteria from the *Bacteroidetes* phylum. **2B.** The LefSe analysis (adjusted for delivery type) showed that babies born from IBD mothers presented an enrichment in bacteria from the *Gammaproteobacteria* and a decrease in bacteria from the *Actinobacteria* class. **2C and 2D.** Plots show relative abundance of bacteria from the *Actinobacteria* (2C) and *Proteobacteria* (2D) phylum between babies born to IBD mothers and control mothers. * $p<0.05$, ** $p<0.001$ (Wilcoxon).

Results: At the time of surgery, the inflamed mucosa had a lower abundance of Actinomyces (FDR=0.05) compared to the non-inflamed mucosa.

Six months after resection, alpha diversity increased significantly compared to baseline samples in patients with recurrence (p=0.011) but not in patients without recurrence. An enrichment in Lachnospiraceae was observed in all patients at month 6 when compared to baseline samples (FDR<0.001). In recurrence patients, also Fusobacteriaceae (FDR=0.002) and Halomonadaceae (FDR=0.07) increased significantly after surgery when compared to baseline. Patients without recurrence on the other hand showed a decrease of Peptostreptococcaceae (FDR=0.08).

At month 6, patients with POR had a higher abundance of taxa belonging to Negativicutes (FDR=0.04) and Fusobacteria (FDR=0.04) compared to the remission patients.

A small subset of CD patients was on antibiotics at the time of

surgery. Alpha diversity of the inflamed and non-inflamed mucosal microbiota was significantly reduced in antibiotics users (N=6 and 7; p=0.004 and 0.009 respectively). A strong impact was seen on many taxa including a reduction of Clostridia, Bacteroidaceae and increase of Flavobacteria and Bacilli.

Conclusions: At the time of resection, differences in microbiome composition between inflamed and non-inflamed mucosa are limited. The impact of ileocecal resection on the mucosal microbiome is defined by an increase of Lachnospiraceae. Recolonization after resection in patients developing POR differs from patients without recurrence by an increase of members belonging to Fusobacteriaceae and Halomonadaceae families. Postoperatively, the increased levels of Fusobacteria and Negativicutes (Veillonellaceae), which previously have been associated with inflammation in pediatric patients with new onset of CD, may be involved in the development of early POR.

Digital oral presentations

DOP Session 1: Epidemiology, environment and nutrition

DOP001

European Crohn's and Colitis Organisation topical review on environmental factors in IBD

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Background: This ECCO topical review of the European Crohn's and Colitis Organisation (ECCO) focuses on the role of environmental factors in respect to the development of IBD as well as the influence on the course of established IBD. The objective was to reach expert consensus to provide evidence-based guidance for clinical practice.

Methods: The ECCO Environmental Factors Working Group was selected from applications following response to an ECCO call. A literature search was undertaken by members of the group. The search was conducted via PubMed. Drafting of text and statements was divided between members of the Working Groups. Statements were voted upon anonymously during a face-to-face meeting in Amsterdam at ECCO 2016. Statements with >80% agreement from all members were included within the paper in accordance with ECCO standards.

Results: The literature research and discussion of the workgroup members led to the development of a total of 22 ECCO current practice positions.

Established risk factors for CD, beside smoking are oral contraception before the development of IBD, exposure to antibiotics, previous tonsillectomy and probably appendectomy. Risk factors for UC are oral contraceptive and moving to areas with high prevalence. A positive association with IBD is found with caesarian sections, high animal fat and animal proteins, food additives and low fibre, symbiosis, urban air pollution and vitamin D deficiency. Data regarding hygiene hypothesis, exercise, sedentary, and seasonality are conflicting or lacking. Protective factors for CD are having been breastfed as well as smoking cessation, while appendectomy appears to be protective against UC onset.

Conclusions: Questions regarding the influence of environmental factors are among the most frequent ask questions from patients. This topical review will help the treating IBD team to get an updated balanced overview of the enormous number of published studies on the role of environmental factors with often conflicting results.

DOP002

Trends in small bowel resections for Crohn's disease with and without short bowel syndrome in the era of biologics

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Background: The advent of monoclonal antibody therapies has markedly improved the treatment of Crohn's disease (CD) and reduced the need for resection surgery. However, the impact of these therapies on the development of short bowel syndrome and/or intestinal failure (SBS-IF), a severe complication of CD, is yet unknown. This study evaluated temporal trends in hospitalizations and small bowel resections among CD patients with and without SBS-IF.

Methods: The Nationwide Inpatient Sample was analyzed for all CD hospitalizations in the United States between 1998 and 2011. A diagnosis of SBS-IF was determined using ICD-9-CM codes in all diagnosis positions. The incidence of hospitalizations and small bowel resections were estimated for CD patients with and without SBS-IF. Poisson regression was used to evaluate trends of these hospitalizations and surgeries across the years. The role of patient and hospital factors (ie, age, sex, race, payer, teaching hospital status, and hospital size) in small bowel resections was also evaluated. Statistical analyses accounted for the complex sampling design of the national database.

Results: Between 1998 and 2011, there were 533,708,517 overall hospitalizations with 2,049,733 for CD. The annual rate of CD hospitalizations increased from 2.7 to 5.3 per 1000 overall hospitalizations ($p_{\text{trend}} < 0.01$). Those for SBS-IF similarly increased from 16.5

to 17.4 per 1000 CD hospitalizations ($p_{\text{trend}} < 0.01$). The rate of small bowel resections had a 33.6% reduction from 98.9 to 65.7 per 1000 CD hospitalizations ($p_{\text{trend}} < 0.01$); this trend was consistent across age groups, sexes, payers, teaching and non-teaching hospitals, and hospital sizes.

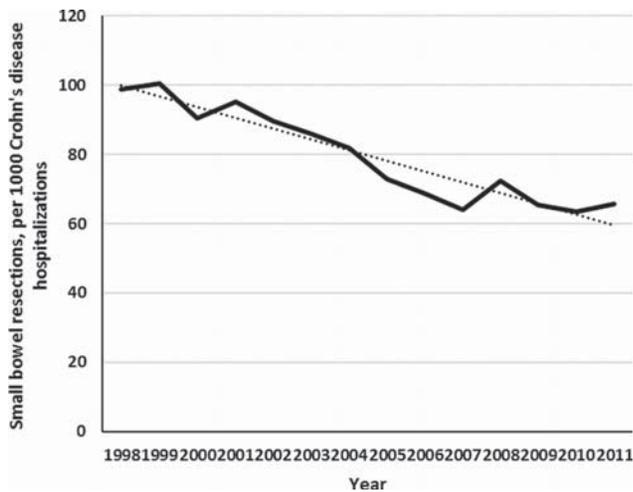


Figure 1

However, small bowel resections for SBS-IF remained unchanged from 0.56 to 0.64 per 1000 CD hospitalizations ($p_{\text{trend}} = 0.39$).

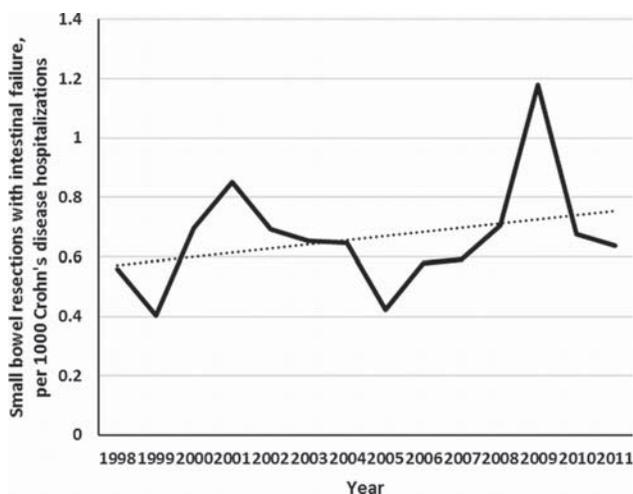


Figure 2

Conclusions: An overall reduction in the risk of small bowel resection has occurred over the past decade, but not enough to stem those for SBS-IF. These findings suggest that although monoclonal antibody therapies may modify the natural history of CD and risk of surgery, there may be subpopulations, such as those with long-term accumulated bowel damage, that do not respond as well. These data further underscore the need for early intervention in CD.

DOP003

Proximal disease extension in patients with limited ulcerative colitis: a Danish population-based inception cohort

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Background: Disease extent classified in ulcerative colitis (UC) as E1 (proctitis), E2 (left-sided) or E3 (extensive) is one of the major factors determining disease prognosis over the long-term. UC is a progressive and dynamic disease. We investigated the risk of UC extension and subsequent risk of surgery in a Danish population-based cohort from the biological era.

Methods: All incident patients diagnosed with UC in a well-defined Copenhagen area 1.1.2003–31.12.2004 were followed prospectively until 31.12.2011. Disease extension was defined in patients with limited UC at diagnosis (E1 or E2) as a progression from the initial extent defined by endoscopy or surgery. The risk of colectomy was assessed in all incident patients. Associations between progression or colectomy and multiple covariates (age, gender, initial disease extent, type of medical treatment, diagnostic delay and smoking status) were analysed by Cox regression analyses using the proportional hazard assumption.

Results: Among a total of 300 incident UC patients 220 (73%) had E1 or E2 at diagnosis. Extent at diagnosis and during follow-up is shown in Table 1. During the follow-up period, 50 (23%) patients with E1/E2 progressed to E3, and 22 (10%) patients with E1 progressed to E2. Disease extent at diagnosis was the sole significant predictor of extension to E3 with a higher risk in E2 than in E1 patients (HR = 2.2 CI95%: 1.2–4.2). No significant predictors were found for extension from E1 to E2.

During follow-up, a total of 34 (11%) patients had a colectomy. Of patients with E1/E2 as initial extent a total of 18 (8%) patients had a colectomy. Analyses of risk factors associated with colectomy are shown in Table 2. Progression from E1/E2 to E3, female gender and past history of smoking were significant risk factors for colectomy.

Table 1. Disease extent in UC at diagnosis and follow-up

At diagnosis	At follow-up			Total (diagnosis)
	E1	E2	E3	
E1	58 (26%)	22 (10%)	13 (6%)	93 (42%)
E2	–	90 (41%)	37 (17%)	127 (58%)
Total (follow-up)	58 (26%)	112 (51%)	50 (23%)	220 (100%)

Table 2. Risk factors associated with colectomy in ulcerative colitis patients

	Hazard ratio (95% CI)
Ex-smoker at diagnosis	3.54 (1.26–9.94)
Younger age at diagnosis	0.98 (0.95–1.02)
Gender (female vs male)	2.86 (1.04–7.85)
Any increase in extension	6.69 (0.39–113.92)
Extension from E1/ E2 to E3	9.80 (1.16–82.84)
Diagnostic delay <6 months	2.65 (0.92–7.58)
Disease extent at diagnosis (E2 vs E1)	0.72 (0.26–1.96)

Conclusions: After seven years follow-up, one out of three patients with limited UC experienced disease extension. Only extent at diagnosis was a clinical predictor for disease extension. The risk of colectomy was increased in ex-smokers, and patients who progressed to extensive colitis. This highlights the need of preventing progression in patients with limited UC as well as to identify new histological or molecular markers that enable physicians to identify patients at risk for disease progression.

DOP004**Ethnicity and country of birth are associated with phenotypic differences in patients with inflammatory bowel disease**

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Background: The number of patients with Inflammatory Bowel Disease (IBD) from non-Caucasian descent in Western-Europe is increasing. We aimed to explore the impact of ethnicity and country of birth on IBD the phenotype.

Methods: IBD patients treated in the eight University Medical Centres in the Netherlands and enrolled in the Dutch IBD Biobank were divided into three groups 1) Caucasian patients from West and Central-European descent (CEU) 2) patients born in the Netherlands or Western-Europe from non-Caucasian descent (non-CEU European born) and 3) non-Caucasian patients born outside Western-Europe that migrated to the Netherlands (non-CEU non-European born), and analyzed for phenotype differences (by chi-square test). Analyses were repeated in an independent Dutch IBD cohort (COIN cohort).

Results: The Dutch IBD Biobank included 2,921 CEU patients and 233 non-CEU patients. Non-CEU patients more often had upper Gastro-Intestinal disease (16% vs. 8%, $p=0.001$) and anal stenosis (10% vs. 4%, $p=0.002$). Non-CEU patients born in Europe ($n=116$) were diagnosed at a younger age than non-CEU patients born outside Europe ($n=115$) (22.7 vs. 28.9 years old, $p<0.001$). In the COIN cohort (2,170 Europeans and 98 non-Europeans), non-Europeans more often had fistulas or abscesses (29% vs. 13%, $p<0.001$), used more anti-TNF- α compounds (45% vs. 20%, $p=0.001$) and had a lower Health-related Quality of Life (mean IBDQ 161 vs. 177, $p<0.001$).

Conclusions: Non-CEU patients born in Europe are diagnosed at a younger age with IBD compared to those born outside Europe. Ethnicity and country of birth are associated with different phenotypes in IBD. In clinical IBD care, a tailored approach to the non-CEU patient is warranted.

DOP005**Proximal disease extension in limited ulcerative colitis: a systematic review and meta-analysis**

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Background: Disease extent is classified in ulcerative colitis (UC) as E1 (proctitis), E2 (left-sided colitis) or E3 (pancolitis) according to Montreal classification. Extent is one of the major factors that determine disease prognosis over the long-term. Pancolitis is associated with greater medication use, more frequent hospitalizations, and higher rates of surgery, colorectal cancer, and mortality. Disease extension over time in patients with limited disease has also been associated with poor prognosis. A systematic review and meta-analysis were conducted to assess the rate of disease extension in patients with limited UC at diagnosis.

Methods: The PubMed/MEDLINE, Embase, and Scopus databases were systematically searched from their inception through April 2015 to identify epidemiological studies reporting on extension of UC.

Results: Overall, 40 studies were eligible for inclusion but only 28 were included for meta-analysis. The cumulative risk for colonic extension was 18.8% at 5 years and 31.1% at 10 years. Extension was 27% (95%CI 24.1–30.2) from E1 to E3, 27.5% (95%CI 24.1–31.5) from E2 to E3 and 22.9% (95%CI 19.7–26.4) from E2 to E3. Thirteen studies reported information on age at diagnosis with a median of 37.3 years. Rate of extension was significantly higher in patients younger than 37.3 years (27.5%; 95% CI 24.5–30.8) than in the older patients (16.8%; 95%CI 15.6–18.1) ($p<0.0001$). Risk of extension was significantly higher in patients from North America (52%) than in patients from Europe (20.1%) ($p<0.0001$).

Conclusions: In this meta-analysis, approximately one fourth of patients with limited UC extend over time with most of extension occurring during the first 10 years. Rate of extension depends on age at diagnosis and geographic origin. Predicting disease extension from diagnosis could lead to personalized therapeutic strategies in patients at risk or not of disease extension.

DOP006**Research gaps in diet and nutrition in inflammatory bowel disease. A topical review by ECCO**

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Background: The role of diet in IBD has recently attracted substantial interest by the scientific community and dietary influences are likely to explain the rapid rise in disease epidemiology.

Methods: The D-ECCO working group along with other ECCO experts reviewed the evidence looking at the role of diet and nutritional therapy in the onset, perpetuation and management of IBD.

Results: Evidence pertinent to the role of diet in IBD is summarized collectively under three main thematic domains: i) the role of diet in IBD aetiology; ii) the role of diet as induction and maintenance therapy in IBD; and assessment of nutritional status and supportive nutritional support in IBD. Future research should:

- Address causation in the interaction between diet, microbiome and IBD
- Investigate the ability to modify the gut microbiota by dietary interventions, and its effect on disease activity
- Study the role of industrialized food, including, but not limited to nutrients, additives and processing in IBD
- Explore mechanisms of action of Exclusive Enteral Nutrition (EEN)
- Evaluating optimal food reintroduction following EEN
- Assess the optimal regimen of Partial Enteral Nutrition (PEN) for maintenance of CD and type of accompanying diet
- Evaluate the efficacy of elimination diets for induction and maintenance of remission in IBD
- Study evolution of malnutrition following diagnosis and whether this is predictive of disease outcomes
- Develop new biomarkers that can predict, diagnose, monitor intestinal failure or insufficiency in IBD
- Study mechanisms of food-related functional symptoms in IBD
- Study the efficacy and safety of dietary therapies for the management of functional symptoms in patients with inactive IBD

Conclusions: This summary of research gaps is anticipated to be agenda setting for future research in the area of diet and nutrition in IBD.

DOP007

Crohn's disease exclusion diet and partial enteral nutrition (CDED+PEN) vs exclusive enteral nutrition (EEN). Microbiome changes of a randomized clinical trial (RCT) in pediatric CD: remission is associated with similar structural + functional profiles

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Background: EEN is able to induce remission in CD patients, but can be difficult to maintain. A novel dietary intervention that combines partial enteral nutrition with an exclusion diet, that excludes foods proposed to trigger dysbiosis and inflammation (CDED+PEN) has been shown effective. We aim to compare the gut microbiome of CD participants in a prospective RCT comparing these diets, and to assess whether microbiome profiles can identify subgroups that are able to sustain remission.

Methods: 24 pediatric patients received either CDED + 50% Modulen for 6 weeks, then CDED+25% Modulen for 6 weeks (Group 1) or EEN with Modulen for 6 weeks followed by free diet plus 25% Modulen (Group 2). Remission was present in 11/14 (78.5%) in Group 1, and 8/10 (80%) in Group 2. One patient from Group 1 relapsed by week 12. DNA from fecal samples collected at three time points (baseline, w6 and w12) was sequenced for 16S and whole metagenome. Taxonomic composition was inferred from 16S (QIIME) and from metagenomes (Metaphlan) and inferred for function (Diamond/HUMANn).

Results: Both interventions induced an increase in alpha diversity by w12. EEN patients experienced a transient reduction in diversity at w6, whereas CDED+PEN did not. Taxonomic and functional profiles were similar by w12. Pooling the results for both diets, the taxonomic composition of the 18 patients who sustained remission differed significantly from the 6 patients who did not. Twenty-two 16S-derived operational taxonomic units had different relative abundance ($p \leq 0.05$), with a subgroup of eleven identified according to a false discovery threshold (q-value) of 0.15. Similar taxonomic results were inferred from the metagenome. Analysis of the functional repertoire yielded a similar pattern; 1811 genes differed between patients who sustained remission and those who did not, with 711 identified according to q-value < 0.05 . To confirm that these results (taxonomic and functional) were not being driven by the signal associated with a single diet, we separately compared the remission patients for each diet to the pooled set of patients who did not maintain remission. Results were consistent for both diets, but with slightly smaller subgroups of genes. Supervised modeling is currently underway to investigate if functional and taxonomic profiles can be exploited to predict patient outcomes.

Conclusions: Microbiome changes induced by CDED+PEN 50% are comparable with EEN in a pediatric RCT with active CD. Remission achieved with either dietary intervention is associated with similar structural and functional profiles.

DOP008

Dietary manipulation of the healthy human and colitic murine gut microbiome by CD-TREAT diet and exclusive enteral nutrition; a proof of concept study

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Background: The extensive modulation of gut microbiome in children with Crohn's disease (CD) treated with exclusive enteral nutrition (EEN) offers clues about EEN's potential mode of action; but also on the development of novel therapies through dietary manipulation of the gut microbiota. This proof of concept study compared the effect of a novel "ordinary" food-based diet (CD-TREAT diet) and EEN on healthy human and colitic murine gut microbiota.

Methods: A) Healthy adults followed two experimental diets for 7 days with a 15 day wash out period in between; EEN and CD-TREAT, an "ordinary" food diet which has similar nutrient and food ingredient composition to EEN (e.g., fibre, gluten, lactose content and fatty acid composition). Participants were randomly allocated to start with EEN or CD-TREAT first. Fresh faecal and urine samples were collected before and after each dietary intervention and 16s rRNA sequencing, untargeted faecal and urine metabolomics (using LC-MS) were performed;

B) 10-month-old HLA-B27 and HLA-B7 transgenic rats received EEN, CD-TREAT diet or regular rat chow for 4 weeks. Faeces were collected at baseline, 1, 2, 3 and 4 weeks post treatment initiation. Gut contents, ileal and colonic tissue were harvested at sacrifice. Disease activity was quantified by blinded histological scores and gut microbiota metabolic activity was measured by faecal short chain fatty acids (SCFA) quantification.

Results: A) 100 samples were collected from 25 healthy subjects. During EEN and CD-TREAT gut bacterial community structure (using OTUs) significantly changed after both EEN and CD-TREAT ($R^2=0.15$, $R^2=0.05$, $p<0.004$) and shifted towards the same direction. EEN's and CD-TREAT's impact on 3% OTU community structures was strongly correlated (Adj $R^2=0.38$, $p<2.2e-16$). Similarly, untargeted faecal metabolomics revealed a strong correlation between the changes during EEN and CD-TREAT (Pearson's $R=0.31$, $p<10^{-14}$);

B) 100 faecal samples were collected from 12 HLA-B27 and 8 HLA-B7 adult transgenic rats. Both dietary interventions increased the body weight of the HLA-B27 rats (Median %weight change, EEN:+9.2 vs CD-TREAT:+15.7 vs Control:-2.1) and decreased the weight of caecum and colon contents. Faecal concentration of total SCFA, acetic, propionate decreased while iso-butyric and isocaproic increased during both dietary interventions [Δ Median $\mu\text{mol/g}$, EEN: -324, -271, -44.8, +4.7, +2.2 vs CD-TREAT: -354, -292, -56.2, +3, +1.5]. Histopathology scores revealed that both dietary interventions benefited moderately ileal but not colonic inflammation.

Conclusions: We have developed an "EN composition alike" food based diet which induces similar effects on gut microbiome with EEN. This proof of concept study supports a subsequent pilot trial in people with active CD.

DOP009

Choice of corticosteroids or exclusive enteral nutrition as the first induction of remission therapy does not affect disease behavior within two years of diagnosis

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Background: Exclusive enteral nutrition (EEN) has been shown to be equivalent to corticosteroids (CS) for induction of remission in mild to moderate Crohn's disease (CD) but superior for normal CRP remission and mucosal healing. Our goal was to evaluate if EEN or early IMM at diagnosis at diagnosis would reduce risk for early complicated disease in mild to moderate CD.

Methods: The GROWTH CD study (Growth, Relapses and Outcomes With Therapy) is designed to identify associations between treatments and early adverse outcomes by 24 months. Newly diagnosed children were evaluated at baseline, 8, 12, 78 weeks, complications recorded at week 104. Remission was defined as PCDAI ≤ 10 at both week 8 and week 12. Treatment was recorded at each visit. We evaluated intention to treat outcomes among patients receiving CS or EEN, and outcomes for patients in remission with these treatments. Patients failing to obtain remission, with complicated behavior at diagnosis, or requiring biologics by 12 weeks were excluded from the remission analysis.

Results: Among 152 mild to moderate children (mean age 12.9 ± 3.1 years) treated with either EEN or CS as a first line treatment, a complication was already present in 19.7%, CS 18/91 (19.8%), EEN 12/61 (19.7%). Baseline median PCDAI was slightly higher among CS (CS 30, EEN 25), $p=0.002$ while remission rates were higher in EEN treated patients, 51 (56.7%) CS and 43 (70%) EEN, $p=0.08$. Relapse rates for these obtaining remission did not differ (20/49, 40.8% CS vs. 14/42, 33.3% EEN) $p=0.46$.

Complications by two yrs developed in 34 (22.4%) and were higher with CS (CS 25/91 29.7% EEN 9/61 15.5%, $p=0.051$). Early IMM did not affect complications which developed in 28/114 (24.6%) with IMM vs. 6/28 (21.4%) without IMM, $p=0.73$.

Correcting for baseline complications and remission, we analyzed 74 uncomplicated patients in CS or EEN induced remission. New complications developed in 6/40 (15%) CS vs. 6/34 (17.6%) EEN, $p=0.91$.

Conclusions: EEN and CS induce similar remission rates in mild to moderate CD. The choice of CS or EEN as a first line therapy does not seem to affect complicated disease behavior as if clinical remission is obtained. Immunomodulators do not seem to reduce the risk of complications by two years.

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DOP Session 2: New tips for clinical practice

DOP010

ECCO topical review on transitional care in inflammatory bowel disease

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Background: This topical review of the European Crohn’s and Colitis Organisation (ECCO) focuses on the transition of adolescents with IBD from child-centered to adult-oriented care. The objective was to achieve evidence-supported, expert consensus that provides guidance for health professionals taking or wanting to take part in transition.

Methods: Initially by means of an online survey we determined which ideas on transition were most important to health professionals involved in the care of adolescents with IBD. Thereafter an expert panel of 9 paediatric and 5 adult gastroenterologists was formed to identify critical elements for the transition programme and to prepare core messages as “current practice points”.

Results: Because there is limited literature about transition, the review was mainly based on expert opinion and consensus, rather than on specific evidence. We generated 21 practice points for an online voting round. Practice points that reached >80% agreement were considered as final. Those that did not reach 80% agreement were refined during a face-to-face consensus meeting and put to a vote again. Ten practice points were selected for this abstract.

1. IBD patients taking part in a transition programme are likely to have better compliance and less adverse outcomes after transfer to adult care compared to those that do not take part.
2. Transition in IBD is a continuous process involving the patient, parents, paediatric and adult healthcare providers.
3. Patients, parents, paediatric and adult healthcare providers may have different attitudes towards transition. It is important to identify and harmonise these attitudes in advance.
4. The skills for successful transition comprise disease relevant knowledge, self-efficacy and decision making.
5. The education of patients should be age-appropriate and addressed from at least 1 year before transfer.
6. Validated assessment of a patient’s progress through transition, and the impact of targeted interventions, should occur throughout transition and be reassessed as required.
7. Education of parents to devolve responsibility for disease management to their child is desired.
8. A joint paediatric-adult clinic as part of a transition programme is considered the ideal model.
9. Transfer to adult services requires a handover letter written by the pediatric team.
10. Patients, parents and healthcare providers should all be involved in the evaluation of the transition programme.

Conclusions: We present a consensus-based framework of transitional care in IBD that provides guidance for clinical practice.

DOP011

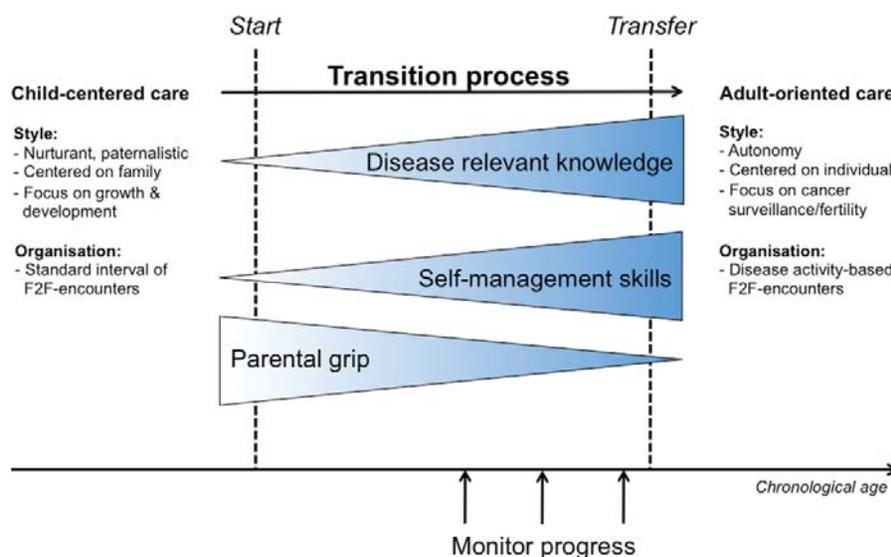
Risk of opportunistic infection in healthcare personnel with inflammatory bowel disease: a case-control study of the GETAID

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Background: The increased use of immunomodulators and biological agents for the treatment of patients with inflammatory bowel disease (IBD) is associated with a key safety concern considering potential opportunistic infection. Healthcare personnel were thought to be at substantial risk for acquiring such infection due to daily and close interactions with infected patients and asymptomatic carriers of pathogens.

Methods: We performed a retrospective observational study, collecting data from the GETAID, between January 2015 and June 2016, on



Abstract DOP010 – Figure 1. Conceptual model of transition from child-centred to adult-oriented care.

all 482 consecutive patients with IBD (68.5% with Crohn's disease, 28.4% with ulcerative colitis and 3.1% with IBD undetermined) who work as healthcare personnel (27.2% of physicians, 33.0% of nurses; 13.1% of nurses' aides and 26.7% of other healthcare personnel), in 17 tertiary centers in France and Belgium. We selected a control group of patients with IBD from the monocentric MICISTA database. Controls were matched on age (± 2.5 years), sex, IBD type and date of IBD diagnosis (± 2.5 years). Opportunistic infection was defined as (1) *Clostridium difficile* infection (2) community-acquired pneumonia (3) Mycobacterium tuberculosis infection (4) any community-acquired infection that required hospitalization. Opportunistic infection-free survival was studied with Kaplan-Meier method, log-rank test and Cox regression model.

Results: 482 patients (126 male; median age: 24.0 [IQR 19.9–32.1] years) were included in the present study. The median follow-up period was 9.3 [4.6–16.2] years. A total of 60 opportunistic infection was recorded including 10 *Clostridium difficile* infection, 13 EBV or CMV-related serious viral infection, 6 tuberculosis infection including 3 tuberculosis and 3 tuberculous primo-infection, 6 community-acquired pneumonia and 5 gastrointestinal infection. The probabilities of opportunistic infection-free survival were 0.7%, 6.4%, 13.1% and 17.8% at 1, 5, 10 and 15 years. The multivariate analysis demonstrated that patients with Crohn's disease (OR=0.50, CI95% [0.30–0.83], $p=0.007$) were less likely to experience opportunistic infection. No difference was found between healthcare personnel and patients from the control group regarding the occurrence of opportunistic infection. Only one case of Mycobacterium tuberculosis infection was observed in the control group.

Conclusions: Although there is a higher exposure to potential pathogens in healthcare personnel, this is not associated with an higher risk of opportunistic infection as compared with controls. Prospective studies are needed to confirm that the level of occupational exposure to potential pathogens should not be taken into account when discussing the introduction of immunomodulator or biological agents.

DOP012

Impact on clinical practice of Epstein-Barr virus infection in patients with inflammatory bowel disease

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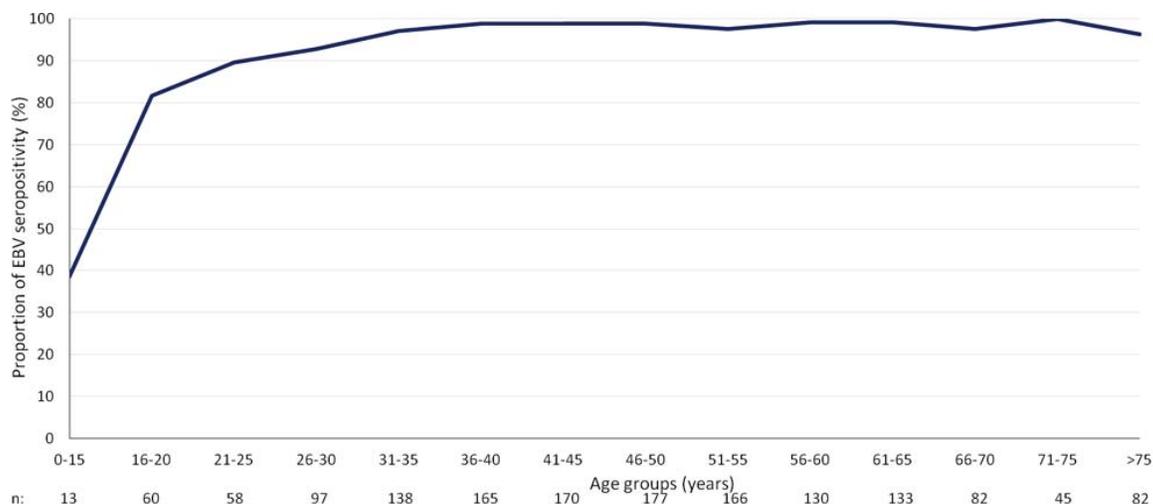
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Background: Under immunosuppression, Epstein-Barr virus (EBV) infection has been associated with severe complications. The real-life impact of EBV infection in patients with IBD is not well known. The present study was designed to know the prevalence of past EBV infection in patients with IBD; to analyze the percentage of seroconversion according to age; and, to describe the complications associated with acute and latent EBV infection.

Methods: All IBD patients attended between 2007 and 2016 in a tertiary hospital underwent a baseline determination (at diagnosis or at the first visit in the IBD unit) of IgG antibodies against the viral capsid antigen of EBV (VCA-IgG). In seronegative patients, this determination was repeated, at least at the last visit. The presentation of acute infection (mononucleosis, hemophagocytic syndrome) and complications associated with latent infection (lymphomas) by EBV are described.

Results: 1516 patients were included in the study (44% ulcerative colitis, 52% Crohn's disease, and 4% unclassified colitis; 50% female, median age at IBD diagnosis 37 ± 16 years, 847 previous or current treatment with thiopurines). 1463 patients (96.5%) were VCA-IgG positive. Figure 1 shows seroprevalence by age intervals.

Sex (97.5% in women vs. 95.5% in men, $p=0.036$) and age (98.5% in >35 years vs 90.2% in ≤ 35 years, $p<0.0001$) were associated with IgG-VCA seropositivity. In 51 of 53 seronegative patients the determination was repeated after an average of 3.5 ± 2.4 years; 11 of 35 (31%) patients ≤ 35 years in the first determination presented seroconversion (2 mononucleosis, 6 pharyngitis and 3 asymptomatic); 9 of them were receiving thiopurines and 8 antiTNF. 5 of 16 (31%) patients >35 years of age also presented seroconversion (1 pharyngitis, 1 hemophagocytic syndrome plus diffuse large B-cell lymphoma with fatal evolution, and 3 asymptomatic); 4 of 5 (one of them the case of lymphoma) were receiving thiopurines in that period. During the prospective follow-up, 8 patients with lymphoma (7 with past infection and 1 with acute EBV infection) were diagnosed in a total of 1.22 cases/1000 patient-years; 6 of them had been treated with thiopurines, and another one received immunosuppressive treatment for liver transplantation by primary sclerosing cholangitis.



Abstract DOP012 – Figure 1. Seroprevalence of EBV infection by age intervals.

Conclusions: The prevalence of past EBV infection is high. The risk of complications associated with primoinfection by EBV persists in patients older than 35 years. The risk of lymphomas in a population of IBD with a high rate of EBV infection and widespread use of thiopurines is high.

DOP013

Definition of therapeutic response criteria using MRI in Crohn's disease patients treated with anti-TNF therapy: a multicenter prospective study (the IRMA study)

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Background: As Crohn's disease (CD) presents with transmural inflammation, mucosal healing remains an imperfect target. Magnetic resonance enterocolonography (MREC) has been showed as a reliable tool to assess CD activity. However, the definition of MRI therapeutic response is yet to be established in CD.

We aimed to identify the variations of MRI parameters between baseline and week 12 (W12), which are predictive of corticosteroids-free deep remission (CFREM) at week 52 (W52) in patients treated with anti-TNF, to define MRI criteria of therapeutic response.

Methods: CD adult patients needing anti-TNF therapy with CDAI

>150 and at least one diseased-bowel segment on MRI were consecutively included in this multicenter prospective study. All the patients underwent MREC including diffusion-weighted sequences with no bowel cleansing and no rectal enema, before starting anti-TNF agents and at W12. CFREM was defined at W52 as CDAI <150 and CRP <5 g/L and faecal calprotectin <250 µg/g with no switch of anti-TNF agents and no bowel resection.

Results: Overall 55 CD patients with 212 digestive segments were analyzed (Table 1).

Among diseased-segments at baseline, we observed significant improvement at W12 for ulcerations (54.2% vs 36.2%, p=0.037), oedema (95.8% vs 63.8%, p=0.001), comb sign (56.2% vs 36.2%, p=0.013), enlarged mesenteric lymph nodes (55.3% vs 31.1%, p=0.001), bowel thickness (8.3 vs 6.3mm, p<0.001), affected length (13.9 vs 11.9cm, p=0.015), apparent diffusion coefficient (ADC) (1.4 vs 1.57, p=0.001), Clermont score (26.8 vs 19.9, p<0.001) and MaRIA index (26.7 vs 19.8, p=0.001).

We assessed the variation of MRI parameters between baseline and W12 in patients achieving CFREM at W52 compared to those who did not among 55 CD patients. Using ROC curves, we identified that 25%-decrease of Clermont score (AUC=0.76, Se=85.5%, Spe=66%, NPV=75%, PPV=75%) or MaRIA index (AUC=0.68, Se=76%, Spe=60%, NPV=75%, PPV=75%) were highly predictive of CFREM at W52. In addition, five factors evaluated at W12 were predictors of CFREM at W52: disappearances of ulcerations (OR=6.4, p=0.05), of oedema (OR=3.3, p=0.05), of enlarged mesenteric lymph nodes (OR=5.9, 0.041), or of sclerolipomatosis (OR=12, p=0.03), and 10%-increase of ADC (OR=4.3, p=0.02). The likelihood of achieving CFREM at W52 was 17% when 0 or 1 factor was observed compared to 70% with at least 2 factors (p=0.001).

Conclusions: MREC is a reliable tool to monitor therapeutic response in CD. Our MRI response criteria are highly predictive of CFREM at W52, supporting their use in daily practice and clinical trials.

DOP014

Transmural healing is better than mucosal healing in Crohn's disease

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Background: Mucosal healing (MH) is currently accepted as the optimal target in Crohn's disease (CD), and is associated with improved long-term outcomes including reduced hospitalizations and surgery. However, even in patients with sustained MH, residual transmural inflammation may persist. The benefits of obtaining complete transmural healing (TH) have not been previously assessed. The aim of the study was to evaluate the long-term outcomes of TH in CD.

Methods: This was a multicenter observational study including patients from a prospective database of Inflammatory bowel disease (Grupo de Estudos de Doença Inflammatory Intestinal). Patients with CD with a MRI-enterography (MRE) and colonoscopy performed in a 6-month interval were included. MRE was classified as active/inactive based on abnormal bowel wall thickening, contrast enhancement, fat creeping, Comb sign, and complications (stricture,

Table 1: Characteristics of the 55 Crohn's disease patients .

Age at diagnosis, (years), mean ± SD	25.6 ± 12.0
Disease duration at inclusion, (years), mean ± SD	7.7 ± 9.0
Male gender, n (%)	28 (51.0%)
Active smokers, n (%)	22 (40.0%)
Previous intestinal resection, n (%)	10 (18.2%)
Montreal Classification	
Disease location	
L1, n (%)	25 (45.5%)
L2, n (%)	6 (10.9%)
L3, n (%)	24 (43.6%)
L4, n (%)	0 (0.0%)
Behaviour	
B1, n (%)	17 (30.9%)
B2, n (%)	21 (38.2%)
B3, n (%)	17 (30.9%)
Concomitant therapies	
Corticosteroids, n (%)	10 (18.1%)
Immunosuppressive therapy, n (%)	31 (56.4%)
Anti-TNF agent	
Infliximab, n (%)	24 (43.6%)
Adalimumab, n (%)	31 (56.4%)
CDAI, mean ± SD	254 ± 220
CRP, mean ± SD	30.0 ± 44.2
Faecal Calprotectin (µg/g), median [IQR]	1023 ± 707
Corticosteroid-free deep remission at week 52	43.7%

abscess or fistula). In non-operated patients, colonoscopy was classified as active/inactive based on the presence of ulceration. In operated patients, colonoscopy was classified as active/inactive if the Rutgeerts score was ≥ 2 . We defined 3 groups: TH (inactive MRE with inactive colonoscopy); MH (active MRE with inactive colonoscopy), No healing (NH) (active colonoscopy). We evaluated several outcomes at 1 year including the need for surgery, hospital admission, therapy escalation (immunomodulator, biologic or escalation of biologic), and a compound outcome including any of the former. Patients with disease restricted to the colon were excluded.

Results: A total of 214 patients [TH (n=33), MH (n=52), NH (n=129)], 91 (41.7%) previously operated, were included in the study. MRE and colonoscopy showed active inflammation in 162 (74.3%) and 132 patients (60.6%), respectively. At 12 months, patients with TH showed lower rates of hospital admission than patients with MH and NH (6.1% vs 17.3%, $p=0.188$ (ns) and 24.0%, $p=0.014$), therapy escalation (15.2% vs 36.5%, $p=0.027$ and 54.3%, $p<0.001$), surgery (0% vs 11.5%, $p=0.047$ and 11.6%, $p=0.027$), and any outcome (18.2% vs 44.2%, $p=0.011$ and 63.6%, $p<0.001$). Patients with TH showed longer times to surgery ($p=0.045$ and $p=0.044$ for MH and NH), therapy escalation ($p=0.046$ and $p<0.001$ for MH and NH), and to reach any endpoint ($p=0.019$ and $p<0.001$ for MH and NH). Increasing age (OR 0.971, 95% CI [0.951–0.992], $p=0.006$), MH (OR 0.384, 95% CI [0.208–0.707], $p=0.002$), and TH (OR 0.336, 95% CI [0.171–0.660], $p=0.002$) were independently associated with a lower likelihood of reaching the compound outcome.

Conclusions: TH is associated with improved long-term outcomes in patients with CD, including lower risk of hospital admission, therapy escalation and surgery. Our data suggests that TH is a better suitable target than MH in CD.

DOP015

International differences in gastroenterologists' perspective on stopping therapy for patients with Crohn's disease

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Background: When patients with Crohn's disease (CD) are in remission on combination therapy including an anti-tumor necrosis factor (TNF) agent and an immunomodulator (IM), a frequent question is if it is appropriate to stop one of these medications. The aim of this study was to understand gastroenterologists' (GI) perspectives on stopping therapy for patients with CD who are in remission, and to identify differences between European and United States (US) providers.

Methods: Two focus groups, one consisting of European GIs and another with US GIs, were conducted to explore domains to be used for an internet distributed survey. Based on these responses, a questionnaire was developed including quantitative responses and a media component where respondents react to audio recorded during the provider focus groups. US providers were identified from the Crohn's and Colitis Foundation of America (CCFA) professional membership and an established cohort of GIs experienced in internet surveys. The European GIs were identified from a combination of the European

Crohn's and Colitis Organisation (ECCO) and French, German and Belgian GI providers.

Results: 309 GIs from the US (182) and Europe (127) completed the questionnaire. Providers from over 30 US states and 16 countries were included. GIs had range of ages from 25–65+. A majority of GIs see 20 or more patients per month and have 10 or more years experience. Almost 30% of US GIs report that more than half of their patients are currently on combination therapy as compared to 10% of European GIs ($p<0.05$). European GIs were significantly more likely to recommend stopping combination therapy for an average CD patient in remission (44% Europe, 18% US were very likely, $p<0.05$). 41% of US GIs and 36% of European GIs responded that they would consider stopping combination therapy if there was evidence-based research supporting this strategy. However, a majority of GIs (73% Europe, 52% US) believe that patients at high risk for disease complications should continue on combination therapy. The most compelling reasons to stop therapy were to reduce overall side effects or long term risk of cancers related to the medications. GIs were more likely to stop the IM (75% Europe, 61% US, $p<0.05$) as opposed to biologic therapy (23% Europe, 29% US). Cancer was the top reason for stopping IMs while cost was the key factor for biologics.

Conclusions: US GIs are more likely than European GIs to have a majority of their CD patients on combination therapy, and European GIs are more likely to de-escalate therapy for patients in remission. If de-escalating, the majority of GIs would stop the IM driven by cancer risk; the main reason to stop a biologic was cost.

DOP016

Long-term safety of in utero exposure to anti-tumor necrosis factor for the treatment of inflammatory bowel diseases: results from the multicenter European TEDDY study

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Background: Long-term safety of anti-tumor necrosis factor therapy (anti-TNF) during pregnancy has hardly been studied.

Aims: To estimate the relative risk of severe infections in offspring of mothers with inflammatory bowel disease (IBD) exposed in utero to anti-TNF

Methods: For this retrospective multicenter cohort study we identified: offspring of mothers with IBD under anti-TNF (with or without thiopurines) at any time during pregnancy or 3 months before conception (Exposed group, EG). The non-exposed group (NEG) consisted of offspring of mothers with IBD treated neither with anti-TNF nor with thiopurines during this time period. The cumulative incidence of severe infections after birth was estimated using Kaplan-Meier curves, which were compared by the log-rank test. Cox-regression analysis was performed to identify independent predictive factors for severe infections. AEG-REDCap provided the study e-CRF

Results: In total, 841 children were included, 388 (46%) of them exposed in utero to anti-TNF drugs; 38% of the mothers maintained anti-TNF throughout the whole pregnancy. From children exposed to anti-TNF, 99 (25%) were also exposed to thiopurines. Median (IQR) follow-up after delivery was 54 (9–202) months in the EG and 72 (13–216) months in the NEG ($p < 0.01$). The proportions of CD diagnosis and previous surgery were higher in the EG than in the NEG (75 vs. 42%, $p < 0.001$, and 35 vs. 18%, $p < 0.01$, respectively). Other relevant characteristics were similar between both groups. The proportion of pregnancy complications was similar among both groups. Delivery complications were more frequent in the EG (57 vs. 43%, $p < 0.01$), with a higher rate of caesarean sections in the EG (44 vs. 32%, $p < 0.01$). The proportion of newborn complications was higher in the EG (25 vs. 16%, $p < 0.01$), with a higher rate of low-

birth weight in this group (11 vs. 7%, $p = 0.05$) and more frequent need of intensive care unit admission in the EG (7 vs. 3%, $p < 0.01$). The proportion of breastfed babies was higher in the NEG in comparison with the EG (79 vs. 57%, $p < 0.001$). A total of 90 children (11%) developed severe infections during follow-up. The incidence rate of severe infections was similar between NEG and EG (1.6 vs. 2.8% person-years, $p = 0.2$). In multivariate analysis, preterm delivery was the only variable associated with a higher risk of severe infection (HR=2.5; 95% CI: 1.5–4.3). anti-TNF exposure during pregnancy was not associated with a higher risk of severe infections (HR: 1.2; 95% CI: 0.8–1.8)

Conclusions: The exposition to anti-TNF α in utero seems not to be associated with a higher risk of infections in children, neither in the short, nor in the long-term

DOP017

Patterns of anti-TNF use and associated treatment outcomes in inflammatory bowel disease patients: results from an analysis of Dutch health insurance claims data

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Background: Patterns of anti-TNF use, associated treatment outcomes and drug costs have never been investigated in a large, real-life population of IBD patients.

Methods: Health insurance claims data from 22,082 Dutch IBD patients were provided by Achmea Healthcare. Patients starting with anti-TNF treatment from January 2008 till December 2014 were studied. The primary analysis was time to anti-TNF discontinuation. Furthermore, time to anti-TNF treatment intensification, corticosteroid free survival and time to hospitalization were analyzed, as well as treatment regimens.

Results: The proportion of infliximab (n=855) and adalimumab starters (n=1,199) who received intensified treatment increased over time (infliximab at 3 vs. 24 months: 22.2% vs. 33.6%, $p = 0.01$; adalimumab at 3 vs. 24 months: 10.5% vs. 19.3%, $p < 0.001$). Median time to anti-TNF discontinuation was 600 days (IQR 156–1693). Cessation of anti-TNF treatment was less common in Crohn's disease patients (HR 0.79, $p = 0.001$) and in patients receiving intensified treatment regimens (HR 0.62, $p = 0.001$). Immunomodulator use was not related to longer drug survival (HR 0.99, $p = 0.617$), but was significantly associated with longer time to corticosteroid use (HR 0.80, $p = 0.048$). Hospitalization was significantly more common in Crohn's disease patients (HR 1.49, $p = 0.011$). Corticosteroid

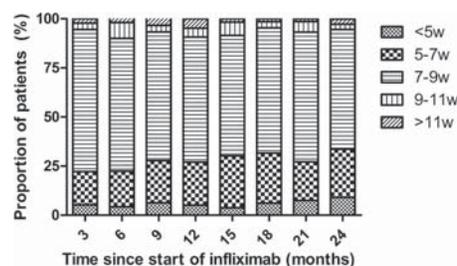


Figure 1. The distribution of infliximab intervals over time.

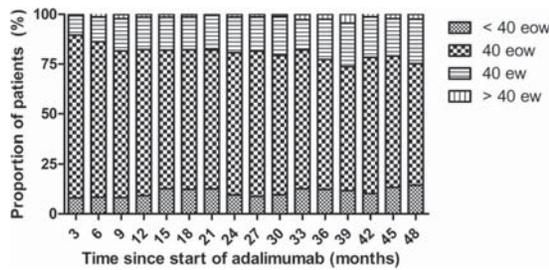


Figure 2. The distribution of adalimumab intervals over time.

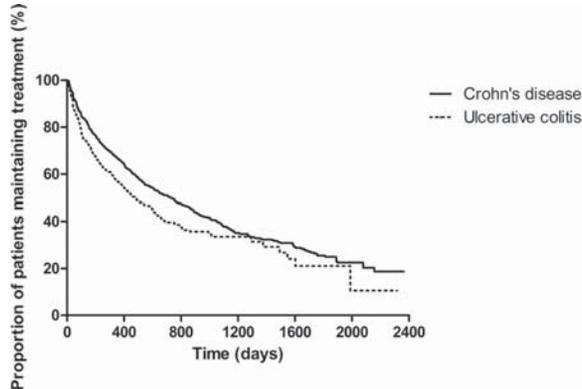


Figure 3. Kaplan-Meier curve of time to anti-TNF treatment discontinuation in Crohn's disease vs. ulcerative colitis patients.

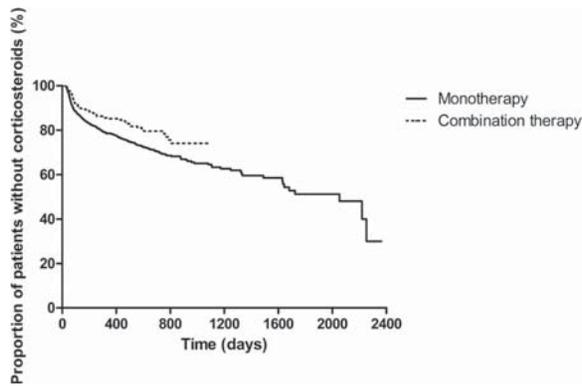


Figure 4. Kaplan-Meier curve of time to corticosteroid use in patients on monotherapy vs. combination therapy.

use was significantly lower in Crohn's disease patients (HR 0.57, $p < 0.001$) and in patients using infliximab (HR 0.55, $p < 0.001$).

Conclusions: Discontinuation of anti-TNF therapy occurred earlier than previously reported and was associated with ulcerative colitis and non-intensified anti-TNF treatment regimens. Immunomodulator use at the start of anti-TNF treatment was associated with longer time to corticosteroid use, but not with longer drug survival.

DOP018

Effect of adalimumab on extraintestinal manifestations among patients with ulcerative colitis in a clinical practice setting: results from INSPIRADA

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Background: Extraintestinal manifestations (EIMs) are common in patients with ulcerative colitis (UC) and can have a significant impact on patient morbidity and quality of life [1]. We assessed the effect of adalimumab (ADA) therapy on the resolution of EIMs among patients with moderate to severe UC in clinical practice.

Methods: INSPIRADA was a single-arm, multi-country, open-label study evaluating the effect of ADA on clinical outcomes, costs of care, treatment satisfaction and work productivity in patients with UC treated according to usual clinical practice. Adults with active UC, Physician's Global Assessment (PGA) ≥ 2 , and Short Inflammatory Bowel Disease Questionnaire ≤ 45 at baseline (BL) who failed conventional treatment and who experienced rectal bleeding ≤ 7 days of BL were enrolled. Patients received 160/80 mg ADA at Week 0/2 followed by 40 mg of ADA every other week at Week 4 through Week 26. Patients who did not respond to ADA by Week 8 were to discontinue ADA. Patients who lost response at or after Week 8 could escalate to 40 mg ADA weekly. The presence of EIMs (arthritis, pyoderma gangrenosum, erythema nodosum, and uveitis) was collected in the SCCAI at BL and Weeks 2, 8, and 26. McNemar's test was used to compare the presence of any EIM at Weeks 2, 8, and 26 with BL. In a subset of patients with EIMs at BL, EIM resolution was assessed at Week 2, 8, and 26, defined as no reported EIM at the respective visit; durable EIM resolution at Weeks 2 and 8 was defined as no EIM at the respective visit and subsequent visit(s). Missing data were imputed using last observation carried forward.

Results: Data from 461 patients were analysed. At BL, 88 patients (19.1%) had an EIM. The most commonly reported EIM was arthritis (84 of 88 patients). Pyoderma gangrenosum, erythema nodosum, and uveitis each were reported in $< 1\%$ of patients at BL and at Weeks 2, 8, and 26. The overall percentage of patients with any EIM decreased significantly ($p < 0.001$) from BL over time: 13.2%, 11.7%, and 10.8% had any EIMs at Weeks 2, 8, and 26, respectively. Similar decreasing percentages were seen for patients with arthritis: 13.0%, 11.7%, and 10.8% at Weeks 2, 8, and 26, respectively. Among those with any EIM at BL, resolution of EIMs increased over time: 39.8%, 52.3%, and 63.6% at Weeks 2, 8, and 26, respectively; durable resolution was 23.9% and 44.3% at Weeks 2 and 8, respectively. Among those with arthritis at BL, resolution rates were 36.9%, 50.0%, and 61.9% at Weeks 2, 8, and 26, respectively; durable resolution was 20.2%, 41.7%, and 61.9%, respectively.

Conclusions: ADA therapy reduced EIMs among patients with moderate to severe UC in usual clinical practice, with EIM resolution in 60% by Week 26.

References:

[1] Vavricka SR et al, (2015), *Inflamm Bowel Dis*, 21(8):1982-92

DOP Session 3: Vedolizumab and ustekinumab therapies

DOP019

Effect of vedolizumab treatment on extraintestinal manifestations in patients with Crohn's disease: a GEMINI 2 post hoc analysis

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Background: Extraintestinal manifestations (EIMs) pose an additional burden to patients with IBD (reported frequency: 6–47%) [1]. Vedolizumab (VDZ) is approved for the treatment of moderately to severely active Crohn’s disease (CD) and ulcerative colitis. This post

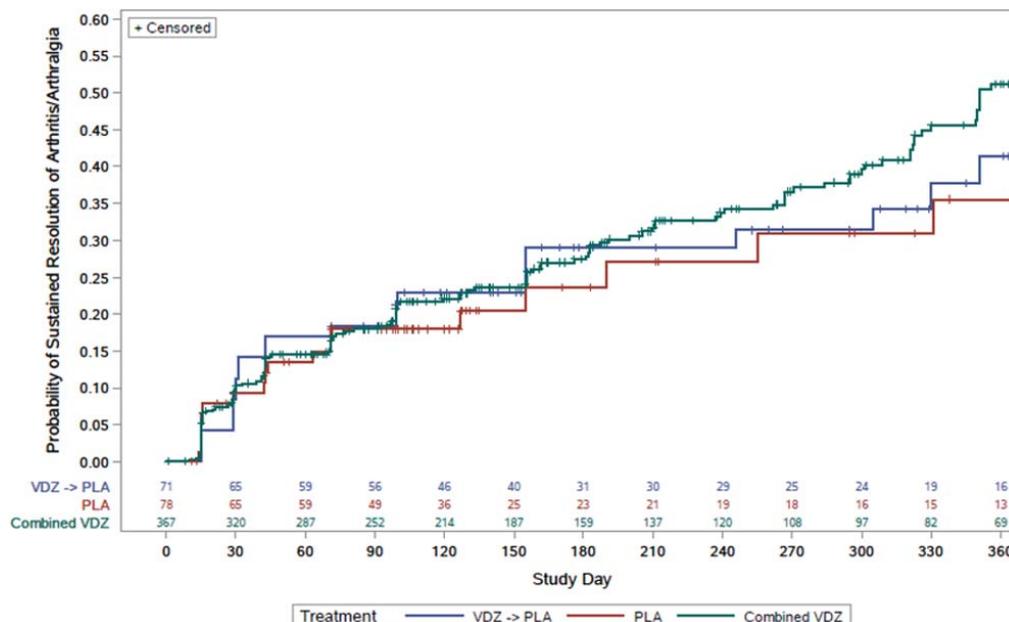
Abstract DOP019 – Table 1. EIMs in patients with CD enrolled in GEMINI 2

GEMINI 2 population (N=1115)			
	VDZ Q4W or Q8W (n=814)	VDZ/PLA (n=153)	PLA (n=148)
Arthritis/Arthralgia			
Existing at baseline, n (%)	367 (45)	71 (46)	78 (53)
Sustained resolution of existing cases, n (%)*	128 (35)	23 (32)	18 (23)
HR vs PLA (95% CI)	1.32 (0.81–2.16)	1.13 (0.61–2.09)	N/A
Worsening of existing cases, n (%)	57 (16)	12 (17)	12 (15)
New occurrence, n (%)	125 (28)	21 (26)	27 (39)
HR [†] vs PLA (95% CI)	0.79 (0.56–1.11)	0.66 (0.42–1.06)	N/A
Aphthous stomatitis			
Baseline, n (%)	39 (5)	6 (4)	6 (4)
New occurrence, n (%)	41 (5)	4 (3)	11 (8)
Erythema nodosum			
Baseline, n (%)	21 (3)	6 (4)	4 (3)
New occurrence, n (%)	11 (1)	2 (1)	6 (4)
Iritis or uveitis			
Baseline, n (%)	14 (2)	0 (0)	3 (2)
New occurrence, n (%)	11 (1)	4 (3)	2 (1)
Pyoderma gangrenosum			
Baseline, n (%)	4 (<1)	1 (<1)	0 (0)
New occurrence, n (%)	1 (<1)	1 (<1)	0 (0)

*Resolution of ar/ar that was sustained to the end of the 12-month study

[†]Time to new or worsening ar/ar

Ar/ar, arthritis/arthralgia; CD, Crohn’s disease; EIM, extraintestinal manifestation; N/A, not applicable; PLA, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; VDZ, vedolizumab



Abstract DOP019 – Figure 1. Time to sustained resolution of arthritis/arthralgia (n=516). PLA, placebo; VDZ, vedolizumab.

hoc exploratory analysis investigated the effect of VDZ treatment on existing and new EIMs in patients with CD enrolled in GEMINI 2 (NCT00783692).

Methods: Data were collected on 5 categories of EIM and assessed using the following definitions: sustained resolution (absence of an EIM symptom, sustained to study end), worsening of existing EIM and occurrence of new EIM. For the category of arthritis/arthralgia (ar/ar), Kaplan–Meier (KM) estimates were used to describe “time to sustained resolution”. A multivariate Cox regression adjusting for potential baseline confounding factors was conducted. In patients receiving corticosteroids (CS), the influence of steroid tapering on the occurrence of new or worsening ar/ar was explored, with prednisone equivalent dose (≤ 30 mg) as a time-dependent covariate.

Results: Patients (pts) received VDZ (n=814), VDZ/placebo (VDZ/PLA; VDZ to Week 6, PLA Week 6–52; n=153) or PLA only (n=148). Baseline EIM incidence was similar across treatment groups (Table). Further analyses focussed on ar/ar as the most common EIM. Predicted annual rates of sustained resolution of ar/ar were 51% (VDZ), 41% (VDZ/PLA) and 36% (PLA; Figure). VDZ pts were 32% more likely to achieve sustained resolution of ar/ar versus PLA (not significant [NS], Table) and 21% less likely to have a worsening/new occurrence (NS, Table). In pts receiving CS (n=530), adjustment for CS withdrawal resulted in ~4% increased likelihood of new or worsening ar/ar in all groups over time (30 mg dose reduction HR 1.04 [95% CI: 0.67–1.60], NS). Hazard reduction for the VDZ groups versus those on PLA was similar (VDZ, 0.73 [95% CI: 0.44–1.22], NS; VDZ/PLA, 0.72 [95% CI: 0.37–1.39], NS).

Conclusions: In this post hoc exploratory analysis there was a trend for both reduced incidence of new or worsening ar/ar and increased rates of sustained resolution of ar/ar in pts receiving VDZ. CS tapering increased the probability of ar/ar in all groups. GEMINI 2 was not sufficiently powered to assess worsening/new occurrences of other EIMs.

References:

- [1] Vavricka SR, Schoepfer A, Scharl M, et al., (2015), Extraintestinal Manifestations of Inflammatory Bowel Disease, *Inflamm Bowel Dis*, 1982–92

DOP020

Higher vedolizumab levels are associated with deep remission in patients with Crohn’s disease and ulcerative colitis on maintenance therapy with vedolizumab

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Background: Vedolizumab (VDZ) has been found to be efficacious in the treatment of Crohn’s disease (CD) and ulcerative colitis (UC), even though some patients present with non-response. The correlation between pharmacokinetics, immunogenicity and response to VDZ is not well understood and may play a role in clinical practice, particularly when optimizing therapy. The aim of this study was to assess correlation between VDZ trough levels and antibodies to VDZ (ATV) with rates of remission in patients with CD and UC.

Methods: This was a prospective cross-sectional study that included patients with CD or UC receiving maintenance treatment with VDZ. Variables included trough VDZ and ATV levels (measured using a

validated drug-tolerant assay). Other variables collected during the study visit were C-reactive protein (CRP), Harvey Bradshaw index (HBI) in CD and Mayo Clinical Score (MCS) in UC. Mayo endoscopic score (MES) in UC and Simple endoscopic score-CD (SES-CD) in CD were also collected when endoscopy was performed. Primary outcome was deep remission (DR) defined as normal CRP and SES-CD ≤ 2 (in CD) - MES ≤ 1 (in UC) in addition to clinical remission (which was defined as an HBI < 5 (in CD)/MCS < 3 (in UC)). Secondary outcome was steroid-free remission (SFR) defined as DR while off steroids for 3 months.

Results: 56 patients were included (73% had CD). Twenty (36%) were on combination therapy with a thiopurine or methotrexate. Forty-three and 16% were in DR and SFR, respectively. Only 1 patient had ATV. VDZ levels were significantly higher in patients with DR and SFR when compared to those who did not achieve these outcomes (12.9 vs 9.4 $\mu\text{g}/\text{mL}$ [p=0.008] – Figure 1, and 15 vs. 9.5 [p=0.02] – Figure 2).

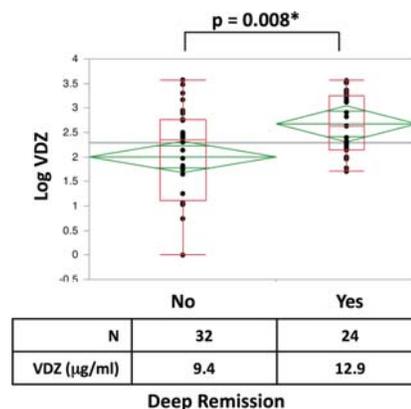


Figure 1. Vedolizumab levels were higher in patient in deep remission.

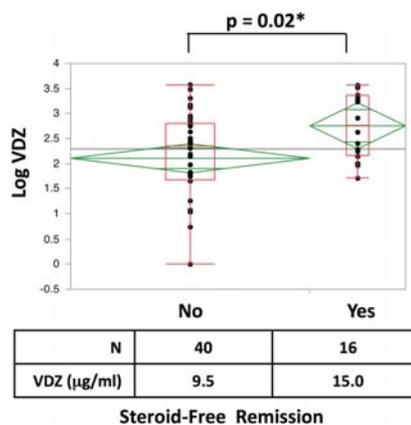


Figure 2. Vedolizumab levels were higher in patients in steroid-free remission.

Patients with VDZ levels ≥ 5.1 $\mu\text{g}/\text{mL}$ (the first interquartile threshold) were more likely to be in DR (OR: 6.6 [95% CI: 1.55–45.8] p=0.009). A VDZ cutoff level of 5.1 $\mu\text{g}/\text{mL}$ best predicted DR (p : 0.713, p=0.03). Secondary outcome was steroid-free remission (SFR) defined as DR while off steroids for 3 months.

Conclusions: There is an association between VDZ drug levels and VDZ efficacy. These results suggest that there may be a role for therapeutic drug monitoring and drug optimization in patients receiving VDZ for CD or UC. Results from larger ongoing studies will be important.

DOP021**Long-term effectiveness and safety of vedolizumab in patients with Crohn's disease: 5-year cumulative exposure of GEMINI 2 completers rolling into the GEMINI open-label extension study**

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Background: Vedolizumab (VDZ), a humanised monoclonal antibody that targets $\alpha_4\beta_7$ integrin, is approved for moderately to severely active Crohn's disease (CD) and ulcerative colitis. The GEMINI open-label extension (OLE) trial is an ongoing study investigating the long-term safety of VDZ (NCT00790933). Here we report the 5-year exploratory analyses of effectiveness and safety in patients (pts) with CD who had completed GEMINI 2 [1] and were enrolled in GEMINI OLE.

Methods: Analyses included pts who had responded to VDZ induc-

tion at Week (Wk) 6 and received VDZ maintenance (every 8 or 4 wks; data were combined) to Wk 52 of GEMINI 2, followed by VDZ every 4 wks in GEMINI OLE. Pts with 248 wks of cumulative VDZ treatment (data were collected from 22 May 2009 to 21 May 2015) were assessed for clinical response (decrease in Harvey-Bradshaw Index [HBI] of ≥ 3 points from baseline [BL]), clinical remission (HBI ≤ 4) and health-related quality of life (HRQoL), including IBD Questionnaire (IBDQ) and Euro Quality of Life-5D visual analogue scale (EQ-5D VAS). Safety was also assessed.

Results: Of 308 pts in GEMINI 2 who responded to VDZ induction at Wk 6 and received VDZ in maintenance, 146 (47%) completed VDZ maintenance and were enrolled in GEMINI OLE (anti-TNF α -naïve n=81; anti-TNF α failure n=57). At the time of this analysis, 61 pts had completed 248 wks of cumulative VDZ treatment, 58 had discontinued (n=11 [19%] due to lack of continued benefit) and 27 are ongoing (have not yet reached 248 wks of treatment). Of pts with data at Wk 248 (n=61), 95% had clinical response and 89% were in remission (Table). HRQoL improvements were observed at Wk 248, with mean change from BL IBDQ and EQ-5D-VAS scores of 59.4 and 29.8, respectively. In the safety population, 134 pts had adverse events (AEs); 15 discontinued due to AEs. Serious AEs were reported in 41 pts (in 3 pts these were drug-related; 8 pts discontinued as a consequence of serious AEs). One death (not drug-related; motor accident) was reported.

Conclusions: Long-term VDZ therapy (~5 years) was associated with clinical benefits including clinical response, clinical remission and HRQoL improvements in pts with moderately to severely active CD who responded at Wk 6, completed GEMINI 2 and enrolled in OLE. Long-term VDZ therapy was associated with no unanticipated AEs, and the safety profile was consistent with that previously observed in a 3-year interim analysis of the OLE study.

References:

[1] Sandborn WJ, Feagan BG, Rutgeerts P, et al., (2013), Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease, *N Engl J Med*, 711–21

DOP022**Vedolizumab and anti-TNF α treatment effectiveness in patients with IBD treated in Germany: a retrospective chart review**

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Abstract DOP021 – Table 1. Effectiveness outcomes in patients with CD and cumulative VDZ exposure for up to 248 wks

Cumulative VDZ exposure (wks)	GEMINI OLE study wk	Combined VDZ, observed cases*			Combined VDZ, non-responder imputation [†]		
		N	Clinical response, n (%)	Clinical remission, n (%)	N	Clinical response, n (%)	Clinical remission, n (%)
52	0	145	128 (88)	107 (74)	145	128 (88)	107 (74)
80	28	134	118 (88)	107 (80)	145	118 (81)	107 (74)
104	52	120	113 (94)	100 (83)	145	113 (78)	100 (69)
128	76	113	104 (92)	94 (83)	145	104 (72)	94 (65)
152	100	106	101 (95)	94 (89)	145	101 (70)	94 (65)
200	148	91	85 (93)	80 (88)	145	85 (59)	80 (55)
248	196	61	58 (95)	54 (89)	145	58 (40)	54 (37)

*Number of patients in clinical response or remission (n) over number of observed cases (N) at study visit

[†]Patients without available data (for reasons including study discontinuation and patients ongoing in the study who have not yet reached specified assessment time points) were included as non-responders

Clinical response was defined as a decrease in HBI of ≥ 3 points from BL; clinical remission was defined as an HBI ≤ 4

BL, baseline; CD, Crohn's disease; HBI, Harvey-Bradshaw Index; OLE, open-label extension; VDZ, vedolizumab; wk, week

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Background: Vedolizumab (VDZ) is a gut-selective monoclonal anti-integrin antibody indicated for the treatment (Tx) of moderate-to-severe Crohn's disease (CD) and ulcerative colitis (UC). Real-world outcomes in patients who received VDZ as 1st/2nd line biologic is limited. This study evaluated VDZ Tx patterns/effectiveness in Germany in comparison to anti-TNF α .

Methods: This was a descriptive retrospective chart review study of CD and UC patients who were biologic naïve or had only one anti-TNF α and initiated Tx with VDZ or an anti-TNF α (adalimumab, infliximab, golimumab) from 15 Jul 2014 to 20 Oct 2015. Data collection ended at death or at chart abstraction initiation. Patient characteristics and VDZ/anti-TNF α Tx effectiveness were analysed. Tx response at 12 months was defined as partial, complete response or stable disease, or in absence of documentation, as positive change from baseline for global physician assessment or endoscopic findings.

Results: 313 patients (47.0% VDZ, 53.0% anti-TNF α) from 13 sites were included in the study; 49.0% VDZ and 62.0% anti-TNF α patients had CD. 22.4% VDZ and 65.7% anti-TNF α patients were biologic naïve; mean (SD) follow-up was 1.4 (0.4) years. Mean (SD) age was 41.0 (13.7) for VDZ and 38.5 (12.6) for anti-TNF α patients. In biologic naïve patients, median (range) Tx duration (years) was 1.5 (0.1–1.9) for VDZ and 1.2 (0.3–2.1) for anti-TNF α . 18.2% VDZ and 18.3% anti-TNF α patients discontinued Tx mostly due to lack of response/inadequate symptom control; 9.1% VDZ and 10.1% anti-TNF α patients switched to a new biologic. 85.8% VDZ and 81.3% anti-TNF α patients with assessable data had documentation of 12 month Tx response. Among patients who had one prior biologic, median (range) Tx duration (years) was 1.2 (0–2.1) for VDZ and 1.2 (0–2.2) for anti-TNF α . 28.1% VDZ and 21.1% anti-TNF α patients discontinued Tx mostly due to lack of response/inadequate symptom control; 17.5% VDZ and 12.3% anti-TNF α patients switched

to a new biologic. 80.4% VDZ and 66.7% anti-TNF α patients with assessable data had documentation of 12 month Tx response.

Conclusions: In biologic naïve patients, VDZ patients appeared to continue Tx longer but had similar rates of discontinuation, Tx switching and Tx response compared to anti-TNF α patients within 1 year. More VDZ patients with one prior biologic experienced discontinuations and Tx switching compared to VDZ treatment in biologic naïve patients. In prior biologic exposed patients, VDZ resulted in a much higher proportion of Tx response compared to anti-TNF α .

DOP023

Predictors of clinical and endoscopic response with vedolizumab for the treatment of moderately-severely active ulcerative colitis: results from the US VICTORY consortium

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Background: Vedolizumab (VDZ) is now widely used for moderately-severely active ulcerative colitis (UC). Quantifying outcomes and identifying predictors of response would be of clinical utility.

Methods: Through a multicentre collaboration (US VICTORY consortium), UC patients starting VDZ were pooled across 9 academic sites. The current analyses include patients with moderately-severely active disease (Mayo endoscopic sub-score 2 or 3) within 12 weeks prior to starting VDZ, and at least one follow-up. Response was based on the physician global assessment: clinically significant response defined as >50% reduction in symptom activity, and remission as complete resolution of all UC-related symptoms. Mucosal healing was defined as Mayo endoscopic sub-score of 0 or 1. Response to induction was assessed within 4 weeks of completing the 3rd dose of VDZ. Time-to-event and Cox proportional hazard analy-

Table 1. Treatment response at 12 months (≥ 9 to <15 months) for patients with assessable measurements of clinical effectiveness

n (%)	VDZ	VDZ	Anti-TNF	Anti-TNF
	Biologic Naïve (N=33)	Prior Biologics (N=114)	Biologic Naïve (N=109)	Prior Biologics (N=57)
Patients with assessable data	14 (100)	51 (100)	48 (100)	21 (100)
Positive (improvement)	12 (85.8)	41 (80.4)	39 (81.3)	14 (66.7)
No change	1 (7.1)	7 (13.7)	4 (8.3)	3 (14.3)
Negative (worsening)	0 (0)	0 (0)	0 (0)	1 (4.7)
Unknown	1 (7.1)	3 (5.9)	5 (10.4)	3 (14.3)

Abstract DOP023

Table 1: Cumulative Rates for Treatment Outcomes at 6 and 12 Months

	6 months				12 months			
	Entire Cohort	Prior TNF-antagonists			Entire Cohort	Prior TNF-antagonists		
		0 (n=53)	1 (n=85)	2+ (n=42)		0 (n=53)	1 (n=85)	2+ (n=42)
Clinical response	53%	67%	50%	41%	73%	77%	75%	64%
Steroid-free response	27%	26%	26%	31%	49%	54%	49%	43%
Clinical remission	37%	50%	33%	28%	51%	61%	51%	40%
Steroid-free remission	22%	22%	19%	28%	41%	52%	35%	41%
Mucosal healing (Mayo 0 or 1)	35%	30%	36%	39%	77%	70%	83%	58%
Mucosal healing (Mayo 0)	20%	21%	19%	22%	53%	56%	59%	33%

ses were used to quantify treatment outcomes and identify predictors of outcomes. Hazard ratios (HR) with 95% confidence intervals (CI) are presented; HR >1 indicates increased probability for achieving the outcome.

Results: The analysis included 180 UC patients (52% male; median follow-up, 9.4 months). Concomitant steroids alone (n=69, 38%), thiopurines alone (n=21, 12%), or both steroids and thiopurines (n=39, 22%) were used at baseline. Cumulative response, remission, and mucosal healing rates at 6 and 12 months are presented in Table 1.

On multivariable analyses, prior TNF-antagonist exposure was associated with a reduction in probability for achieving a significant clinical response (HR, 0.58; 95% CI, 0.39–0.86) and clinical remission (HR, 0.55; 95% CI, 0.35–0.88), but not steroid-free response (HR, 0.72; 95% CI, 0.38–1.37), steroid-free remission (HR, 0.63; 95% CI, 0.31–1.29), or mucosal healing (HR, 1.00; 95% CI, 0.56–1.80). Achieving a significant response to induction (HR 1.98, 95% CI 1.15–3.39) was associated with achieving mucosal healing.

Conclusions: A substantial proportion of UC patients can achieve clinical remission, steroid-free remission, and mucosal healing by 12 months in routine practice. The magnitude of response was generally higher in anti-TNF-naïve patients than anti-TNF experienced patients, and varied by the number of TNF-antagonists previously used. Response to induction therapy was associated with subsequent mucosal healing in VDZ patients.

DOP024

Vedolizumab clinical and post-marketing safety experience of opportunistic infections

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Background: The risk of opportunistic infections (OIs) in IBD increases after treatment with biologics (OR: 1.90) [1]. Vedolizumab (VDZ), a humanised monoclonal antibody, targets $\alpha 4\beta 7$ integrin and selectively blocks gut-specific lymphocyte trafficking. Gut selectivity could be associated with a lower risk of infections compared with anti-TNF α agents, which cause systemic immunosuppression. We assessed the frequency of OIs with VDZ treatment in clinical trials and the post-marketing (PM) setting.

Methods: Safety data from GEMINI 1 and 2 (VDZ vs placebo, in ulcerative colitis [UC] and Crohn's disease [CD], respectively), the ongoing GEMINI open-label extension (OLE) study (VDZ only, UC and CD; data cut-off: 19 May 2015) and the VDZ Global Safety Database (May 2014 – 30 September 2016) were assessed. OI events were identified from a comprehensive list of MedDRA terms that are generally regarded as OIs.

Results: Seven OIs were reported in GEMINI 1 and 2 (N=1731); all received VDZ (n=1434). OIs included *Clostridium difficile* colitis (n=5); cytomegalovirus (CMV) colitis (n=1) and CMV infection (n=1). One event was serious; one (non-serious) led to discontinuation. 51 patients had OIs in GEMINI OLE (N=2243; TPY=5430; Table 1); *C. difficile* colitis was most frequent (n=26; serious: n=11; non-serious: n=15). In the context of ~72,140 patient-years of VDZ

therapy in the PM setting, 127 OI events were reported in 124 patients (serious: 59 events; non-serious: 68 events); the most frequently reported OI was *C. difficile* infection (74 events; 25 serious, 49 non-serious; Table 2). 2 patients had fatal OIs: *Pneumocystis jirovecii* pneumonia in a patient with immunosuppression due to long-term high-dose steroid use, and unspecified OI in a steroid-refractory graft versus host disease patient (off-label use). In the PM setting, VDZ treatment was continued in most patients with OI events (66%).

Table 1. GEMINI OLE: Summary of OI events

Safety population	VDZ								
	Ulcerative colitis n=894 TPY=2285			Crohn's disease n=1349 TPY=3145			Total N=2243 TPY=5430		
	n	%	IR*	n	%	IR*	n	%	IR*
All OI AEs	27	3.0	1.2	24	1.8	0.8	51	2.3	1.0
Drug-related OI AEs	10	1.1	0.4	8	0.6	0.3	18	0.8	0.3
OI AEs resulting in discontinuation	4	0.4	0.2	0	0	0	4	0.2	0.1
OI SAEs	9	1.0	0.4	9	0.7	0.3	18	0.8	0.3
Drug-related OI SAEs	5	0.6	0.2	3	0.2	0.1	8	0.4	0.2
OI SAEs resulting in discontinuation	3	0.3	0.1	0	0	0	3	0.1	0.1
Deaths	0	0	0	0	0	0	0	0	0

*Time-adjusted IR per 100 patient-years = (number of patients experiencing an AE of interest/total patient exposure time in years) x 100

AE, adverse event; IR, incidence rate; OI, opportunistic infection; OLE, open-label extension; SAE, serious adverse event; TPY, total patient-years; VDZ, vedolizumab

Table 2. Post-marketing data: Summary of OI events

MedDRA preferred term	VDZ		
	Serious events, n	Non-serious events, n	Total events, N
Total	59	68	127*
<i>Clostridium difficile</i> infection	25	49	74
<i>Clostridium difficile</i> colitis	5	8	13
CMV infection	7	4	11
CMV colitis	5	2	7
JCV test positive [†]	6	1	7
CMV viraemia	0	2	2
Nocardiosis	2	0	2
Disseminated tuberculosis	1	0	1
Epstein-Barr virus associated lymphoma	1	0	1
Fungal oesophagitis	0	1	1
Herpes zoster infection neurological	1	0	1
Histoplasmosis disseminated	1	0	1
<i>Mycobacterium avium</i> complex infection	1	0	1
Oesophageal candidiasis	0	1	1
Opportunistic infection	1	0	1
<i>Pneumocystis jirovecii</i> pneumonia	2	0	2
Presumed ocular histoplasmosis syndrome	1	0	1

*127 OI events were reported in 124 patients

[†]The background prevalence of anti-JCV antibody positivity is ~33–91%, based on published rates in multiple patient populations and healthy individuals
CMV, cytomegalovirus; JCV, John Cunningham Virus; MedDRA, Medical Dictionary for Regulatory Activities; OI, opportunistic infection; VDZ, vedolizumab

Conclusions: Clinical trial and PM data showed that OIs were infrequent with VDZ. The most common OI was *C. difficile* colitis/*C. difficile* infection: most events were non-serious; most patients continued VDZ. Limitations with PM safety reporting (e.g., limited details in case reports, increased likelihood of reporting more severe events) make confirming a causal association between drug and event difficult, and must be considered when interpreting the PM data.

References:

- [1] Bonovas S, (2016), Biologic Therapies and Risk of Infection and Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis

DOP025 Efficacy of vedolizumab on extraintestinal manifestation in patients with inflammatory bowel disease: a post-hoc analysis of the OBSERV-IBD cohort from the GETAID

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Background: Up to 50% of patients with inflammatory bowel disease (IBD) experience at least one extraintestinal manifestation (EIM). Whether or not vedolizumab (VDZ) is effective on EIM needs to be assessed.

Methods: Between June and December 2014, 173 patients with Crohn's disease (CD) and 121 with ulcerative colitis (UC) were followed up after VDZ introduction during 54 weeks. Efficacy of vedolizumab on EIM was estimated by using a 3-step scale: (1) complete remission meaning absence or almost absence of all clinical symptoms without increasing the steroid dose or introducing any other IBD-specific treatment (2) partial response meaning improvement of symptoms or reduction of the steroid dose without worsening of symptoms (3) no response, meaning no improvement or worsening of symptoms.

Results: Among the 294 patients with IBD, 50 (17.2%) presented with EIM at baseline including 46 (15.6%) with arthropathies and 5 (1.7%) with skin manifestations. At week 14, complete remission was observed in 24 (52.2%) patients with arthropathies and in 4 (80%) patients with skin manifestation. At week 54, 21 (45.7%) and 3 (60%) were still in complete remission for arthropathies and skin manifestations, respectively. During the follow-up period, 32 (15.8%) patients without any EIM at baseline, presented with arthropathies. The probabilities of developing arthropathies during VDZ therapy was 5.2%, 10% 13.9% and 17.5% at weeks 14, 22, 30 and 54, respectively. In multivariate analysis, predictors of arthropathies occurrence were prior ankylosing spondylitis (OR =3.70, IC95% [1.49–9.10], p=0.005) and Crohn's disease (OR =2.50, IC95% [1.04–5.88], p=0.04). During the follow-up period, 14 (4.8%) patients presented with paradoxical skin manifestation of whom 8 (57.1%) had previously experienced paradoxical skin manifestation associated with anti-TNF therapy. Among the 173 patients with Crohn's disease, 35 (20.2%) presented with active perianal dis-

ease at baseline including 30 (17.3%) with perianal fistula and 5 (2.9%) with perianal fissure. At week 14, complete remission of perianal Crohn's disease was observed in 15 (42.9%) of patients whereas partial remission was observed in 2 (5.7%) patients. At week 54, 12 (34.3%) patients were still in complete remission. Additionally, three patients presented with perianal disease during the follow-up period despite VDZ therapy.

Conclusions: VDZ therapy was effective for achieving complete resolution of EIM in patients with IBD in approximately half of the cases. VDZ was also effective for perianal CD in one third of the patients. Paradoxical skin manifestation may occur upon VDZ therapy suggesting as a class effect not restricted to anti-TNF agents.

DOP026 Sustained remission with vedolizumab in patients with moderately to severely active ulcerative colitis: a GEMINI 1 post hoc analysis of week 14 remitters

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Background: Sustained remission is a key therapeutic goal in ulcerative colitis (UC). Vedolizumab (VDZ) was more effective than placebo as induction and maintenance therapy in patients (pts) with moderately to severely active UC in the GEMINI 1 study (NCT00783718). This post hoc analysis assessed sustained remission during the maintenance phase of GEMINI 1.

Methods: Analyses included pts enrolled in GEMINI 1, who received 6 weeks (wks) of induction with placebo or VDZ and entered 46 wks of maintenance continuing placebo or VDZ, respectively; eligible pts could then enrol into an open-label extension (OLE) to receive VDZ every 4 wks. The primary aim was to assess sustained remission (remission at Wks 26, 38 and 52) in pts who achieved remission at Wk 14. Remission was defined as 1) clinical remission (partial Mayo Score [PMS] ≤2 points with no individual subscore >1 point) or 2) rectal bleeding subscore =0. For the analyses, pts who received VDZ maintenance, discontinued before Wk 52 and then entered the OLE had missing maintenance data imputed using OLE data.

Results: In total, 620 pts received VDZ (Wk 6 responders and non-responders) and 149 received placebo throughout GEMINI 1. Patient characteristics were broadly similar between treatment groups. From Wk 4 onwards, a significantly higher proportion of pts receiving VDZ were in clinical remission versus placebo in the overall and

anti-TNF-naïve populations; significance was achieved at Wk 26 in the anti-TNF failure population. At Wk 14, 203 (33%) pts receiving VDZ and 30 (20%) pts receiving placebo were in clinical remission based on PMS, and 293 (47%) pts receiving VDZ and 43 (29%) pts receiving placebo were in remission based on rectal bleeding subscore. Of pts in remission at Wk 14, the VDZ group had a higher proportion of pts with sustained remission versus placebo according to both PMS and rectal bleeding definitions (Table); significance was reached in both the overall and anti-TNF-naïve populations, and a similar nominal trend was observed in the anti-TNF failure population.

Table 1. Patients with remission at Week 14 that was sustained for all visits at Weeks 26, 38 and 52

	Placebo (n=149)		Vedolizumab (n=620)	
	Pts in remission at Week 14 (n)	Pts with sustained remission, n (%) [95% CI]	Pts in remission at Week 14 (n)	Pts with sustained remission, n (%) [95% CI]
Partial Mayo Score				
Overall	30	8 (26.7) [10.8–42.5]	203	135 (66.5) [60.0–73.0]*
Anti-TNF-naïve	16	4 (25.0) [7.3–52.4]	121	83 (68.6) [60.3–76.9]*
Anti-TNF failure	10	4 (40.0) [12.2–73.8]	69	43 (62.3) [50.9–73.8]
Rectal bleeding subscore = 0				
Overall	43	9 (20.9) [8.8–33.1]	293	166 (56.7) [51.0–62.3]*
Anti-TNF-naïve	20	4 (20.0) [5.7–43.7]	152	94 (61.8) [54.1–69.6]*
Anti-TNF failure	19	4 (21.1) [6.1–45.6]	116	61 (52.6) [43.5–61.7]

The vedolizumab treatment group included Week 6 responders and non-responders to vedolizumab induction therapy who received vedolizumab Q4W or Q8W during the maintenance phase.

Remission was defined as partial Mayo Score ≤2 points with no individual subscore >1 point, or rectal bleeding subscore = 0

*Non-overlapping 95% CIs for vedolizumab compared with placebo

Pts, patients; Q4W, every 4 weeks; Q8W, every 8 weeks; TNF, tumour necrosis factor

Conclusions: Wk 6 is most likely too early to ascertain the full clinical benefit of VDZ. VDZ showed a significant difference versus placebo in the proportion of pts achieving clinical remission as early as Wk 4 for the overall and anti-TNF naïve populations. However, as per label, assessment of the clinical benefit should be made after 10–14 wks. In pts with remission at Wk 14 in GEMINI 1, continued VDZ treatment resulted in ~60% of pts maintaining sustained remission based on PMS and rectal bleeding subscore.

DOP027

Long-term efficacy and safety of ustekinumab in refractory Crohn's disease patients: a multicenter retrospective experience

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Background: Ustekinumab has been shown to be effective in Crohn's disease (CD) in phase III trials. However, long-term outcome of ustekinumab has never been evaluated in CD. The aim of the present study was to evaluate the long-term efficacy and safety of ustekinumab and to identify predictive factors of ustekinumab failure-free survival in a multicenter cohort of anti-TNF refractory CD patients. **Methods:** We performed a retrospective observational study in 20 tertiary centers from the GETAID, including all patients who received subcutaneous ustekinumab induction for an active CD from March 2011 to December 2014 and were followed until November 2016. The primary outcome was ustekinumab failure-free; failure was defined as withdrawal of ustekinumab due to loss of response, intolerance or need of surgery. Predictive factors of ustekinumab failure-free survival at 2 years and safety data were also evaluated.

Results: Until December 2014, 122 CD patients received subcutaneous ustekinumab induction. Eighty-eight patients responded to ustekinumab during the first year and were followed until November 2016. Among these 88 patients (64 females, median age: 32.5 years, median disease duration: 11.8 years), all patients have failed to at least one anti-TNF agent and two-third underwent prior intestinal resection. At time of ustekinumab introduction, 13 (15%) patients received immunosuppressant (IS) and 13 (15%) steroids. Median time on ustekinumab was 2.2 (1.1–2.9) years and 42 (48%) patients experienced ustekinumab failure. Ustekinumab failure-free survival was observed in 78.4% at 1 year, 65.8% at 2 years and 54.7% at 3 years. Ustekinumab discontinuation was observed for loss of response in 32 (36%) patients, for intolerance in 4 (5%) patients, for remission in 5 (6%) patients, and for pregnancy in one patient. Five patients underwent intestinal resection during the follow-up. In univariate analysis, concomitant IS at time of ustekinumab introduction and female sex were associated with ustekinumab failure-free survival at 2 years ($p=0.07$; IC95% (1.2–24.8) and $p=0.05$; IC95% (0.11–1.05), respectively). In multivariate analysis, none predictive factor of ustekinumab failure-free survival was identified. An adverse event occurred in 21 (24%) patients. One anal adenocarcinoma was reported during follow-up.

Conclusions: We here report the first real-life experience of long-term outcome of ustekinumab treatment in CD refractory patients, with a median follow-up of more than 2 years. More than 50% of patients maintained ustekinumab during the follow-up without loss of response, intolerance or surgery, with a good safety profile. No predictive factor of ustekinumab failure-free survival was identified in multivariate analysis.

DOP Session 4: Immunogenicity and pharmacokinetics of biologics

DOP028

Antibodies towards vedolizumab appear from week 2 onwards and disappear upon treatment

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Background: Vedolizumab (VDZ), a monoclonal antibody (MA) that specifically binds to $\alpha 4\beta 7$ integrin, has demonstrated efficacy in patients with moderate-to-severe Crohn's disease (CD) and ulcerative colitis (UC). VDZ trough concentrations (TC) are typically >30 $\mu\text{g/ml}$ during induction and >10 $\mu\text{g/ml}$ during maintenance therapy, making it challenging for immunogenicity assays to detect anti-VDZ antibodies (AVA). The GEMINI trials reported AVA at ≥ 2 consecutive time points in 0.4% and 1% of patients with CD and UC, respectively.

Methods: We developed a drug-resistant AVA assay in which AVA are complexed with an excess of VDZ followed by VDZ/AVA complex precipitation, acidification of the precipitate, coating and detection of released AVA using biotinylated VDZ. MA-VDZ19C11, a MA towards VDZ, was validated as calibrator. Drug resistance was examined by determination of the recovery of MA-VDZ19C11 in the presence of 3 different concentrations of VDZ. The cut-off was determined using 20 VDZ naïve patients. Cross reactivity with serum from 2 anti-infliximab antibody and 2 anti-adalimumab antibody positive patients, as well as with serum containing high concentration of rheumatoid factor (150 U/mL) was determined. The assay was subsequently applied to serum samples from 75 VDZ-treated patients (46 CD, 29 UC) taken at trough during induction (w6) and maintenance (w22). VDZ TC, AVA and CRP were determined in all available sera of patients positive for AVA at w6/22.

Results: MA-VDZ19C11 yielded dose-response curve ranging from 25–1600 ng/mL in 1/125 diluted serum allowing detection of AVA concentrations up to 200 $\mu\text{g/ml}$ equivalents. Spiking 1, 10 and 100 $\mu\text{g/ml}$ of VDZ to 40 $\mu\text{g/ml}$ MA-VDZ19C11 yielded recoveries of $89 \pm 7\%$ (mean \pm SD, n=3), $90 \pm 11\%$ and $82 \pm 5\%$, respectively, confirming the complete drug resistance of the AVA assay. Cut-off for quantification was determined to be 1.1 $\mu\text{g/ml}$ MA-VDZ19C11 equivalents and none of the sera tested revealed cross-reactivity. Among the 75 VDZ-treated patients, 1 patient (1.3%) had AVA antibodies at w6 determined by a classical drug-sensitive bridging assay whereas 4 patients (5.3%) were AVA positive on ≥ 2 time points using the drug-resistant AVA assay. AVA antibodies appeared from w2

onwards but disappeared over time (Figure 1). None of the 4 ADA-positive patients required VDZ intensification.

Conclusions: Using a drug-resistant AVA assay, AVA are detected in 5.3% of patients. Antibodies appear from w2 onwards and disappear upon time indicating their transient character.

DOP029

Clinical relevance of detecting anti-infliximab antibodies with a drug-tolerant assay: post-hoc analysis of the taxit trial

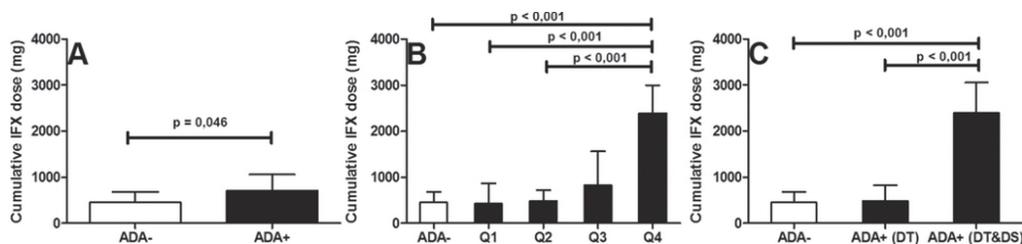
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Background: Anti-drug antibodies (ADA) may develop in up to 51% of patients treated with infliximab maintenance therapy and are associated with infusion reactions and impaired response. Drug-sensitive assays do not detect ADA in the presence of drug and underestimate ADA formation. Drug-tolerant assays have therefore been developed and markedly increased the detection of ADA, although their clinical relevance remains to be shown. Our goal was to evaluate the clinical relevance of anti-drug antibodies (ADA) measured using a drug-tolerant assay in comparison to a drug-sensitive assay in a post-hoc analysis of the Trough Concentration Adapted Infliximab Treatment (TAXIT) randomized controlled trial.

Methods: Patients who presented with an infliximab trough concentration (TC) < 3 $\mu\text{g/ml}$ at screening (n=76) underwent dose escalation to achieve therapeutic TCs between 3–7 $\mu\text{g/ml}$ prior to randomization. Serum samples were re-analyzed at screening, after optimization and one year after randomization using a drug-tolerant ADA assay.

Results: Using a drug-tolerant assay, the immunogenicity detection rate increased from 21% (drug-sensitive assay) to 63% at screening, from 0% to 51% after optimization and from 3% to 42% one year after randomization. ADA concentration (median [interquartile range, IQR]) in ADA+ patients grouped into quartiles according to ADA concentration at screening, decreased throughout the study: from 220 [116–737] ng/mL eq at screening to 112 [78–180] ng/mL eq after optimization and to 95 [0–166] ng/mL eq at the end of the study. Patients in ADA Q4 required a higher cumulative infliximab dose (2390 [880–2998] mg) to achieve target TCs (Figure 1) compared to ADA negative patients (450 [365–680] mg, $p < 0.001$) and patients in ADA Q1/Q2 (425 [344–863]/483 [398–719], $p < 0.001$). However, all but one patient belonging to ADA Q4 were also ADA positive using a drug-sensitive assay. Once dose optimized, patients have similar rates of clinical, biological and endoscopic remission after one year of treatment, regardless of ADA status in a drug-tolerant assay.



Abstract DOP029 – Figure 1. Cumulative infliximab (IFX) dose required to achieve target concentrations between 3–7 $\mu\text{g/ml}$ A) for ADA+ and ADA- patients, B) across ADA+ quartiles (Q1–Q4) and C) according to the assay (DT, drug-tolerant assay; DS, drug-sensitive assay).

Conclusions: Upon dose intensification, low concentration ADA, not detectable using a drug-sensitive assay, disappear in more than half of the patients over time and are clinically non-relevant. In contrast, high concentration ADA which are typically also detected in a drug-sensitive assay, persist over time and necessitate a higher cumulative dose and drug cost. In the latter group, proactive drug switching may be more cost-efficient.

DOP030

Anti-TNF re-induction is as effective, simpler and cheaper compared with dose interval shortening following secondary loss of response in Crohn's disease: a dual centre "real world" study

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Background: Anti-TNF re-induction (RI) refers to re-dosing infliximab (IFX, 5mg/kg) at weeks 0, 2, 6 or adalimumab (ADA, 160mg, 80mg) at weeks 0, 2, prior to resuming standard IFX (8-weekly) or ADA (2-weekly) dosing. RI presents a simple and cost effective alternative to ongoing dose interval shortening (DIS) to recapture response following secondary loss of response (2°LOR) to maintenance anti-TNF therapy. This study aimed to compare the "real world" cost and efficacy of anti-TNF RI and DIS following 2°LOR in Crohn's Disease (CD) and identify factors associated with durability of response.

Methods: CD patients attending two Inflammatory Bowel Disease (IBD) centres in Melbourne, Australia between 1/1/2006–30/8/2016, who developed 2°LOR to maintenance anti-TNF and subsequently underwent RI or DIS, were retrospectively identified from existing IBD databases. DIS was standardised to 6-weekly IFX or weekly ADA. Treatment failure was defined as either CD-related bowel resection, discontinuation of, or switching to another biologic within 12 months of RI or DIS. "Real world" drug costs of RI and DIS were based on Australian Pharmaceutical Benefit Scheme pricing.

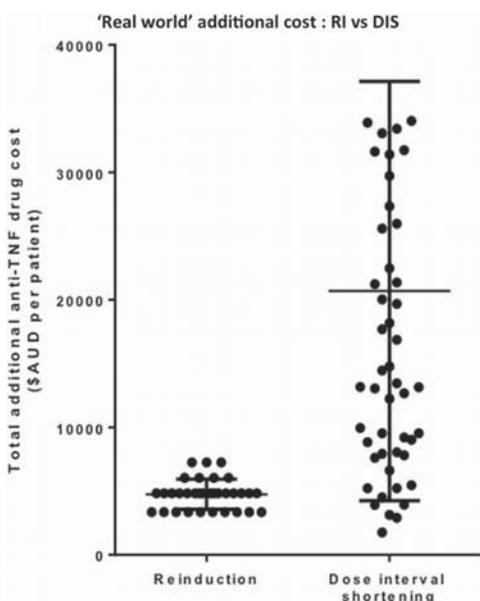


Figure 1. "Real world" comparison of additional anti-TNF drug costs associated with RI vs DIS.

Non-parametric statistics plus bi- and multivariate linear regression depicting variables associated with time to failure were calculated.

Results: Of 423 patients on anti-TNF therapy for CD, 88 (21%) developed 2°LOR to IFX (51, 58%) and ADA (37, 42%) respectively. Median age and disease duration at 2°LOR was 36.6y (17.4–78.0) and 9.4y (0.7–35.2) respectively, with a median duration from anti-TNF initiation to 2°LOR of 2.1y (0.2–8.1). Baseline characteristics were similar between groups, except the RI group had more smokers (48% vs 18%, $p < 0.01$). Subsequent RI or DIS was undertaken in 33 (38%) patients and 55 (62%) patients respectively. Treatment failure rates at 12 months were similar (27% vs 15%, $p = 0.17$). Factors favourably associated with a durable response to either RI or DIS on multivariate linear regression included subtherapeutic serum anti-TNF levels (B 5.37 [4.82, 5.92]), initial RI (B 2.56 [2.24, 2.89]), use of IFX (B 1.52 [1.26, 1.78]), and concurrent, optimised thiopurines (B 0.68 [0.46, 0.91]), $p < 0.01$. RI demonstrated lower median "real world" costs due to fewer anti-TNF doses during the follow-up period (median: AUD \$4,839 vs \$13,170, doses 2.0 vs 7.4, $p < 0.01$). **Conclusions:** This "real world" study suggests that first-line RI following 2°LOR to anti-TNF therapy in CD was as effective, simpler and cheaper than first-line DIS. Larger prospective evaluation is now planned.

DOP031

Subtherapeutic serum infliximab trough levels and complete mucosal healing are associated with sustained clinical remission after infliximab discontinuation in paediatric Crohn's disease patients

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Background: There is limited data regarding the clinical course of Crohn's disease (CD) after stopping infliximab (IFX) treatment in the paediatric population. We aimed to investigate the outcome of paediatric CD patients who had discontinued IFX under clinical remission by combined immunosuppression with IFX and thiopurines, and to reveal risk factors associated with clinical relapse in these patients.

Methods: We conducted a retrospective observational study from January 2009 to June 2016 at the Department of Pediatrics, Samsung Medical Center. The subjects were 63 patients who had discontinued scheduled IFX under sustained corticosteroid-free clinical remission for at least 1 year by combined immunosuppression with IFX and azathioprine, and had been followed for at least 1 year after IFX cessation. Relapse free survival rate and the median time to relapse was estimated by Kaplan-Meier survival analysis. Demographic, clinical, biochemical, and endoscopic factors at IFX cessation were evaluated for their association with clinical relapse using Cox proportional hazard regression analysis.

Results: After a median follow-up period of 4.3 years (range: 1–7.5 years), 60% (38/63) patients had experienced a clinical relapse. The estimated cumulative relapse rate for 1-, 2-, 4-years were 19%, 36%, and 62%, and the median relapse time was 3.3 years from IFX cessation. According to multivariable Cox proportional hazard regression analysis, serum IFX trough levels of ≥ 2.5 $\mu\text{g/mL}$ and incomplete

mucosal healing status were associated with clinical relapse [hazard ratio (HR)=7.199, 95% confidence interval (CI)=1.641–31.571, $p=0.009$, and HR=3.628, 95% CI: 1.608–8.185, $p=0.002$, respectively]. Retreatment with IFX was effective in 30/33 patients (91%).

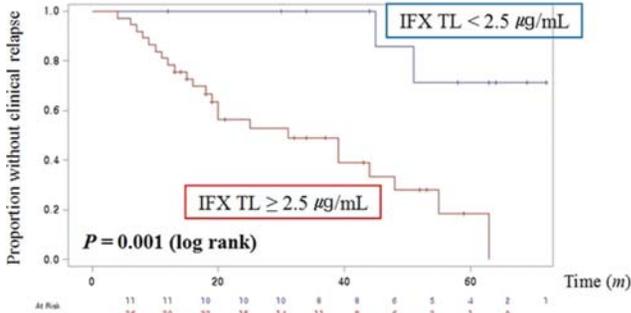


Figure 1. Clinical relapse in patients stratified by mucosal healing status at infliximab cessation.

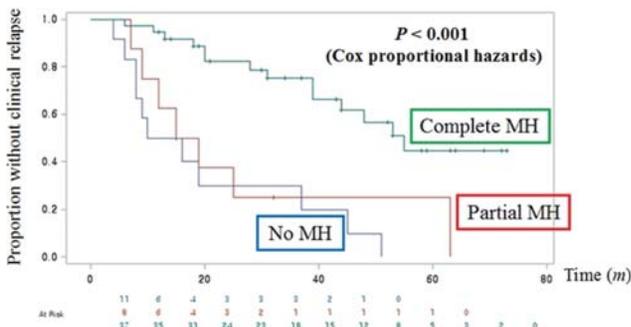


Figure 2. Clinical relapse in patients stratified by infliximab trough levels and mucosal healing status at infliximab cessation.

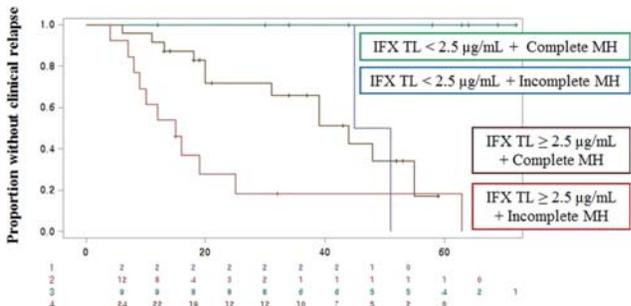


Figure 3. Clinical relapse in patients stratified by infliximab trough levels at infliximab cessation.

Conclusions: Approximately 50% of patients with paediatric luminal CD under sustained clinical remission for at least 1 year by combined immunosuppression will experience a relapse within 3.3 years after IFX cessation. A subgroup of patients with subtherapeutic serum IFX trough levels and a complete mucosal healing status at IFX cessation may better sustain clinical remission under thiopurines after IFX discontinuation.

DOP032

Hydrocortisone premedication withdrawal in patients on stable infliximab maintenance: clinical and pharmacokinetic outcomes

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Background: Infliximab (IFX) is effective in maintenance therapy for Crohn's disease (CD) and ulcerative colitis (UC). IFX efficacy may be limited by immunogenicity. It was previously shown that intravenous hydrocortisone premedication reduces IFX antibodies (ATI) formation [1]. This premedication is still now commonly used although its benefit is unclear. The aim of our study was to determine short-term impact of hydrocortisone withdrawal on ATI formation and IFX pharmacokinetic in a cohort of patients treated with IFX.

Methods: Patients were included between February and April 2016. Inclusion criteria were: – diagnosis of CD or UC; – IFX treatment with a stable dose for at least 6 months. Exclusion criteria were: – modification in IFX and/or immunosuppressant dosage; – pregnancy. Hydrocortisone premedication was withdrawn in all patients except during induction phase or if patients had a previous IFX-related infusion reaction. Trough levels and ATIs were measured at each infusion on a one year period (during the 3 infusions preceding and the 3 infusions following hydrocortisone withdrawal).

Results: Hydrocortisone premedication was stopped in 246 patients. One hundred and nine patients were included in the study (median age 36 years-old; 62% men; CD: n=82, UC: n=17). Mean duration of the disease was 13.7 years (1–42). Mean duration of IFX treatment was 5 years. IFX was used in combotherapy in 49 patients (thiopurines: n=39, methotrexate: n=10; mean duration of combotherapy 2 years). IFX treatment was modified after hydrocortisone withdrawal in 14 patients (dose diminution: n=8, optimization: n=5, stop for failure: n=1). Pharmacokinetic analysis was performed in 95 patients who had a stable dose. None of the patients developed permanent ATI, 4 patients had transient ATI and high trough level (>3mcg/ml). Mean IFX trough level before hydrocortisone withdrawal was 5.5 mcg/ml (respectively 4.9, 6.9, 5.1, 5.3 at T-3, T-2, T-1 and T0) and 5.9 mcg/ml after (5.6, 6.0, 6.2 at T+1, T+2, T+3), (NS). There was no significant variation of IFX trough levels, even in patients under monotherapy. Seven patients had symptoms after hydrocortisone withdrawal, without trough level variation and didn't change their treatment. There was no significant variation of CRP (2.55 mg/L versus 2.14 mg/L). None of the patients had IFX related infusion reaction.

Conclusions: In our study, performed in patients on stable IFX maintenance, hydrocortisone discontinuation had no impact on IFX trough levels and was not associated with ATI formation or infusion reactions.

References:

- [1] Farrell, (2003), Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial.

DOP033

Severely active ulcerative colitis is associated with high baseline infliximab clearance, reduced serum half-life and worse endoscopic outcomes

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Background: Therapeutic drug monitoring is a useful tool to optimize infliximab (IFX) therapy in clinical practice. The relationship between IFX concentration and change from baseline in endoscopic

disease activity during induction and maintenance therapy is unknown.

Methods: Data from the randomized controlled ACT-1 and -2 trials encompassing 484 patients with ulcerative colitis treated with IFX therapy were analyzed. A two-compartment population pharmacokinetic model was used to estimate IFX clearance (CL) at baseline. The Mayo endoscopic score (MES; range 0–3, with 3 representing most severe inflammation) was available at Week (W) 0, W8 and W30. A test for a linear trend between mean baseline IFX CL and MES (0–3) at W8 was performed. A concentration-effect curve was established by sorting all patients from low to high IFX concentration at specific time points with corresponding change in MES from W0 to W8 (Δ MES8) and from W0 to W30 (Δ MES30). Receiver operating curve (ROC) analysis was performed to identify IFX concentration cut-points with combined maximal sensitivity and specificity that corresponded to a MES of 0–1 or 0. Patients with missing data at W8 and/or W30 were considered treatment failures.

Results: A linear relationship was observed between baseline IFX CL and MES at W8 ($p < 0.001$). Concurrently, approximate median baseline IFX half-life was significantly shorter in patients with W8 MES ≥ 2 vs W8 MES < 2 (12 vs 15 days, respectively, $p < 0.001$). In patients with higher IFX exposure during induction and maintenance therapy, Δ MES8 and Δ MES30 was greater (Fig. 1A and 1B, respectively).

IFX cut-points of 26 μ g/mL at W2, 11 μ g/mL at W6 and 35 μ g/mL at W8 correlated with W8 MES < 2 , and 5.0 μ g/mL at W14 and 2.3 μ g/mL at W30 correlated with W30 MES < 2 (Table 1).

Conclusions: Ulcerative colitis patients with high baseline IFX CL

may benefit from accelerated dosing during induction treatment to achieve drug exposure above the cut-points associated with short- and long-term mucosal healing.

DOP034

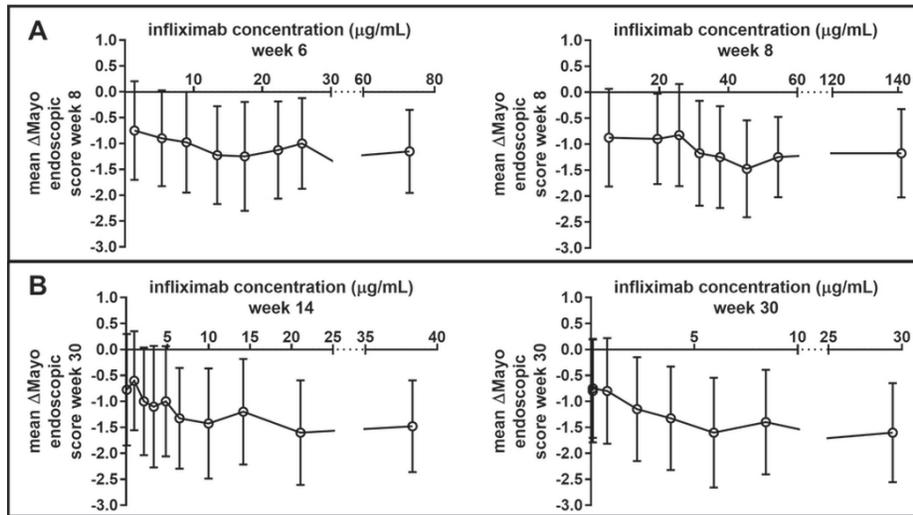
Serum adalimumab concentration 3 months after surgery is correlated with endoscopic recurrence in Crohn’s disease patients treated with adalimumab for prevention of postoperative recurrence

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Background: Despite the use of anti-TNF therapy for prevention of postoperative recurrence, more than 20% of Crohn’s disease (CD) patients present an endoscopic recurrence 6 months after surgery. The aim of our study was to assess the relationship between serum adalimumab (ADA) concentration 3 months after surgery and endoscopic recurrence at 6 months in CD patients treated with adalimumab for prevention of postoperative recurrence.

Methods: This was a prospective, multicenter study between January 2014 and March 2016. All CD patients who underwent an ileocecal resection with ileocolonic anastomosis and were treated with ADA monotherapy (introduced one month after surgery subcutaneously with 160 mg at week 0, 80 mg at week 2 and then 40 mg every



Abstract DOP033 – Figure 1. IFX concentration-effect curve. Each point is the median of ≥ 40 IFX concentrations at specified time-points, stratified in ascending order with corresponding change (Δ) in MES (with standard deviation) from (A) Week 0 to 8 and (B) Week 0 to 30.

Abstract DOP033 – Table 1. Association between IFX cut-points and endoscopic outcomes

Outcome	IFX time point	IFX threshold (μ g/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUROC (95% CI)	P-value
W8 MES<2	W2	26	71	43	66	59	0.571 (0.518-0.624)	0.008
	W6	11	84	40	70	59	0.643 (0.590-0.696)	<0.001
	W8	35	72	54	74	52	0.646 (0.592-0.701)	<0.001
W8 MES<1	W2							NS
	W6	11	88	30	31	87	0.592 (0.536-0.648)	0.002
	W8							NS
W30 MES<2	W14	5.0	67	62	72	56	0.687 (0.635-0.739)	<0.001
	W30	2.3	74	61	79	55	0.709 (0.652-0.762)	<0.001
W30 MES<1	W14	6.6	62	63	46	77	0.650 (0.595-0.705)	<0.001
	W30	3.8	75	60	53	80	0.703 (0.649-0.757)	<0.001

IFX, infliximab; PPV, positive predictive value; NPV, negative predictive value; AUROC, area under receiver operator curve; W, week; MES, Mayo endoscopic score; NS, not significant.

week), for prevention of postoperative recurrence were included in the study. Serum ADA concentration was determined 2 months after ADA introduction. Endoscopic recurrence at 6 months was defined as a Rutgeerts endoscopic score \geq i2.

Results: Fifteen CD patients were included (9 male and 6 female), with a median age of 24 years-old [15–47]. Disease phenotype was considered as penetrating in 8 patients (53%), stricturing in 5 patients (34%) and inflammatory in 2 (13%). Eight (53%) patients had an isolated ileal disease and 7 (47%) an ileocolonic location. Eight patients (53%) had at least 2 risk factors for postoperative recurrence according to ECCO guidelines and 14 (93%) were already treated with anti-TNF before surgery. The overall endoscopic recurrence rate was 46.7%. The median serum ADA concentration 3 months after surgery was 7.9 μ g/mL (0.04–11.8) and no patient had anti-ADA antibodies. Median serum ADA concentration was significantly higher in CD patients without endoscopic postoperative recurrence compared to CD patients with endoscopic postoperative recurrence (8.2 μ g/mL vs 2.5 μ g/mL, $p=0.121$). According to Rutgeerts score, the median serum ADA concentration was 8.2, 5.1 and 0.2 mg/mL in patients with a score \leq i1, i2 and \geq i3, respectively ($p=0.033$). Indeed, the serum ADA concentration was inversely correlated to the Rutgeerts score (Pearson coefficient = -0.61 , $p=0.015$). The ROC curve analysis demonstrated a specificity of 71% and a sensitivity of 87% for serum ADA concentration threshold of 4 μ g/mL to predict endoscopic recurrence (area under the curve = 0.75 ± 0.14). Thus, 83% of CD patients with a serum ADA concentration < 4 μ g/mL had an endoscopic recurrence, compared to 22% of CD patients with a serum ADA concentration > 4 μ g/mL ($p=0.04$).

Conclusions: In our study, there was a significant correlation between serum ADA concentration 3 months after surgery and endoscopic postoperative recurrence at 6 months in CD patients treated with ADA to prevent postoperative recurrence.

DOP035

High gammaglobulin and low albumin serum levels independently predict secondary loss of response to anti-TNF α therapy in IBD

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Background: Loss of response to biological therapy with anti-TNF α drugs occurs frequently in patients with IBD. Possible markers to predict sustained treatment success are currently under investigation. We evaluated the predictive value of serum albumin and gammaglobulin levels for the success of an anti-TNF α treatment in IBD.

Methods: In a prospective trial we included all patients treated with either infliximab or adalimumab for IBD in our outpatient clinic between 2007 and 2015. Secondary loss of response (SLR) was defined as the necessity to increase the dose or to reduce treatment intervals after an initial response to therapy. In addition, trough levels of adalimumab or infliximab and anti-drug antibody concentrations have been measured since they were available. Prior to the initiation of biological treatment all patients were tested for serum- albumin and serum- gammaglobulin levels.

Results: 82 patients (42 female, 40 male; age 39.5 ± 13.5 years) were included in the study. 65 patients with Crohn's disease and 17 patients with ulcerative colitis. Of these patients 66 (80.5%) were treated with infliximab and 16 (19.5%) received adalimumab first line. 7 patients (8.5%) were primary non responders, 29 patients (35.4%) showed a sustained remission under treatment and 46 patients (56.1%) developed a SLR. Of these, 11 patients (23.9%) ex-

perienced loss of response within the first year of treatment, 14 patients (30.4%) during the second year of treatment and 21 patients (45.7%) after more than two years of treatment (Mean time to SLR 25.7 ± 16.1 months). Albumin levels in the sustained response group were significantly higher compared to SLR (37.6 ± 1.3 g/dl vs. 34.4 ± 0.7 g/dl; $p < 0.05$). Gammaglobulin levels in the sustained response group were significantly lower compared to SLR (12.8 ± 0.9 g/dl vs. 17.41 ± 0.9 g/dl; $p = 0.001$). Hypoalbuminemia and/or hypergammaglobulinemia were independently associated to the loss of response.

Conclusions: Our study supports previous investigations showing that low albumin levels at the beginning of an anti-TNF α therapy are strongly associated to treatment failure. To our knowledge, this is the first report to show that increased gammaglobulin levels prior to the initiation of a biological therapy in IBD are independently associated and predictive to identify patients with a higher risk for loss of response to an anti-TNF α treatment. Increased serum gammaglobulines represent a higher B-cell activity with either a higher risk to produce anti-drug antibodies, a different phenotype of disease less responsive to anti-TNF α treatment or both.

DOP036

The therapeutic efficacy of anti-TNF requires Fc-gamma receptors and can be improved by antibody hypo-fucosylation

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Background: Treatment with the IgG1 anti-TNF antibodies infliximab and adalimumab achieves complete mucosal healing in a considerable proportion of patients with Crohn's disease. In contrast, the Fab' fragment certolizumab showed only 4% endoscopic remission. These observations suggest that the Fc-region of anti-TNF contributes to the induction of mucosal healing. We have previously showed that anti-TNF induces CD206+ regulatory macrophages and that these macrophages were increased in the lamina propria of anti-TNF responders, but not in non-responders. Here, we investigate the importance of Fc-gamma receptor (Fc γ R) engagement by anti-TNF for achieving therapeutic efficacy in IBD.

Methods: Rag1 $-/-$ mice lacking all activating Fc γ R were generated. We constructed hypo-fucosylated anti-murine TNF and hypo-fucosylated adalimumab. *In vivo* studies were performed in the T-cell transfer colitis model. For *in vitro* studies, T-cell proliferation and CD206+ macrophage percentages were measured in mixed lymphocyte reactions containing human PBMC from healthy donors.

Results: Anti-TNF treatment achieved near complete intestinal healing in the T-cell transfer model. However, mice lacking Fc γ R were completely unresponsive to anti-TNF therapy. In line with our previous human data, colons of mice treated with anti-TNF contained increased amounts of CD206+ macrophages, but this effect was completely abrogated in animals mice lacking Fc γ R. *In vitro* studies revealed that blocking Fc γ R III impaired the generation of human CD206+ macrophages. Further emphasizing the role of Fc γ R III, CD206+ macrophage formation was increased in cultures composed

of cells homozygous for high affinity FcγRIIIa158V compared to low affinity FcγRIIIa158F. Interestingly, hypo-fucosylation of the antibody Fc region enhances binding affinity specifically for FcγRIIIa. Indeed, hypo-fucosylation of anti-TNF increased the amount of CD206+ macrophages *in vitro*, especially for cells expressing low affinity FcγRIIIa158F. Finally, hypo-fucosylated anti-TNF increased the generation of CD206+ macrophages in the colon and displayed significantly improved therapeutic efficacy *in vivo*.

Conclusions: FcγR engagement by anti-TNF is required for the therapeutic efficacy in IBD. Increasing the Fc binding affinity of anti-TNF with hypo-fucosylation significantly improved therapeutic outcome. Anti-TNF therapy currently achieves mucosal healing in less than 50% of patients, antibody glycoengineering could be an effective future strategy and might be of special interest for patients carrying the low affinity FcγRIIIa158F allotype.

DOP Session 5: Surgical treatment

DOP037

A model for prediction of early surgery and complications in paediatric Crohn's disease: results of the prospective GROWTH CD study

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Background: Children with Crohn's disease (CD) are at a high risk for complications from both disease and treatment. The ability to predict risk and adverse outcomes at or close to diagnosis would allow patients to be stratified by risk, in order to avoid under treatment or overtreatment while reducing adverse outcomes from drug and disease. The goal of the current prospective study was to identify factors that would predict early complicated disease behavior or surgery.

Methods: The GROWTH CD study (Growth, Relapses and Outcomes With Therapy) is geared to identify factors that could predict early outcomes such as complications (stricturing, penetrating or perianal abscess) and surgery by 24 months. Newly diagnosed children underwent colonoscopy, gastroscopy and imaging. They were phenotyped by the Paris classification and followed at baseline, 8, 12, 26, 52, 78 and 104 weeks. Twenty dichotomous and continuous variables were assessed, including serum biomarkers (ASCA, CBIR1, OMPC), measures of inflammation (ESR, CRP, Calprotectin), disease activity (PCDAI and PGA) and serum albumin. Predictors at

diagnosis and week 12 (post induction treatment) served as prediction time points. Complications and surgery were recorded at weeks 78 and 104. Logistic regression and risk modeling was performed for best fit models.

Results: 285 children, median age 13 yrs, 60% male, were followed prospectively for 2 years, of whom 78 (27.3%) developed complications and 28 (9.8%) required surgery. Use of immunomodulators by 12 weeks was not associated with decreased risk, (complications and surgery both $p=0.9$). Presence of a complication at diagnosis and PCDAI > 30 at week 12 (OR 4.2, CI 1.16–16.77) $p=0.03$, were predictive of complications. Five parameters predicted increased risk of surgery (high ESR > 50 wk 0, stricturing disease at diagnosis, ASCA, hypoalbuminemia or elevated PCDAI > 10 at week 12). The first 4 remained in the best fit model. The combination of Paris B2 (OR 4.2, CI 1.3–12.7) $p=0.01$, ESR > 50 (OR 2.9, CI 1.004–8.642) $p=0.049$ at baseline, and Alb < 3.6 (OR 4.9 CI 1.2–19.6), $p=0.024$, and ASCA IgA (OR 1.02, CI 1.007–1.03) $p=0.001$ after therapy week 12, had a sensitivity 10%, specificity 98.7%, PPV 50% and NPV 89.4%, the model is significant ($p < 0.0001$) and correctly classifies 88.6% of the study population requiring early surgery. CRP and fecal calprotectin were not predictors of complications or surgery at either time point.

Conclusions: We identified a prediction model for early high risk disease based on risk for early surgery in paediatric CD. We could not accurately predict risk of early complications with the biomarkers used. Fecal calprotectin and CRP were not predictive at any time point.

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DOP038

Increased number of enteric glial cells in proximal margin of resection is associated with postoperative recurrence of Crohn's disease

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Background: The enteric nervous system can amplify or modulate intestinal inflammation through secretion of neuropeptides, and enteric glial cells has been implicated in the pathophysiology of Crohn's disease. The goal of the study was to search for an association between the density of neurons, neuropeptides, as well as enteric glial cells and postoperative disease recurrence in patients with Crohn's disease.

Methods: Ileocolonic samples obtained from 30 patients with Crohn's disease receiving azathioprine for prophylaxis in our previously reported clinical trial. The ileal proximal uninfamed section was studied using immunohistochemistry with antibodies directed against vasoactive intestinal polypeptide (VIP), substance P (SP), neuron-specific enolase (NES), and the glial marker protein S100. The density in the submucosa was defined as the ratio between the cumulated surface area and the total microscopic fields, and was expressed as mean percent. The relationship of the density of VIP, SP, NES, and S100 and postoperative disease recurrence was assessed.

Results: There were no significant differences between patients with and without postoperative endoscopic recurrence for the density of NSE-positive (3.38±1.22 versus 3.75±1.45, $p=0.481$), VIP-positive (1.51±0.62 versus 1.24±0.82, $p=0.320$) or SP-positive neurones (1.63±0.94 versus 1.21±0.32, $p=0.201$) in the proximal margin. Interestingly, a significant difference was found concerning the number of EGC (S100-positive) (1.39±0.41 versus 0.55±0.29, $p < 0.001$) in endoscopic recurrence than in cases without endoscopic recur-

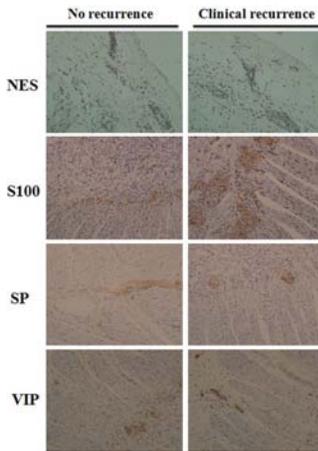


Figure 1. NES, S100, SP, and VIP immunoreactivity in the submucosa of ileal proximal uninfamed section from patient with and without Crohn's disease recurrence.

rence. No differences were found between patients presence and absence of postoperative clinical recurrence in terms of NSE-positive (3.75 ± 0.61 versus 3.40 ± 1.45 , $p=0.528$), VIP-positive (1.26 ± 0.36 versus 1.49 ± 0.76 , $p=0.418$) or SP-positive neurones (1.49 ± 0.97 versus 1.51 ± 0.79 , $p=0.965$). However, the density of S100-positive enteric glial cells (1.70 ± 0.38 versus 0.93 ± 0.43 , $p<0.001$) was significantly increased in patients with clinical recurrence than in subjects without clinical recurrence (Figure 1).

Conclusions: Increased S100-positive enteric glial cells is associated with high risk of both endoscopic and clinical recurrence after surgery. These findings have implications in individualized postoperative prophylaxis for Crohn's disease.

DOP039

Postoperative infectious complications in Crohn's disease: results from PRACTICROHN study

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Background: Crohn's disease (CD) surgery is related to postoperative complications in 11 to 14% of all cases. Infectious complications (IC) are the most common. The aim of this study is to describe the prevalence and factors associated with the postoperative IC in a cohort of patients with CD

Methods: PRACTICROHN was a study that included patients aged ≥ 18 years-old from 26 spanish centers who underwent CD-related ileocolonic or ileorectal resection with ileocolonic or ileorectal anastomosis between January 2007 and December 2010. Clinical data and treatments, including surgery was retrospectively collected from medical records. IC analyzed were: intra-abdominal abscess, wound infection, catheter-related sepsis and extra-abdominal infections. Categorical variables were compared with the χ^2 test or Fisher's exact test Kaplan-Meier method was used to assess time to clinical recurrence and a log-rank test to obtain statistical significance.

Results: Three hundred and sixty four patients were analyzed (mean age 32 years [SD13], 50% men). Median time from CD diagnosis to surgery was 6 years (IQR 1–12). Indication for surgery was: structuring disease ($n=169$, 48%), penetrating ($n=114$, 45%), penetrating +stricturing ($n=51$, 14%) and/or resistance to treatment ($n=21$, 6%). Sixty nine patients presented some IC (19%), with a hospitalization of median 19 days (IQR 10–30) vs 9 days (IQR 7–12) in patients without IC ($p<0.001$). The most frequent IC were wound infection (33/69, 48%) and abscess (28/69, 40%); extra-abdominal infections

Abstract DOP039

Table 1

Reason for surgery	Total sample n=364	Without ICs n=294	ICs n=69	p
Penetrating disease, n(%)	165(45.33)	136 (46.26)	28 (40.58)	0.472
Abscess, n(%)	77(46.67)	63 (46.32)	14 (50.00)	0.883
Mass, n(%)	61(36.97)	50 (36.76)	11 (39.29)	0.971
Fistulae, n(%)	85(51.52)	72 (52.94)	12 (42.86)	0.445
Perforation, n(%)	38(23.03)	27 (19.85)	11 (39.29)	0.048
Stenosis, n(%)	220(60.44)	184 (62.59)	36 (52.17)	0.145
Resistance to treatment, n(%)	132(36.26)	106 (36.05)	26 (37.68)	0.909

Abstract DOP039

Table 2

Treatment received	No IC	IC	p
Corticosteroids, n (%)	70 (24.48)	20 (29.85)	0.452
Immunosuppressants, n (%)	133 (45.70)	32 (47.76)	0.866
Anti-TNF, n(%)	49 (16.84)	15 (22.39)	0.372

(12/69, 17%) and infections of the catheter (4/69, 5%). No IC was associated with mortality. IC were more frequent in patients in which perforation was the reason for surgery (11/69 vs 27/69 $p=0.048$). No differences in IC were observed related to age, gender, smoking habit location or length of intestinal resections. No treatment was correlated with a higher rate of IC.

Conclusions: 19% of patients who underwent a CD related surgery presented a postoperative IC, with perforation as the most common cause of surgery-associated IC. Type of CD treatments was not associated with the occurrence of IC.

DOP040

Postoperative surgical recurrence in Crohn's disease decreases significantly in the biologic era

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Background: A large proportion of Crohn's disease (CD) patients undergo bowel resection within 10 years after diagnosis. Previous reports estimated postoperative surgical recurrence rates around 30–50% within 10 years. However, pre- and postoperative treatment paradigms have shifted significantly over the past decades. In this study, we aimed to assess recent time trends of ileocecal resection (ICR) in CD patients and postoperative surgical recurrence.

Methods: Adult CD patients who underwent ICR in the period from January 1991 to December 2015 were identified in PALGA, the Dutch nationwide histopathology archive. Histology reports on oncologic resections and tissue revision were excluded. Data on demographics, ICRs and subsequent bowel resections were recorded. Surgical recurrence was defined as a re-resection of the colon, small bowel or rectum. Follow-up data were evaluated to December 2015. Survival data on patients without follow-up in the database were imputed using survival data of the general Dutch population. Patients were divided into four groups according to year of ICR to evaluate time trends. Risk of surgical recurrence was assessed using Kaplan-Meier survival statistics. Hazard ratios (HR) were assessed using Cox regression.

Results: The identified cohort comprised 2614 CD patients (M 979/ F 1635), who underwent ICR at a median age of 31.0 years (IQR 25–45). An increase in the absolute number of ICRs was observed during the study period, from 471 in the period 1991–1996, 610 in 1997–2002, 605 in 2003–2008, to 928 in 2009–2015.

A total of 542 patients underwent re-resection after a median follow-up of 5.6 years (IQR 2.2–10.1). The overall risk of re-resection af-

ter 5, 10 and 20 years was 7.7%, 15.7% and 28.0% respectively. The 5-year risk of re-resection after ICR decreased significantly during the study period from 13.6% in 1991–1996 to 7.0% in 1997–2002, 6.7% in 2003–2008 and 4.8% in 2009–2015. The 10-year risk decreased from 24.7% in 1991–1996 to 14.0% in 1997–2002 and 13.8% in 2003–2008. Corresponding HRs were 0.55 for 1997–2002, 0.52 for 2003–2008 and 0.36 for 2009–2015.

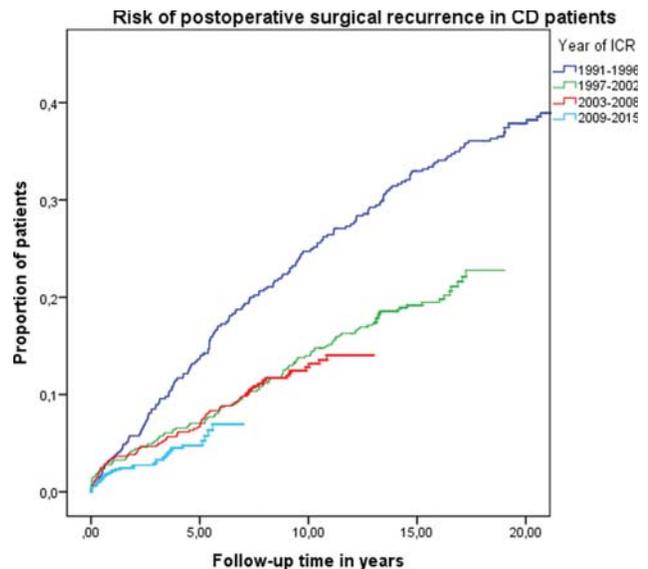


Figure 1. Risk of postoperative surgical recurrence in Crohn's disease patients.

Conclusions: CD patients have an overall risk of postoperative surgical recurrence of 8% within 5 years and 16% within 10 years after ICR. The risk of surgical recurrence within 5 years has declined significantly with an absolute risk reduction of 9% during the period from 1991 to 2015. This observation might be explained by implementing improved (post)operative treatment strategies, including availability of biologics.

DOP041

Prepouch ileitis after ileal pouch anal anastomosis for ulcerative colitis: patterns of presentation and risk factors for failure of treatment

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Background: Ileal pouch anal anastomosis (IPAA) after proctocolectomy for ulcerative colitis could be complicated by the prepouch ileitis (PI), a still unperceived condition which presents as an inflammation of the afferent limb of the pouch. Little is known about the onset of disease and the factors associated with more aggressive patterns and failure of treatments

Methods: From a prospectively maintained database of 1238 IPAA's performed in a single centre since 1985, all cases with a diagnosis PI were selected. Data concerning the outcomes of the IPAA, diagnosis and treatment of PI and long-term follow-up were compared between a subgroup of patients requiring surgery (SURG) or not (NOSURG) for the treatment of PI

Results: 59 patients (4.6% of IPAA) were included. 19 (32.2%) required surgery at some point. At the time of the IPAA a higher rate of extraintestinal diseases (27.8 vs 10%, $p=0.05$) and ASA score 3 (21.4

vs 0%, $p=0.01$) were seen in SURG group. PI was diagnosed after 5 and 6.3 years from the IPAA in SURG and NOSURG groups ($p=0.4$). At diagnosis, SURG group had a higher rate of outlet obstruction (47.4 vs 2.7%). The endoscopy revealed a significantly higher rate of afferent limb stenosis (68.4 vs 33.3%, $p=0.01$) in the SURG group and of pouchitis (94.6 vs 68.4%, $p=0.008$) in the NOSURG one. SURG patients were more likely to receive steroids (77.8 vs 45.7%, $p=0.02$), anti TNF- α (44.4 vs 20%, $p=0.05$) than NOSURG patients, while a similar rate of patients had antibiotics, immunosuppressors or endoscopic treatment. Clinical and/or endoscopic response to antibiotics (0 vs 56.6%, $p<0.001$), steroids (7.1 vs 37.5%), immunosuppressors (0 vs 50%, $p=0.02$) or anti TNF- α (0 vs 50%, $p=0.01$) was significantly lower in SURG group. Only the endoscopic treatment had similar temporary success between groups (40 vs 66.6%, $p=0.4$).

In the SURG group, 10 partial ileal resections (52.6%), 4 ileostomies (21.1%), 2 pouch excisions (10.5%), 2 stricturoplasties (10.5%), 1 redo pouch (5.3%) were performed. The histological examination revealed Crohn's disease in 5 (31.2%) and non specific inflammation in 14 (68.8%) patients. Three (15.8%) patients had postoperative complications. After a median follow up time from PI diagnosis of 97 and 76 months ($p=0.3$), the 3, 5 and 10 year pouch failure rates in SURG and NOSURG groups were 12.2 vs 3.2%, 26.2 vs 4.2% and 45.3 vs 17.3%, respectively ($p=0.007$).

Conclusions: Prepouch ileitis occurs in about 5% of IPAA patients and is associated with Crohn's disease only in a minority of cases. A conspicuous rate of those patients require multiple medical and endoscopic treatments. Especially when a stricture persists, a lack of response to treatment usually leads to surgery and to a much higher chance of pouch failure.

DOP042

Omentectomy is not necessary during laparoscopic total colectomy and ileal pouch-anal anastomosis for inflammatory bowel disease. A comparative study in 247 consecutive patients from 4 expert centres

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Background: Today, there is no consensus about the indication of associated omentectomy during the (sub)total colectomy. Data about its impact on later small bowel obstruction are conflicting. The objective was thus to evaluate possible impact of omentectomy during total colectomy and ileal pouch-anal anastomosis (IPAA) for inflammatory bowel disease.

Methods: All the patients who underwent laparoscopic 2-stage IPAA for inflammatory bowel disease from 2005 to 2015 in 4 expert European centres were included and divided into 2 groups: omentectomy (Group A) and no omentectomy (Group B). Comparisons were performed between groups for the following findings: demographic features, inflammatory bowel disease characteristics, preoperative treatment in the three last months, intraoperative features, postoperative outcomes and long-term results.

Results: During the study period, 247 patients (148 males, median age =45 [14–78] years) were divided into Groups A ($n=109$) and B ($n=138$). Patients in Gr. A were more frequently under steroids before

IPAA (63% vs 50%, $p=0.04$), and required more frequently conversion into laparotomy (6% vs 1%, $p=0.02$). Surgical morbidity rate (31% vs 33%, $p=0.78$), Dindo ≥ 3 morbidity (35 vs 39%; $p=0.84$) and unplanned reoperation (12 vs 16%; $p=0.46$) rates were similar in both groups. Median length of stay was longer in Gr. A than B (12 vs 10 days; $p<0.0001$). At the end of follow up, small bowel obstruction rate was higher in Gr. A than Gr. B (10 vs 1%; $p=0.003$).
Conclusions: This study suggests that omentectomy during laparoscopic IPAA do not modify operative results but seems to increase conversion rate, length of stay and long-term small bowel obstruction rates. Thus, omentectomy is probably not necessary during laparoscopic IPAA.

DOP043

High risk of pouch dysplasia in IBD-PSC patients following total proctocolectomy

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Background: Patients with inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC) have an increased risk of colorectal neoplasia compared to patients with IBD alone. Data on risk of pouch-related dysplasia following total proctocolectomy with ileo-anal anastomosis (IPAA) in this high-risk group are scarce. Nevertheless, some authors recommend yearly surveillance pouchoscopies. Our aim was to describe the incidence of pouch dysplasia in IBD-PSC patients after IPAA.

Methods: This is a retrospective analysis of all IBD-PSC patients who underwent IPAA with subsequent surveillance pouchoscopies between 2005–2015 at a single tertiary IBD referral center. Patient demographics, indication for IPAA, as well as gross and histologic findings on pouchoscopy were recorded.

Results: Among 156 patients with IBD-PSC, 18 (16 with ulcerative colitis and 2 with Crohn's disease) underwent IPAA, with a mean follow-up of 3 years. Mean ages for IBD and PSC diagnosis were 25 ± 11 and 34 ± 13 years, respectively; 89% were men. Sixty-seven percent of patients had exposure to ursodeoxycholic acid (UDCA). Indications for IPAA included: refractory colitis (61%, $n=11$), advanced colorectal neoplasia (aCRN: high-grade dysplasia or cancer) (22%, $n=4$), and low-grade dysplasia (17%, $n=3$). Median number of pouchoscopies per patient was 2 (range 1–10). Histologic evidence of chronic pouchitis was present in all cases. During follow-up 11% of patients ($n=2$) developed dysplasia: 1 case of unifocal indefinite dysplasia of the pouch and 1 case of multifocal high-grade dysplasia of the pouch and rectal cuff. Median time between IPAA and dysplasia development was 7 years (range 1–13). Both patients had undergone IPAA for aCRN, had persistent chronic pouchitis and UDCA exposure. Having aCRN as the indication for IPAA was significantly associated with development of pouch dysplasia ($p=0.04$). The cumulative incidence of pouch dysplasia was 5.6% at 1 year and 30% at 13 years after IPAA overall, while the cumulative incidence of pouch dysplasia in patients undergoing IPAA for any aCRN was 25% at 1 year and 63% at 13 years ($p=0.049$ log-rank test; vs other indications for IPAA).

Conclusions: In this relatively small single-center cohort there seems to be a high risk of pouch dysplasia in IBD-PSC patients following IPAA, especially if the indication for IPAA was aCRN. As we await validation of our findings for this high-risk subset of patients, pouch surveillance appears to be justifiable. Larger, multi-center prospective studies with longer follow-up are needed.

DOP044

Relationship between microbiota and development of early postoperative Crohn's disease recurrence

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Background: Dysbiosis of the intestinal microbiota is implicated in Crohn's disease (CD) and may play an important role in triggering postoperative disease recurrence (POR).

We hypothesized that the fecal microbial recolonization process after ileocecal resection differs between patients developing recurrence and patients remaining in remission, and further aimed to identify other factors influencing the microbial composition.

Methods: Fecal samples from 54 CD patients undergoing ileocecal resection were prospectively collected before surgery and at month 1, 3 and 6 after surgery. POR - defined by a modified Rutgeerts score ≥ 2 on endoscopy was assessed at month 6. The microbiota was evaluated by 16S rDNA sequencing using an Illumina MiSeq platform. Calculation of alpha and beta diversity and statistical analysis were performed in QIIME.

Results: Patients developing early POR (N=23) harbored more Coriobacteriaceae, Corynebacteriaceae and Micrococcaceae in their faecal samples before surgery, than patients without recurrence (N=31) ($p < 0.04$). During the first 3 months postoperatively, no significant taxonomic differences were observed between both patient groups. At month 6, recurrence patients had a higher relative abundance of Fusobacteria (FDR=0.09). The impact of resection on the fecal microbiome was shown by an increase of Negativicutes (FDR=0.02) and reduction of Bifidobacteriales (FDR=0.04) in all CD patients whereas recurrence patients additionally were marked by an increase of Fusobacteria (FDR=0.03) and decrease of Faecalibacterium ($p=0.04$).

Smoking (N=16) was not associated with early POR in this cohort, but smoking did impact on the fecal microbiota. Alpha diversity was significantly reduced in active smokers at baseline ($p=0.028$), month 3 ($p=0.016$) and month 6 ($p=0.023$) after surgery. In general, smokers were characterized by an enrichment of Veillonellaceae (FDR=0.09) and reduction of Ruminococcaceae (FDR=0.005) and Lachnospiraceae (FDR=0.03). Within these families, the relative abundance of essential types of butyrate and other short-chain fatty acids-producing bacteria such as Faecalibacterium, Roseburia, Dorea, Coprococcus, Blautia and Ruminococcus were depleted.

Conclusions: Ileocecal resection has an impact on the fecal microbiota composition which mostly affects members of Negativicutes and Bifidobacteriales. The microbial differences between patients developing recurrence and patients remaining in remission are minor during the first 3 months whereas early recurrence at month 6 was mainly associated with an enrichment of Fusobacteria. Although

smoking was not associated with early POR, it did show a significant impact on the microbial composition which might have potential implications at later stages of the disease.

DOP045

Post-operative complications in elderly-onset inflammatory bowel disease: a population-based study

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Background: Inflammatory Bowel Diseases (IBD) diagnosed after the age of 60 are increasing. Surgical rates are similar to those in the younger population. Post-operative complications (POC) in elderly-onset IBD have never been investigated at the population level. We reported the incidence and factors associated with POC in a well-defined population-based registry.

Methods: Among 841 elderly-onset IBD patients from the EPIMAD registry (1), 139 (16.5%) patients underwent surgery: 100 had Crohn's Diseases (CD) and 39 ulcerative colitis (UC). Medical charts for early (≤ 30 days of surgery) and late (> 30 days of surgery) POC were reviewed using the Dindo's classification (2). Associated factors were analyzed by logistic regression for early POC and Cox regression models for late POC.

Results: After a median follow-up of 7.3 years [Q1=3-Q3=12], 50 patients (50/139, 36.0%) had at least one POC (n=69), without significant difference between UC and CD. Thirty-two early POC were observed in 23 of 50 patients; 48% of POC (15/32) were infectious and 52% of patients (12/23) had severe POC (defined by a Dindo's grade > 2). Six (6/23, 26%) patients died because of early POC. Among the 37 late complications observed in 33 patients, 56% of POC (20/37) were mechanical (bridle, eventration, anastomotic stricture) and 42% of patients (15/33) had severe POC. The cumulative probability of late POC was 10.9% at 1 year (6.5–18.1), 22.8% at 5 years (16.0–32.0) and 30.5% (21.8–41.4) at 10 years. In multivariate analysis, emergency surgery (HR=4.46 [1.75–11.36]) and acute severe ulcerative colitis (HR=7.84 [2.15–28.52]) were significantly associated with early POC. Female gender (HR=2.10 [1.01–4.37]) and time between diagnosis and surgery > 3 months (HR=2.09 [1.01–4.31]) were significantly associated with late POC.

Conclusions: In elderly-onset IBD patients who underwent surgery, POC were frequent and half of them were severe. Emergency surgery and acute severe ulcerative colitis were significantly associated with early complications, while female gender and delay between diagnosis and surgery were associated with late POC. These results reinforce the need for specialized and dedicated management of elderly patients undergoing surgery.

References:

- [1] Charpentier et al. Gut 2014
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DOP Session 6: Towards personalised medicine

DOP046

Genome-wide association study of baseline disease characteristics and response to Ustekinumab in moderate to severe Crohn's disease

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Background: Both genetic & environmental risk factors contribute to Crohn's disease (CD) susceptibility, & genetic biomarkers may allow for the characterization of disease activity & severity as well as response to therapeutic agents. Here, we evaluated the association of genetic polymorphisms with baseline disease characteristics & the response to ustekinumab (UST), an anti-IL12/23p40 monoclonal antibody, in the phase 3 UNITI program.

Methods: The UNITI studies assessed the safety & efficacy of UST induction & maintenance therapy in patients (pts) with moderate-severe CD who had previously failed TNF-antagonist therapy (UNITI-1) or who had previously failed conventional therapy & were largely TNF antagonist-naïve (UNITI-2). Pts that responded in the induction studies were re-randomized in IM-UNITI maintenance study. 902 pts were genotyped genome-wide on the Illumina Infinium Omni5Exome platform (UNITI-1 n=479, UNITI-2 n=423). We evaluated genetic associations with baseline disease, induction wk8 response, & maintenance wk44 response phenotypes using linear or logistic regression models. Analyses were conducted separately within each study & meta-analyzed. We performed both targeted & genome-wide analyses, where the targeted analyses evaluated associations with 185 candidate SNPs in the IL12/23 pathway or previously associated with IBD risk. Significance thresholds were set at 2.7×10^{-4} for candidate gene analyses & 5×10^{-8} for the GWAS to account for multiple testing.

Results: We did not identify any statistically significant associations with IL12/23 candidate SNPs, suggesting that pts respond equally well to UST regardless of genotype or that we did not have the power to detect these associations given our limited sample size. GWAS analyses identified two associations with response phenotypes that met statistical significance. The first was an association at a locus upstream of the TWSG1 gene on chromosome 18; these SNPs were associated with change in CDAI & remission at wk8, where pts carrying the minor allele had better response to UST. Interestingly, SNPs at this locus have been associated with TWSG1 expression within the GTEx dataset (www.gtexportal.org), suggesting a possible functional link. The second association was between change in CDAI at wk8 & an intergenic locus on chromosome 8 located between the SFRP1 & GOLGA7 genes, where pts carrying two copies of the minor allele had the greatest decrease in CDAI after treatment.

Conclusions: These results suggest that SNPs in the IL12/23 pathway & SNPs associated with IBD disease risk may not influence responses to UST. Additionally, the genome-wide analyses nominate new candidate genes that may be influencing UST response, although these results must be replicated in an independent cohort.

DOP047

Early fibrostenosis in Crohn's disease is associated with multiple susceptibility loci on ImmunoChip analysis

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Background: Fibrostenosis is a common complication of Crohn's disease (CD) occurring in 30% of patients. Although the pathophysiology of intestinal fibrosis is incompletely understood, evidence suggests a genetic contribution. Previous genetic association and candidate gene studies were based on clinical definitions which lack both sensitivity, specificity and have a high inter-observer disagreement. Additionally, the recent genotype-phenotype analysis by the IIBDGC did not consider the time to development of fibrostenotic disease. As the genetic risk may be more important in patients with early fibrostenosis, we aimed to identify novel genetic markers by focussing on early fibrostenotic disease.

Methods: In this multicenter, retrospective nested case-control study computed tomography (CT) and magnetic resonance imaging (MRI) from CD patients obtained between 2002 and 2016 were examined for the presence of ileal fibrostenotic disease. Patients with early fibrostenosis, defined as the presence of bowel thickening with luminal narrowing and prestenotic dilatation on CT/MRI occurring within 5 years following diagnosis of ileal or ileocolic disease (Montreal L1 or L3), and with available Illumina ImmunoChip data were included. The control cohort consisted of inflammatory CD patients (Montreal L1 or L3) without arguments for fibrostenotic disease after minimum 10 years follow up. Allelic association was assessed using PLINK v1.07.

Results: In total 3024 CT or MRI scans of 2042 CD patients were screened. 112 patients were selected because of fibrostenosis occurring within 5 years of diagnosis. Of these, ImmunoChip data were available in 60 cases and 49 (82%) had confirmed stenosis on histopathology. 343 inflammatory CD controls with genotype data were included in the analysis. Of the 156,500 SNPs analysed, only rs35223850 in the MIS18BP1 gene passed genome-wide significance level for association with early fibrostenosis. The protein encoding MIS18BP1 is known to bind to the SP1 transcription factor which has been associated with cardiac, liver and kidney fibrosis. Five additional SNPs reached a statistically suggestive significance level of $p < 5 \times 10^{-6}$, including rs116630177 in the IL23R gene, which has previously been associated with systemic sclerosis.

Table 1. Identified SNPs associated with early fibrostenosis

SNP	Minor allele	Chromosome	Gene	p-value	OR	Freq cases	Freq controls
rs35223850	A	14	MIS18BP1	8.32×10^{-7}	3.945	17.5%	5%
rs116630177	A	1	IL23R	1.63×10^{-6}	NA	3%	0%
rs17554931	A	19	GPX4	3.39×10^{-6}	3.998	15%	4.2%
rs113661016	A	6	Intergenic region	4.80×10^{-6}	10.58	5%	0.5%
rs12072417	C	1	Genomic	7.45×10^{-6}	8.09	6%	0.8%
rs4925207	G	20	CDH4	4.94×10^{-6}	3.36	19%	6%

Conclusions: This carefully phenotyped study reveals an important

role for genetic contribution to early development of fibrostenotic complications in CD. Our data suggest a role for MIS18BP1 and the SP1 transcription factor as well as the IL23 pathway in the pathogenesis of early intestinal fibrosis.

DOP048
PROFILE trial: predicting outcomes for Crohn’s disease using a molecular biomarker

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Background: The course of Crohn’s disease (CD) varies substantially between affected individuals, but reliable prognostic markers are not available in clinical practice. This hinders disease management because patients with aggressive disease will be undertreated by conventional “step-up” therapy, while those with indolent disease would be exposed to the risks and side-effects of unnecessary immunosuppression if a “top-down” approach was indiscriminately used. Previously, we have described a transcriptional signature that is detectable within peripheral blood CD8 T cells at diagnosis and which correlates with subsequent disease course. To overcome the technical challenges of separating cell populations, which would not be possible in a routine clinical setting, we sought to develop a whole blood qPCR-based biomarker that can re-capitulate the CD8 subgroups without the need for cell separation. Here we describe the development and

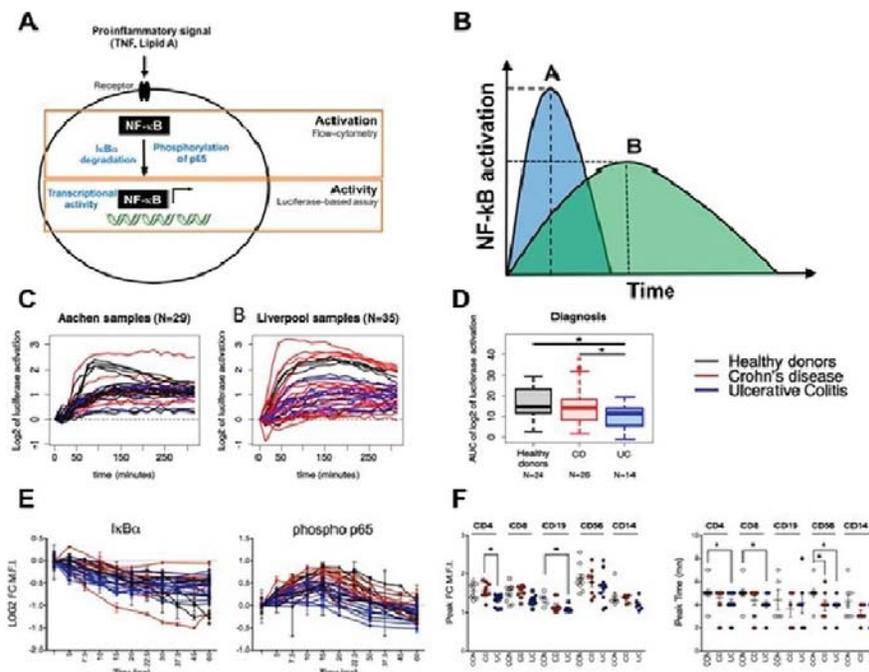
validation of this biomarker and the upcoming biomarker-stratified trial that will test whether it can deliver personalised medicine in CD. **Methods:** From a training cohort of 67 newly diagnosed IBD patients, we simultaneously obtained a whole blood PAXgene RNA tube and peripheral blood CD8 T cell sample. Gene expression in both samples was measured by microarray. After confirming that the CD8 transcriptional signature was detectable and correlated with prognosis, we used machine learning to identify a transcriptional classifier in whole blood gene expression data that would re-capitulate the CD8 transcriptional subgroups. This was initially trained using leave-one-out cross-validation, and the genes identified were subsequently tested by qPCR and optimized to produce an 18 gene qPCR assay.

Results: Independent validation of this biomarker was established using a second, independent cohort of 85 newly diagnosed patients with CD from 4 sites around the United Kingdom. This validated the biomarker and confirmed that the subgroups it identified had significantly different disease courses (analogous to those observed with the CD8 T cell subgroups). The hazard ratio for time to treatment escalation in this validation cohort was 3.52 (1.84–6.76, 95% confidence intervals, p=0.0002). We now propose to conduct the first ever biomarker-stratified trial in any inflammatory disease to determine whether this biomarker can deliver personalised medicine in CD.

Conclusions: We have developed, optimized and validated a whole blood qPCR classifier that is able to predict disease course from diagnosis in IBD patients. This represents a major step towards personalised therapy in IBD, and we will soon investigate whether this could make personalised medicine a reality in CD.

DOP049
Inflammatory dyskinesia: defects of NF-κB dynamic behaviour as a new potential biomarker for personalized medicine in inflammatory bowel disease

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Abstract DOP049 – Figure 1. NF-κB responses in immune cells of IBD patients and controls.

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Background: To improve stratification and optimize treatment strategies for individuals with inflammatory bowel diseases (IBD) new precision medicine approaches based on innovative biomarkers are needed. Most current biomarkers are collected at fixed time points, while biological processes are intrinsically dynamic. The NF- κ B family of transcription factors regulate immune responses to multiple signals. In this study, two methods were combined to monitor dynamic NF- κ B activation in response to cytokines and LPS in immune cells of control and IBD patients.

Methods: Peripheral blood mononuclear cells (PBMC) were donated by controls (n=40), patients with Crohn's disease (CD, n=50) or with ulcerative colitis (UC, n=30). NF- κ B activation (phosphorylation of p65 and degradation of I κ B α) and transcriptional activity of NF- κ B were assessed by flow cytometry in PBMC-derived immune cells stimulated by TNF, LPS and MDP. Independently, PBMC-derived macrophages were transduced with a lentiviral construct encoding an NF- κ B luciferase reporter. Luciferase activity in response to LPS was quantified. NF- κ B dynamic responses were analysed using the area under the curve (AUC), the peak intensity and time of the response.

Results: NF- κ B activation and activity respectively peak 15mn and 2h following stimulation on average. UC patients displayed significantly lower delayed NF- κ B activation as compared to controls in CD4, CD8 and NK cells while AUC for luciferase activity was significantly lower in both UC and CD patients as compared to controls in PBMC-derived macrophages. Interestingly, 10/26 CD patients exhibited either hyperactive or suppressed NF- κ B activities. compared with control and CD patients. Similar results were obtained with PBMCs collected in two different clinical centres, ruling out a batch effect.

A. Methods B. Hypothetical NF- κ B response profiles C. Luciferase activity in LPS-stimulated macrophages D. Area under the curve of log₂ luciferase activity E. NF- κ B response curves of TNF-stimulated CD4+ cells obtained by flow cytometry. F. Peak intensity and time of NF- κ B responses in different cell types upon TNF stimulation. (* p<0.05)

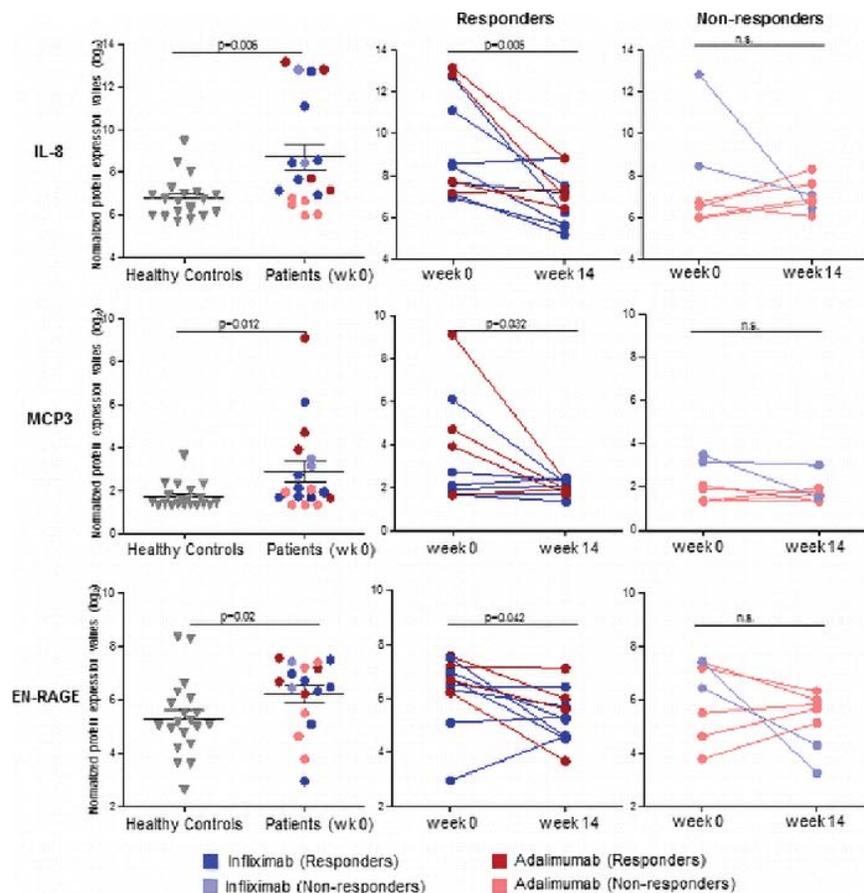
Conclusions: These early findings suggest that NF- κ B dynamic response may provide a new method for stratification of IBD patients. It remains to be seen whether this stratification correlates with other clinically relevant phenotypes

DOP050

Serum proteomic analysis defines novel circulating inflammatory markers for Crohn's disease and response to anti-TNF therapy

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Abstract DOP050 – Figure 1. Circulating biomarkers in CD patients compared to controls and in responders/non-responders following anti-TNF therapy.

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Background: A major challenge in understanding and managing inflammatory bowel disease (IBD) is the tremendous heterogeneity of the disease. Most therapeutic strategies are nevertheless aiming at reducing proinflammatory cytokines such as tumor necrosis factor (TNF). Anti-TNF agents are effective for IBD, but clinical remission and mucosal healing are observed in only 30–50% of patients. This calls for more tailored diagnostic and/or management practices implementing biomarkers of disease activity and predictors of response to therapy.

Methods: Using the Proximity Extension Assay (PEA) technology, proteomic analysis was performed on paired serum samples from 18 patients with Crohn's disease (CD) before (week 0) and after (week 14) initiation of anti-TNF therapy (infliximab and adalimumab), as well as 20 healthy controls. A total of 90 parameters were analyzed with the Proseek Inflammation Panel (OLINK). Patients featuring endoscopic response (evaluated within a median of 41 days after the last sampling date) were grouped as responders. Wilcoxon rank-sum and Mann-Whitney tests (GraphPad Prism) were used and $p < 0.05$ were considered significant.

Results: A biomarker signature was observed for active CD with increased baseline levels of IL-8 ($p=0.006$), MCP3 ($p=0.012$), MCP4 ($p=0.048$), CXCL1 ($p=0.012$), TNFSF14 ($p=0.025$), CASP-8 ($p=0.01$), EN-RAGE ($p=0.02$), PDL-1 ($p=0.003$), TGFbeta1 ($p=0.031$), IL10RB ($p=0.038$), and decreased levels of 4E-BP1 ($p=0.034$) and FGF19 ($p=0.03$) compared to healthy controls. Three markers (IL-8 ($p=0.005$), MCP3 ($p=0.032$) and EN-RAGE ($p=0.042$)) decreased significantly in patients responding to therapy (Figure 1). Decreased levels of additional markers following response to anti-TNF therapy was observed (VEGFA ($p=0.009$), CDCP ($p=0.032$), IL-6 ($p=0.011$), MCP1 ($p=0.027$), IL17A ($p=0.024$), OSM ($p=0.014$), TGFA ($p=0.042$), CCL11 ($p=0.019$) and CCL3 ($p=0.032$). Finally, patients responding to treatment showed higher levels of IL-8 ($p=0.037$), SCF ($p=0.033$) and DNER ($p=0.026$) compared to their non-responder counterparts.

Conclusions: Utilizing the novel PEA technology, we identified a panel of inflammatory markers associated with CD activity. A combination of markers of IL-8, MCP3 and EN-RAGE was associated with response to therapy. Our results show the potential for serum proteomics to identify response following anti-TNF therapy, but validation in an independent cohort is required.

DOP051

Serological biomarkers of tissue turnover can early identify responders to infliximab in Crohn's disease

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Background: Anti-TNF α agents such as Infliximab (IFX) are effective

in inducing and maintaining remission in Crohn's Disease (CD). However, approximately 40% do not reach clinical remission and there are no serological biomarkers available that can predict adequate response. Inadequate response to IFX has been associated with increased submucosal fibrosis. Therefore, we investigated if serological collagen formation and degradation markers could predict for response to IFX.

Methods: Markers for matrix metalloproteinase degraded collagens III and IV (C3M, C4M) and formation of collagens III, IV and V (Pro-C3, P4NP, Pro-C5) were measured using competitive ELISAs in serum from 60 CD patients with active disease, drawn before starting 5mg/kg IFX (week 0), and after 2, 6 and 14 weeks. Clinical disease activity was classified by physician's global assessment (PGA, 0: disease in remission, 1: mild disease, 2: moderate disease, 3: severe disease) and the Harvey Bradshaw Index (HBI). Clinical response was defined as a reduction of >1 in PGA and thereby induction of remission according to PGA and HBI during follow-up due to IFX. Clinical non-response was defined as <2 PGA decrease and IFX failing to induce clinical remission (in PGA and HBI) during follow-up. Patients with clinical response, who stopped IFX due to pregnancy or side effects, were defined as responder.

Results: Sixty patients started IFX after median disease duration of 9.3 years. Forty-four (73%) patients responded, whereas 16 (27%) patients did not respond (median follow-up 3.9 years). None of these patients had primary non-response before week 14. Levels of P4NP and C3M were lower after 2, 6 and 14 weeks in responders.

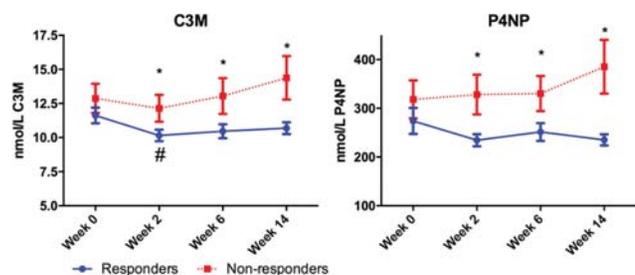


Figure 1. C3M and P4NP serum levels in response to Infliximab. *Significant between responders and non-responders ($p < 0.05$), #Significant compared to baseline ($p < 0.05$). Marker levels are presented as mean and standard error of the mean.

C4M ($p: 0.012$) levels were higher in non-responders at week 14. Pro-C3 levels increased in responders after week 2 and 6 ($p: 0.010$, 0.002 respectively) whether non-responder levels remained stable. P4NP levels at week 2 were able to predict responders (AUC: 0.715). C3M, P4NP and Pro-C5 levels at week 14 were also able to predict responders (AUCs: 0.758, 0.827, 0.730 respectively).

Conclusions: Serological markers for collagen type IV formation (P4NP) and collagen type III degradation (C3M) can identify CD patients responding to IFX within the first 14 weeks of treatment. These markers could be used as early biomarkers for response to IFX and aid in early therapy decision-making.

DOP052

Molecular response to ustekinumab in moderate-to-severe Crohn's disease by serum protein and biopsy gene expression analysis: results from Ustekinumab phase 3 studies

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Background: Objective measures of Crohn's Disease (CD) are sought to monitor disease and therapeutic activity. Biopsy mRNA and serum protein analyses were completed to assess the molecular impact of ustekinumab (UST), an anti-IL-12/23 p40 monoclonal antibody, on CD.

Methods: The phase 3 UNITI-1 & 2 studies evaluated the safety and efficacy of IV UST induction (I) in patients (pts) with moderately-to-severely active CD who had failed ≥ 1 TNF antagonists (UNITI-1) or conventional therapies (UNITI-2). UST induction responders (R) entered IMUNITI to evaluate SC UST maintenance (M) therapy. Gene expression was profiled using biopsies from UNITI-1 (n=69) and UNITI-2 (n=170) pts at Iwk0, Iwk8 & Mwk44. UST effects on transcriptome were assessed via Gene Set Variation Analysis (GSVA). Ten protein analytes including SAA, IL17A & F, MMP1, 3 & 9, MPO, TNFa, IFNg & IL6 were measured in serum from UNITI-1 (n=766) & UNITI-2 (n=593) pts at Iwk0, Iwk6, Mwk8 & Mwk44. Serum and biopsies from 14–30 healthy subjects was analyzed as control (cntl) for each dataset. Modulations with $\text{lfold changel} > 1.5\times$ and $p < 0.05$ were considered significant.

Results: Biopsy Transcriptome: CD expression profiles in UNITI-2 pts were significantly normalized by both UST induction and maintenance therapies while the UST normalization was notable in R in UNITI-1 but not significant. A trend of greater effects with UST 90 mg SC q8w vs q12w was observed in both cohorts at Mwk44. Serum: CD pts in UNITI-1 & 2 had similar serum profiles with SAA, IFN- γ , IL-17A & MMP9 significantly elevated vs healthy cntl while the elevation of SAA was greater in UNITI-1. IFN γ was identified as a pharmacodynamic marker, with similar significant modulation by UST in R and non-responders (NR) (greater effects with UST 6 mg/kg vs. 130 mg dosing), but not in PBO-treated pts. SAA & IL-6 were significantly reduced by UST induction in R and less so or not at all in NR. These markers remained reduced with SC UST maintenance. Elevated IL-17A and MMPs in CD were normalized, but not significantly, following UST induction in R. The trend of normalization became larger during UST maintenance, with MMPs achieving significance in UST R in UNITI-2, and IL-17A in both cohorts. TNFa was uniquely elevated in UNITI-1 vs healthy cntl, but it was not significantly normalized by UST therapies. Placebo induction pts did not show notable changes in biopsy mRNA or serum proteins.

Conclusions: Transcriptomic and protein analyses in the Phase 3 UST studies demonstrate normalization of CD-associated markers in induction which were maintained or magnified during maintenance. These results provide insight into the mechanisms of UST efficacy and identify potential biomarkers to monitor CD activity and UST pharmacodynamics.

DOP053

The fecal microbiome as a tool for monitoring and predicting response outcomes in ustekinumab-treated, anti-TNF α refractory Crohn's disease patients: results from the CERTIFI study

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Background: We investigated the relationship between the fecal microbiome and clinical phenotypes in subjects with moderate to severe CD treated with ustekinumab (UST) to determine whether the fecal microbiome at baseline is predictive of disease severity and therapeutic response and to assess changes in the fecal microbiota due to therapy. **Methods:** CERTIFI was a phase 2b multicenter, double-blind, placebo-controlled trial to evaluate the efficacy of UST in patients with moderate to severe CD who had not responded to anti-TNF α therapy. The 16S rRNA gene from stool samples collected from roughly 350 patients at baseline and following treatment with UST or placebo (PBO) was sequenced using the Illumina MiSeq platform. Sequences were assigned to taxonomic groups using the mothur software package to determine the relative abundance of bacterial taxa. The relative abundances in addition to clinical metadata were used as input to a random forest (RF) machine-learning algorithm to predict disease severity and clinical response to treatment with UST.

Results: Fecal microbiome richness at baseline significantly correlated with clinical parameters, including CDAI, stool frequency, and disease duration (Table 1). Changes in the community structure of the microbiome (beta diversity) were significantly associated with stool frequency, CRP, fecal lactoferrin, fecal calprotectin, corticosteroid use, disease duration, and tissue involvement (Table 1). Community structure and species diversity were significantly different between Week 6 clinical responders and non-responders to UST and between clinical remitters and non-remitters. The microbiome of responders and remitters also changed over time but did not change in non-responders. Faecalibacterium, among other taxa, was significantly more abundant in responders and remitters. Using RF, the differences in the baseline microbiome and clinical metadata were able to predict response to UST with AUC values of roughly 0.85.

Conclusions: The ability to predict response to treatment using the microbiome has the potential to provide a quantitative clinical tool for guiding the treatment of CD patients. In addition our results point to specific microbes that might contribute to CD pathogenesis and maintaining CD remission. Microbes related to achieving remission could be investigated as co-therapies designed to increase the likelihood of response to anti-inflammatory therapeutics.

Abstract DOP053

Table 1. Relationship between the microbiome at week 0 and clinical variables (N=306 subjects)

Clinical Variable	Summary	Species Richness (alpha-diversity)	Community Structure (beta-diversity)
CDAI	Min=154, Median=319, Max=483	Spearman P=0.005 (rho=-0.2)	P=0.3
Loose Stool Frequency (per week)	Min=2, Median=5.1, Max=100	Spearman P=7e-04 (rho=-0.2)	P=0.01
C-Reactive Protein (mg/L serum)	Min=0.1, Median=11.7, Max=199	Spearman P=0.3 (rho=0.06)	P=0.04
Fecal Calprotectin ($\mu\text{g/g}$)	Min=14, Median=582.5, Max=28070	Spearman P=0.1 (rho=0.08)	P=0.001
Fecal Lactoferrin ($\mu\text{g/g}$)	Min=0.25, Median=83.78, Max=3141	Spearman P=0.03 (rho=0.1)	P=0.001
BMI	Min=15, Median=24, Max=55.3	Spearman P=0.2 (rho=0.07)	P=0.2
Weight (kg)	Min=40, Median=69, Max=150	Spearman P=0.2 (rho=0.07)	P=0.09
Age (years)	Min=18, Median=37, Max=78	Spearman P=0.4 (rho=-0.05)	P=0.02
Sex	F=189, M=117	Wilcoxon P=0.5	P=0.2
Corticosteroid Use	No=174, Yes=132	Wilcoxon P=2e-04	P=0.003
Disease Duration (years)	Min=0.48, Median=10.44, Max=44.92	Spearman P=7e-05 (rho=-0.2)	P=0.001
Tissue Involvement	Colon=85, Colon-Ileum=148, Ileum=73	Kruskal-Wallis P=0.1	P=0.001

DOP054**High-throughput sequencing of T cell receptors from pediatric ulcerative colitis patients reveals distinct tissue-specific repertoires**

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Background: Various T cell subsets take part in mediating mucosal damage in IBD patients. The antigenic specificity of these cells occurs via generation and rearrangement of a functional T cell receptor (TCR), in a process involving complex recombination of different genes. High throughput sequencing platforms allow detailed assessment of TCR repertoire patterns in different diseases. There is very limited data whether TCR repertoires are altered in IBD patients and whether common clones are shared between the blood and the gut. We hypothesized that pediatric UC patients possess unique TCR repertoires resulting from clonotypic expansions in the inflamed tissue.

Methods: Peripheral blood mononuclear cells (PBMCs) and rectal biopsies were collected from newly diagnosed treatment-naïve pediatric UC patients and healthy control aged-matched subjects, without signs of intestinal inflammation. DNA was isolated and sent for high throughput sequencing to determine the TCR β repertoire. Such a strategy, which employs massive parallel sequencing to process millions of rearranged TCR products simultaneously, permits an in-depth analysis of individual TCRs at a nucleotide level while expanding coverage of the total lymphocyte repertoire. ImmunoSeq analysis software was used for analysis.

Results: Paired PBMCs and rectal biopsies were collected from 4 control subjects and 6 UC patients (4 moderate activity, 2 severe activity). In both patients and controls, the TCR repertoire was more clonal in the tissue, compared to the blood. Moreover, the repertoire was further restricted in both PBMCs and tissue of UC patients vs. controls, and in several patients, specific clones were highly expressed in the inflamed rectum (>5% of total clones). Despite a similar clinical phenotype, the frequency of shared common clones between patients was very low. However, several unique clones were upregulated only among UC patients and vice versa. Finally, in a single patient with limited distal disease, the TCR repertoire was significantly different between inflamed and non-inflamed areas.

Conclusions: High throughput sequencing of the TCR is a powerful tool for studying adaptive immune cell function in the gut. The oligoclonality observed among UC patients suggests specialization of unique mucosal T cell clones, that likely have a role in mediating tissue damage. Additional studies are required to characterize which antigens interact with these clones.

DOP Session 7: Management of perianal and luminal disease**DOP055****Results of the Fifth Scientific Workshop of the ECCO (II): clinical aspects of perianal fistulising Crohn's disease – the unmet needs**

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Background: Perianal fistulas affect up to one third of Crohn's patients during the course of their disease. Despite the considerable disease burden, current treatment options remain unsatisfactory. The fifth scientific workshop (SWS5) of the European Crohn's and Colitis Organization (ECCO) focused on the pathophysiology and clinical impact of fistulas in the disease course of patients with Crohn's disease (CD).

Methods: Whereas one working group of SWS5 focused on pathophysiology, the ECCO SWS5 Working Group on clinical aspects of perianal fistulising Crohn's disease (pCD) consisted of 13 participants, gastroenterologists, colorectal surgeons and a histopathologist, with expertise in the field of inflammatory bowel diseases. A systematic review of literature was performed.

Results: Four main areas of interest were identified: natural history of pCD, morphological description of fistula tracts, outcome measures (including clinical and patient-reported outcome measures, as well as MR imaging) and randomized controlled trials on pCD.

Conclusions: The treatment of perianal fistulising Crohn's disease remains a multidisciplinary challenge. To optimise management a reliable classification and proper trial endpoints are needed. This could lead to standardized diagnosis, treatment and follow-up of Crohn's perianal fistulas and the execution of well-designed trials that provide clear answers. The prevalence and the natural history of pCD needs further evaluation.

DOP056**Pathophysiology of perianal fistulising disease**

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Background: Fistulae represent a critical clinical complication in Crohn's disease (CD) patients. Up to 50% of CD patients are affected during disease course from fistulas and about one third of patients suffer from recurring fistulae formation. Since medical treatment op-

tions often fail, surgical approaches are often needed, however frequently also not successful.

Methods: The fifth scientific workshop of the European Crohn's and Colitis Organization (ECCO) focused on the relevance of fistulas in patients with CD. The aim of subgroup II was to obtain a better understanding of the pathophysiological mechanisms underlying the formation of CD fistulas and to identify future topics in fistula research that might support the development of novel therapeutic approaches.

Results: Current knowledge suggests that CD fistulas develop as a result of a process called epithelial-to-mesenchymal transition (EMT), probably in areas with chronic ongoing inflammation. During EMT, differentiated and resident intestinal epithelial cells (IEC) become dedifferentiated and acquire a mesenchymal phenotype. In particular, IEC downregulate epithelial markers, such as E-cadherin and upregulate the expression of mesenchymal markers, such as vimentin or alpha-SMA. Furthermore, fistula-associated cells acquire markers associated with cell invasiveness what then contributes to the development of invasive fistula tracts. Emerging evidence suggests that a specific immune cell and cytokine profile can be detected around CD fistulas, in examples high expression levels of tumour necrosis factor (TNF), interleukin (IL)-13 and transforming growth factor beta (TGF-beta) what seems to promote onset of EMT and cell invasiveness. Notably, also genetic factors as well as the intestinal microbiota might be involved in fistula development. A major drawback in investigating fistula pathogenesis and in the development of novel fistula therapies is the absence of a suitable animal model.

Conclusions: Current knowledge about fistula pathogenesis is still poor. Future research needs to be directed towards the generation of an *in vivo* model to allow fistula research in real-life circumstances. The aim would be to identify the driving forces for fistula development, fistula progression and, ideally, fistula closure *in vivo*. This might critically support the development of new and more effective therapeutic strategies for the treatment of patients suffering from CD fistula.

DOP057 Perianal pediatric Crohn's disease is associated with a distinct phenotype and greater inflammatory burden

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Background: Data on the outcomes of children with perianal Crohn's disease (pCD) are limited, although its presence is often used for justifying early use of biologics. We aimed to assess whether pCD in children is associated with more severe outcomes as found in adults.

Methods: Data were extracted from the ImageKids database, a prospective, multicenter, longitudinal cohort study. The study enrolled 246 children at disease onset or thereafter. All patients underwent comprehensive clinical, endoscopic, and radiologic evaluation at enrollment; 98 children had repeat evaluation at 18 months.

Results: Of the 234 included patients [mean age 14.2±2.4 years; 131 (56%) males], 57 (24%) had perianal findings while only 21 (9%) had fistulizing perianal disease. Children with pCD had reduced weight and height z-scores compared with non-pCD patients (-0.9 vs. -0.35, p=0.03 and -0.68 vs. -0.23, respectively; p=0.04), higher weighted pediatric Crohn's disease activity index [32 (IQR 16-50) vs. 20 (8-37); p=0.004], lower serum albumin (3.6±0.7 vs. 4.5±0.8, p=0.016) and higher magnetic resonance enterography (MRE) global inflammatory score (p=0.04). Children with pCD had more rectal (57% vs. 38%, p=0.04), and jejunal involvement (31% vs. 11% p=0.003) and a higher prevalence of granulomas (64% vs. 23%, p=0.0001). MRE-based damage scores did not differ between groups. Patients with skin tags/fissures only, had similar clinical, endoscopic and radiologic characteristics as patients with no perianal findings.

Conclusions: Pediatric pCD patients with fistulizing disease have distinct phenotypic features and a predisposition to a greater inflammatory burden.

DOP058 Does biologic therapy increase the risk for fistula-associated mucinous adenocarcinoma in long standing perianal Crohn's disease?

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Background: Perianal adenocarcinoma in Crohn's disease is rare and poorly known. Single cases or small series have been reported identifying long-standing perianal disease as a risk factor. The effectiveness of biologic therapy combined with surgical drainage has been widely proved while a possible relationship between biologics and perianal carcinoma development has been suggested. The objective of the study was to evaluate features and outcomes of fistula-associated anal mucinous adenocarcinoma in perianal Crohn's Disease together with the influence of biologic therapy on its incidence

Methods: Among 535 patients operated in our Unit for perianal Crohn's Disease since 2005, in 12 patients (2.24%) a fistula-associated anal mucinous adenocarcinoma was diagnosed. We retrospectively reviewed their medical records to characterize presentation, treatment, and clinical outcome. Additional 40 pts with long-standing PCD and without cancer were selected and included in the study in order to evaluate the influence of biologics on adenocarcinoma development

Results: Average age at diagnosis was 53.4 years. All patients had long-standing fistulas (mean duration of disease of 21.3 (15-29) years). Ten had been treated with biologics in different settings (before/after surgery). All patients had extensive local disease; abdominoperineal resection (10 pts) or pelvic exenteratio (2 pts) was performed. Seven patients died due to metastatic disease and 5 are alive with evidence of recurrency.

Overall risk of cancer was not influenced by the use of biologics (2.7% vs 1.8% respectively, p=n.s.). However, considering surgical history, risk of cancer was significantly increased if biologic therapy had been previously given in patients with undrained chronic tracts

(62.4% vs 7.9%, $p=0.02$). On the other hand, prolonged biologic therapy administered in patients after surgical drainage of fistulas did not increase the risk (20.5% vs 12.9%, $p=n.s.$). This was confirmed by a multivariate analysis evaluating duration of disease, biologics type and treatment strategy

Conclusions: Perianal mucinous adenocarcinoma in CD is being increasingly reported. The Outcome, even after aggressive surgical treatment, is poor. Our data show that the risk of occurrence of mucinous adenocarcinoma is significantly increased in patients with long-standing disease when biologic therapy is not preceded by complete surgical excision of all the fistulous tracts, thus suggesting that immunomodulation could play a key role in the progression from chronic inflammation left *in situ* to carcinoma. In patients with long-standing disease surgical drainage with biopsies of the fistulous tracts is mandatory prior to initiating biological therapy

DOP059

New human gut xenograft mouse model for intestinal fistulas

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Background: Fistulas represent a frequent complication in Crohn's disease (CD) and surgical resection is often required. Despite some progress in the understanding and treatment of inflammatory bowel disease (IBD), more effective medical treatments are still required, especially for CD patients with fistula formation. Previously we demonstrated that epithelial-to-mesenchymal transition (EMT) plays a critical role for fistula development in CD patients. Preceding up-regulation of TGF- β , IL-13, TNF & their receptors along fistula tracts in CD patients seems to orchestrate a number of events contributing to the onset of fistulas, by inducing EMT. Due to a lack of a reliable *in vivo* model, new drug developments are complicated. Here, we are describing a new xenograft (XGR) mouse model of intestinal fistula, resembling the human condition.

Methods: 12–18 weeks (w) old human fetal small intestine was transplanted subcutaneously onto the backs of SCID mice. After 12–16w, ~15% of the mature xenografts spontaneously developed enterocutaneous fistulas. Using systemic LPS treatment followed by mild skin irritation adjacent to the transplant, we established a reproducible model system, resulting in enterocutaneous fistulas 2–4w later. Tissue specimens were immunohistochemically stained (IHC) for EMT & immune cell markers.

Results: Morphological analysis of the fistulating XGR samples revealed flattening of the intestinal epithelial cells lining the fistula tract, resembling transitional cells described in human patient samples. IHC stainings for various EMT markers (e.g. SLUG, β -6 Integrin) revealed similar expression patterns like for human fistulating CD patient samples. The expression of the mesenchymal marker alpha-smooth muscle actin confirmed the hypothesis that EMT plays a critical role for the fistula development in the XGR samples, as well.

H&E staining also showed inflammation in the gut XGR up- & downstream to the fistulous tracts. Most of this inflammatory re-

sponse consisted of human CD45+ round cells & very few murine CD45+ cells, mostly polymorphonuclear. Collagen staining revealed these inflammatory regions were also associated with massive fibrosis, suggesting extracellular matrix remodeling.

Besides we observed many potential necroptotic paneth cells in the XGR samples & a loss of this cells in the crypts adjacent to the fistula. RNA sequencing showed significant upregulation of genes related to IBD, necroptosis, ripoptosome, & NF- κ B signaling in inflamed LPS-treated XGRs.

Conclusions: Our data demonstrate that the *in vivo* model recapitulates both morphologically & mechanistically, the human disease. Necroptosis might be the underlying molecular mechanism driving inflammation, EMT and finally resulting in fistula formation.

M. Scharl and N.Y. Shpigel contributed equally.

DOP060

Real-world treatment pathway visualizations show low use of biologic therapies in Crohn's disease and ulcerative colitis in the United States

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Background: Treatment for Crohn's disease (CD) and ulcerative colitis (UC) has advanced over the past 20 years with the introduction of biologics. Despite their availability, patients (pts) may not be optimally managed. The aim of this study is to visualize CD and UC treatment pathways to gain insight into real-world treatment patterns.

Methods: The Truven Health MarketScan database was used to assess treatment pathways in a large US insured population. Included pts were those who had ≥ 2 consecutive health claims for CD (ICD-9-CM: 555x; ICD-10-CM: K50x) or UC (ICD-9-CM: 556x; ICD-10-CM: K51x) ≥ 30 days apart, with ≥ 1 occurrence of NDC/HCPCS codes for CD or UC medications from January 1, 2008-March 31, 2016, and a minimum continuous enrolment criterion of 12 months pre-index and 24 months post-index date. The index date is the date of the first diagnosis (CD or UC) in the database for each pt. In the CD analysis, pts' UC diagnoses were excluded, and vice versa. Sankey diagrams, used to visualize treatment pathways, depicted unique sequences of IBD treatments and quantified pts across different pathways. Treatment pathways were defined by the introduction of discreet agents in the patient's treatment course. A monotherapy (monotx) pathway was defined as the use of the same single agent, once or repeatedly, throughout the treatment course.

Results: 16,260 CD and 28,120 UC pts were included. Corticosteroid (CS) monotx was the most common first-line agent (42%) and treatment pathway (26%) for CD pts. The CS monotx pathway represents nearly two-thirds of pts initially using CS; 63% of these CD pts had ≥ 2 steroid cycles; 108 had ≥ 10 cycles in the observed period. 5-ASA monotx was the second most common treatment pathway for CD (12%) and most common for UC (24%). CS monotx was the second most common pathway for UC pts (16%). Pts using 5-ASAs as initial treatment had a longer time to biologic initiation vs pts using other first-line therapies. Overall, biologic pathways were relatively rare (CD pts: 19%; UC pts: 6%), and even fewer pathways use biologics combined with other agents (CD pts: 15%; UC pts: 5%). The most common biologic pathway in these populations was adalimumab (ADA) monotx (CD pts: 0.5%; UC pts: 0.04%), followed by infliximab monotx (CD pts: 0.3%) or 5-ASA switching to ADA (UC pts: 0.03%).

Conclusions: This real-world data analysis identified unique treatment pathways visualized through Sankey diagrams. Our findings indicate few pts are treated with biologics; of those using biologics, few receive combination therapy, despite support for this approach. These findings suggest current treatment guidelines and disease management recommendations may not be uniformly followed in the real-world setting.

DOP061

Phase III randomised, double-blind, controlled trial to compare biosimilar infliximab (CT-P13) with innovator infliximab in patients with active Crohn's disease: early efficacy and safety results

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Background: CT-P13 is a biosimilar of innovator infliximab (INX) and has been approved for all indications by the European Medicines Agency in 2013 and Food and Drug Administration in 2016.

Methods: This study was a randomised, double-blind, parallel-group, phase III study conducted in patients with moderate to severe CD. The primary objective of the study was to compare efficacy between CT-P13 and INX in terms of Crohn's Disease Activity Index (CDAI)-70 response rates at Week 6. CDAI-70 response and CDAI-100 response were defined as reductions from baseline in the CDAI score of at least 70 and 100 points, respectively. Clinical remission was defined as an absolute CDAI score of less than 150 points [1]. Comparisons between the 2 treatment groups up to Week 6 were evaluated.

Results: Of 220 patients randomised in 58 study centres across 16 countries, 214 patients completed study up to Week 6. At Week 6, CDAI-70 response rate of CT-P13 was quite similar to that of INX (CT-P13, 71.4%; INX, 75.2%; p-value = 0.5613). Similar and consistent trends were observed in proportion of patients achieving CDAI-100 response (CT-P13, 61.9%; INX, 64.4%; p-value=0.7744) and clinical remission rate of 42.9% and 44.6% (p-value = 0.8329) in CT-P13 and INX treatment group, respectively (Table 1). The

number of patients with at least one treatment-emergent adverse event (TEAE) showed a similar proportion in the 2 treatment groups (CT-P13, 30.6% [34/111]; INX, 35.8% [39/109]). The proportion of number of patients with at least one treatment-emergent serious adverse event (TESAE) was also comparable between treatment groups (CT-P13, 1.8% [2/111]; INX, 1.8% [2/109]). TEAEs of special interest including infusion-related reactions and infections related to study drug were reported in similar between the 2 treatment groups (CT-P13, 5.4% [6/111]; INX, 5.5% [6/109] as infusion-related reactions, CT-P13, 2.7% [3/111]; INX, 1.8% [2/109] as infections).

Table 1. Efficacy Results at Week 6 for Per-Protocol Population

	CT-P13 (N=105)	INX (N=101)
CDAI-70 response n (%), CI*	75 (71.4%) [61.8, 79.8]	76 (75.2%) [65.7, 83.3]
CDAI-100 response n (%), CI*	65 (61.9%) [51.9, 71.2]	65 (64.4%) [54.2, 73.6]
Clinical remission n (%), CI*	45 (42.9%) [33.2, 52.9]	45 (44.6%) [34.7, 54.8]

*95% confidence interval

Conclusions: The efficacy of CT-P13 was similar to INX in terms of CDAI-70, CDAI-100 and clinical remission up to Week 6 in patients with CD. In addition, CT-P13 was well tolerated with a similar safety profile to that of INX up to Week 6. These results are consistent with randomised controlled studies of INX and other published studies and further reinforced now within the randomised controlled settings [1–3].

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DOP062

Biosimilar infliximab (CT-P13) is not inferior to originator infliximab: explorative IBD subgroup-analyses in Crohn's disease and ulcerative colitis from the NOR-SWITCH trial

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Background: TNF-inhibitors have improved treatment of Crohn's disease (CD), ulcerative colitis (UC), spondyloarthritis (SpA), rheumatoid arthritis (RA), psoriatic arthritis (PsA) and chronic plaque psoriasis (Ps). The aim of the Nor-Switch study was to examine switching from originator to biosimilar infliximab regarding efficacy, safety and immunogenicity.

Methods: The study was designed as a 52-week randomised, double-blind, non-inferiority trial. Patients with a diagnosis of CD, UC, SpA, RA, PsA or Ps on stable maintenance treatment with the originator infliximab (Remicade[®], INX) were randomized 1:1 to either continued INX or switch to biosimilar infliximab (Remsima[®], CT-P13). The primary endpoint was disease worsening according to disease activity indices during follow-up.

Results: In total, 481 patients at 40 Norwegian study centres were randomised, with 202/206 patients in the INX/CT-P13 arms (Per Protocol Set). There were 129 (32%) and 75 (18%) patients with CD and UC. Overall disease worsening occurred in 26.2% and 29.6% of patients in the INX and CT-P13 arms, respectively, and the 95% confidence interval (CI) of the adjusted difference was within the pre-specified non-inferiority margin (-4.4; 95% CI -12.7, 3.9%). In CD, disease worsening occurred in 21.2% and 36.5% (CI -29.3 to 0.7%) and in UC 9.1% and 9% (CI -15.2, 10.0%). The CI for CD was close to non-inferiority for CT-P13, but disease specific analyses were pre-specified as exploratory and NOR-SWITCH was not powered for demonstrating non-inferiority in the single diagnoses.

The baseline characteristics in CD and UC showed no difference between treatment arms regarding previous biologic therapy, use of immunosuppressives, trough drug levels, disease duration, distribution, behaviour and activity (Harvey-Bradshaw Index (HBI) and Partial Mayo Score (PMS)), bowel surgery, smoking, CRP, fecal calprotectin, and EQ-5D.

Changes in parameters from baseline to study end showed similarity between arms (adjusted difference, (95% CI)) in CD and UC, respectively, regarding CRP (-0.07 (-0.17, 0.04) and -0.04 (-0.18, 0.10)), fecal calprotectin (-0.08 (-0.27, 0.10) and 0.21 (-0.03, 0.44)), HBI (-0.41 (-1.14, 0.33)), PMS (0.14 (-0.30, 0.59)), HBI and PMS remission. Changes in Patient's and Physician's global assessment of disease activity showed some larger improvement in the INX compared to the CT-P13 arm in the CD group (-0.65 (-1.22, -0.07) and -0.42 (-0.85, 0.001)). Comparable results were also seen for through serum levels, presence of anti-drug antibodies and reported adverse events.

Conclusions: Explorative subgroup analyses of CD and UC in the Nor-Switch study showed similarity between patients treated with INX and CT-P13 with regard to efficacy, safety and immunogenicity.

DOP063

Serial tuberculin skin test improves the detection of latent tuberculosis infection in inflammatory bowel disease patients

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Background: Despite preventive action, active tuberculosis (TB) still occurs in patients on anti-TNF therapy. Steroids and/or immunosuppressants markedly reduce sensitivity of tuberculin skin test (TST) performed before anti-TNF therapy. The risk of conversion of serial TST in inflammatory bowel disease (IBD) patients whose initial 2-step TST was negative is not well known. This study aimed to determine the likelihood of detecting latent TB infection by the positive conversion of annual TST in IBD patients.

Methods: This prospective multicentre controlled study included consecutive IBD patients on anti-TNF therapy and a control cohort of IBD patients not receiving anti-TNF therapy. All patients with a negative initial 2-step TST had a second test one year later. We evaluated the rate and predictors of TST conversion (including change in number of immunosuppressive drugs [steroids and/or immunosuppressants and/or anti-TNF]). We recorded management of cases of TST conversion and occurrence of active TB during follow-up.

Results: The 412 patients enrolled (mean age 44 years, 54% male) included 192 patients (47%) on anti-TNF and 220 controls (53%). Thirty-five patients (8.5%, 95% confidence interval [CI]: 5.7–11.3) had a positive conversion in the annual TST (median TST induration 13 mm, range 5–20]). Eleven of 192 anti-TNF patients (5.8%, 95% CI 2.2–9.3) vs. 24 of 220 controls (10.9%, 95% CI 6.6–15.2) had TST conversion (p=0.037). In multivariate analysis patients receiving anti-TNF therapy had a lower rate of TST conversion (odds ratio [OR] 0.36, 95% CI 0.15–0.83, p=0.017). Conversely, smokers had a higher rate of TST conversion (OR 3.62, 95% CI 1.66–7.88, p=0.001). The likelihood of conversion according to changes in immunosuppressive therapy from baseline was 16.6%, 7.9%, 7.3%, 4.5% and 0% for patients with 1 drug less, same number of drugs or 1, 2 or 3 drugs more, respectively (p=0.016). All 11 anti-TNF cohort patients with an annual positive TST received treatment for latent TB infection and continued with anti-TNF therapy. Eleven of 24 control patients with TST conversion received preventive therapy. No patient developed active TB after 607 and 676 patient-years of follow-up of anti-TNF exposed and control patients, respectively.

Conclusions: Patients with IBD were at high risk of conversion in the annual TST after an initial negative 2-step TST. Anti-TNF therapy reduced the likelihood of annual TST conversion. Although the exact significance of these positive conversions is not well known, annual TST seems to be advisable as baseline false negative responses to latent TB infection or new TB contacts are possible in IBD patients receiving long-term anti-TNF therapy, especially in countries with a moderate to high prevalence of TB.

DOP Session 8: Endoscopy in IBD: Assessment of activity and surveillance

DOP064

High rate of advanced neoplasia after detection of low-grade dysplasia in inflammatory bowel disease patients with primary sclerosing cholangitis

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Background: Primary sclerosing cholangitis (PSC) is the strongest risk factor for colorectal neoplasia (CRN) in inflammatory bowel disease (IBD). While prior studies in this population have estimated the prevalence of advanced CRN (aCRN) (high-grade dysplasia or colorectal cancer), little is known about the incidence rate of aCRN after a diagnosis of low-grade dysplasia (LGD) to, and its potential risk factors.

Methods: PSC-IBD patients were identified from two existing large surveillance databases (the Mount Sinai Hospital Surveillance Database (2005–2015) and the Dutch multicentre surveillance database (2000–2013)) and compared to non-PSC IBD patients. All patients had undergone at least two surveillance colonoscopies. Clinical information, as well as endoscopic and histologic data were recorded. The prevalence of LGD and aCRN and the incidence of aCRN after an index LGD lesion (first LGD within study period) were compared between groups. Cox-regression was used to determine predictors of dysplasia progression.

Results: 301 patients with PSC-IBD were compared to 1100 non-PSC IBD patients. Patients with PSC-IBD were younger at IBD diagnosis [median 24 y (range 69) vs 28 y (72), $p=0.003$], more frequently male (69% vs 50%, $p<0.001$), and had a shorter IBD duration (median 10y [51] vs 14y [52], $p<0.001$). Median time of follow-up for the total cohort was 4.8 years. PSC-IBD patients had a statistically significant increase in the frequency of aCRN as compared to non-PSC IBD patients (Hazard ratio [HR] 3.1, 95% CI 1.7–5.8). The overall incidence rate of developing aCRN in PSC-IBD compared to non-PSC IBD patients was 1.3 versus 0.4 per 100 patient-years follow-up (pty). Despite similar frequencies of LGD between PSC-IBD and non-PSC IBD patients (20.3% versus 21%, $p=0.8$, Table 1), the rate of developing aCRN following detection of LGD was higher in PSC-IBD patients (HR 2.8, 95% CI 1.2–6.5). The incidence rate of aCRN after a diagnosis of LGD was 7.4/100 pty for PSC-IBD patients compared to 2.3/100p ty for non-PSC IBD patients. Using Cox-regression analysis, older age at study entry and a history of prior neoplasia were significant risk factors for development of CRN (LGD, or HGD, or CRC) among PSC-IBD patients; there was a non-significant trend for an association of multifocal dysplasia with higher risk of developing aCRN after an LGD diagnosis (HR 3.2, 95% CI 0.8–11.8, $p=0.086$).

Conclusions: PSC-IBD patients have a similar incidence of LGD compared to non-PSC IBD patients, but the risk of developing aCRN after a diagnosis of LGD is significantly higher in PSC-IBD patients. Our findings substantiate recommendations for annual surveillance in this very high-risk population.

DOP065

Use of chromoendoscopy versus white light endoscopy for colorectal cancer surveillance in inflammatory bowel disease patients with primary sclerosing cholangitis; a six year experience

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Background: Patients with inflammatory bowel disease (IBD) are at increased risk for development of dysplasia and colorectal cancer (CRC), with a further 6-fold increased risk in those with primary sclerosing cholangitis (PSC) versus their non-PSC-IBD counterparts. Preneoplastic tissue in IBD patients is often flat and multifocal and may not be appreciated in up to one-third of colonoscopies. The dysplasia yield from surveillance colonoscopy can be improved by spraying dyes that highlight subtle changes in the architecture of the colonic mucosa. Limited data exists on outcomes of chromoendoscopy in PSC-IBD population. Our aim was to audit the endoscopic outcomes of CRC surveillance in PSC-IBD patients, comparing chromoendoscopy (CE) versus white-light endoscopy (WLE), over a six-year period.

Methods: Retrospective study analyzing our Oxford PSC database to identify patients actively followed up since January 1st, 2010. Patients were excluded who did not have a diagnosis of IBD, had a colectomy prior to January 1st, 2010, or did not undergo endoscopic surveillance at our institution. Endoscopic and histological findings were recorded from endoscopic electronic reporting systems (EndoBase and UNISOFT), and histology reports from NHS Casenotes. Procedures were excluded if bowel preparation was inadequate or evidence of moderate inflammation.

Results: 140 PSC patients were followed up during study period, of which 58 PSC-IBD patients attended our institution for their endoscopic surveillance (38 UC, 10 Crohn's disease, and 10 IBD-U). The median disease duration at time of colonoscopy was 12.4 years (7.3–24.5). 178 colonoscopies were performed on this population, of which 57 were excluded due to poor prep and active inflammation. 122 procedures were analysed. 74 were performed with CE while 48 with WLE. High definition scope was more likely to be used at CE than WLE procedures (58.3% versus 28.2%, $p=0.005$). Targeted biopsies were taken at time of 23/74 (31.1%) CE procedures (one high grade dysplasia (HGD), two low grade dysplasia (LGD), one indefinite for dysplasia (IFD), one sessile serrated polyp (SSP), and three hyperplastic changes (all right colon)) versus 1/48 (2.2%) WLE procedures (normal) ($p<0.001$). More visible lesions were identified at chromoendoscopy ($p=0.04$), with 78 identified in CE procedures (one HGD, two LGD, one IFD, three SSP, 24 hyperplastic polyps (15 right sided), and 5 adenomatous polyps) versus 18 in WLE procedures (no dysplastic lesions, five hyperplastic (two right sided)). Premalignant lesions were more likely to be detected at CE ($p=0.006$).

Conclusions: This study shows evolving clinical practice at a single centre with increased detection of premalignant lesions with CE versus WLE for PSC-IBD patients.

DOP066

Strict surveillance colonoscopy should be performed for the ulcerative colitis patients who underwent ileorectal anastomosis

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Background: Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) has become a standard surgical treatment for patients with UC. Although long-term functional outcomes of the IPAA are good in the large majority of patients, they still have risks of anastomotic failure, pelvic sepsis and developing pouchitis. On the other hand, total colectomy with ileorectal anastomosis (IRA) requires less complex techniques with lower complication rate that has been considered as a treatment of choice for a selected group of UC patients. Among these two surgical procedures, patients who underwent IRA have a higher risk of developing neoplasia than those who underwent IPAA, and the incidence of rectal cancer was reported in up to 18% after IRA.

The aim of this study was to clarify the cumulative rate of developing neoplasia after IRA and IPAA. Additionally we describe the clinical course of patients who developed neoplasia after IRA and IPAA.

Methods: We evaluated 131 UC patients who underwent either IPAA or IRA in our institution between 1965 and 2016 by reviewing medical and endoscopic records. All patients underwent surveillance colonoscopy at least once after surgery. We retrospectively reviewed for the development of neoplasia based on endoscopic and pathological findings. The cumulative rate of developing neoplasia was calculated using the Kaplan-Meier method. The clinical features and clinical course of patients who developed neoplasia after IRA or IPAA were retrospectively reviewed.

Results: Among 131 patients, 31 patients underwent IRA and 100 patients underwent IPAA. A total of 392 endoscopy sessions were conducted after IRA and 673 pouchoscopy sessions were conducted after IPAA. There were no statistical differences between IRA group and IPAA group for sex, age at onset, or age at surgery. Since we perform IPAA for UC patients who develop neoplasia, there were statistical difference between IRA group and IPAA group in the surgical indication. A total of seven patients were detected with neoplasia during postoperative surveillance colonoscopy. Among them neoplasia was found in six of 31 patients in IRA group and in one of 131 patients in IPAA group. In IRA group high-grade dysplasia was detected in three cases and low-grade dysplasia in three cases from the retained rectum at the time of surveillance colonoscopy. Neoplasia were detected more frequently in the IRA group than in the IPAA group. The cumulative rate of developing neoplasia after IRA at 10 and 20 years was 7.4% and 18.6% respectively.

Conclusions: Cumulative incidence of neoplasia after IRA in UC patients was 18.6% after 20 years. IRA should be performed in selected patients and strict surveillance colonoscopy with biopsies is important.

DOP067

Risk of malignant and non-malignant complications of the rectal stump in patients with inflammatory bowel disease

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Background: A considerable number of patients with inflammatory

bowel disease (IBD) have refractory disease and therefore often require a subtotal colectomy with construction of an ileostomy. When pouch surgery is not appropriate this can be a definitive procedure. Due to the potential risk of pelvic nerve damage and pelvic septic complications, the rectum is often left *in situ*. The primary objective of this study was to assess the incidence rate of non-malignant (diversion colitis, stenosis) and malignant (dysplasia or cancer) complications of RS patients with IBD. Secondary objectives were to evaluate the management strategies after colectomy in IBD patients.

Methods: In a single tertiary referral centre, a diagnostic coding system was used to identify all patients with IBD and a history of colonic resection. Patients were stratified according to the presence of intestinal continuity (ileorectal anastomosis [IRA] and ileal pouch anal anastomosis [IPAA]) or discontinuity (ostomy with or without remaining RS). Additional demographic and clinical data were collected for patients with bowel discontinuity. Endoscopically confirmed diversion colitis, stenosis or shortening of the colon were defined as benign RS complications. Neoplasia was defined as the presence of low-grade dysplasia (LGD), high-grade dysplasia (HGD) or carcinoma in the RS.

Results: Out of 1787 patients with IBD, 352 had 1 or more colonic resections. The final anatomical status was IRA in 25 patients (7.1%), IPAA in 89 patients (25.3%) and a colo-ileostomy in 238 patients (67.6%). In 197 patients a RS had been *in situ* for more than 1 year. Out of these 197 patients, 48 had UC (24.4%), 140 had CD (71.0%) and 9 had IBD-unclassified (4.6%). Sixty-nine patients were male (35.0%) and the mean age at colectomy was 38.8 years. Out of 144 patients with endoscopic follow-up, diversion colitis occurred in 115 patients (79.7%) and RS stenosis occurred in 56 (38.9%) patients. In patients with follow-up of the RS (median: 8 years, range 0–39), 5 carcinomas, 1 case of HGD and 6 cases of LGD occurred. Incidence rates were 3.0 and 7.1 per 1000 patient-years of follow-up, for cancer and all neoplasia, respectively. In 45 patients with a RS (22.8%) a completion proctectomy was performed. The main reasons for excision of the RS were treatment or prevention of carcinoma in 7 patients (15.6%) and persisting complaints of the RS such as bloody and mucopurulent rectal discharge in 31 patients (68.9%).

Conclusions: In patients with IBD and a retained RS after colectomy a high prevalence of diversion colitis and RS stenosis was observed during endoscopic follow-up. Cancer occurred in 5 out of 197 patients with an incidence rate of 3.0 per 1000 patient-years.

DOP068

The virtual electronic chromoendoscopy score in ulcerative colitis exhibits very good inter-rater agreement in scoring mucosal and vascular changes after computerised module training: a study across academic and community practice

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Background: Mucosal healing is the desired therapeutic endpoint for clinical trials in ulcerative colitis (UC). However, conventional white light endoscopy may fall short of capturing the full spectrum of inflammatory change; and virtual electronic chromoendoscopy (VEC) can show ongoing disease activity even when Mayo scores suggest healing (Iacucci et al. Endoscopy 2015). Applicability of VEC scoring requires determination outside the expert setting; thus, our aim was to provide external validation among trainees, consultant gastroenterologists and colorectal surgeons, practicing across six general and specialist centres.

Methods: 15 participants reviewed a computerised training module outlining HD and i-Scan modes. Anchor points for the VEC score indicated mucosal changes (crypt distortion, 0 [A–C]; microerosions, I [1–3]; erosions, II [1–3]; and ulceration, III [1–3]) and vascular alterations (non-dilated vessels, 0 [A–C]; dilated/crowded vessels, I [1–3]; mucosal bleeding, II [1–3]; and intraluminal bleeding, III [1–3]). Performance accuracy was tested using a video library pre-/post-training (n=30). Agreement between raters was tested for the Mayo score, UCEIS and VEC score, and results correlated with histology (New York Mount Sinai system; Harpaz et al.).

Results: The inter-rater agreement was very good for the Mayo score, UCEIS scoring erosions/ulcers and overall, and for VEC scoring mucosal patterns in both modules (Table 1). For the vascular components of UCEIS agreement was only moderate, and did not improve post-training; unlike the agreement for VEC vascular patterns which improved significantly to very good. Correlation between histology and VEC score was highly significant for mucosal and vascular scoring (Spearman's ρ : 0.910, $p < 0.001$; and 0.907, $p < 0.001$; respectively, Figure 1). This was superior to the Mayo score (0.876, $p < 0.001$) and UCEIS (0.887, $p < 0.001$).

Conclusions: The VEC score demonstrates very good inter-observer agreement across all levels of experience and provides excellent correlation with histology. Unlike UCEIS, the VEC score does not have subjective elements (e.g. mucosal erythema, incidental/contact fri-

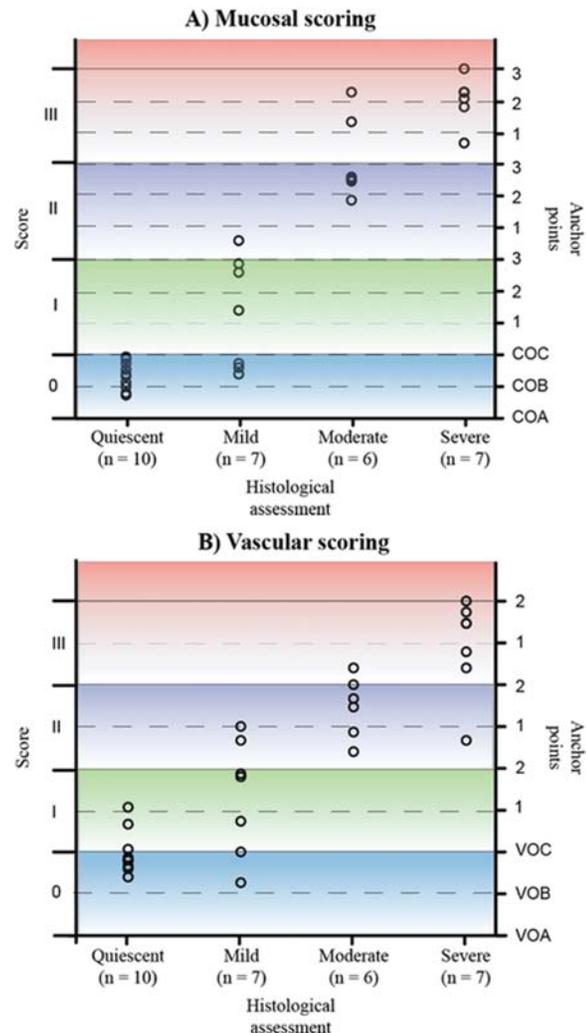


Figure 1. Correlation between the EVC score and histology in ulcerative colitis. Average score per video per participant for each category are presented (post-training).

ability) and may better delineate vascular changes due to filter technology. Given the ability to define subtle endoscopic features, VEC may be applied to further stratify treatment paradigms for patients with UC.

Abstract DOP068 – Table 1. ICCs are from a two-way random model with absolute agreement, and are for single measures. All values are significant at a $p < 0.001$.

Table 1: Intraclass correlation coefficients (ICC) pre- and post-training modules

	Pre-training ICC (95% CI)	Post-training ICC (95% CI)
Mayo score	0.775 (0.678 - 0.864)	0.818 (0.731 - 0.894)
UCEIS Total score	0.786 (0.692 - 0.872)	0.833 (0.753 - 0.903)
- UCEIS vascular pattern	0.429 (0.306 - 0.588)	0.417 (0.295 - 0.577)
- UCEIS bleeding pattern	0.689 (0.574 - 0.804)	0.726 (0.617 - 0.831)
- UCEIS erosion / ulcer pattern	0.770 (0.672 - 0.861)	0.810 (0.723 - 0.887)
VEC score mucosal component	0.754 (0.651 - 0.851)	0.826 (0.743 - 0.899)
VEC score vascular component	0.622 (0.498 - 0.754)	0.746 (0.640 - 0.847)

ICCs are from a two-way random model with absolute agreement, and are for single measures. All values are significant at a $p < 0.001$.

DOP069**Natural history of dysplasia and colorectal cancer in IBD patients in Belgium tertiary care centers**

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Background: Inflammatory bowel disease (IBD) patients are at increased risk of developing dysplasia and colorectal cancer, namely colitis-associated colorectal cancer (CAC). Ulcerative colitis (UC) and Crohn's disease (CD) patients are recommended to undergo screening and surveillance colonoscopy. However, large study populations are needed to understand the natural history of dysplasia and CAC and improve their management in IBD patients.

Methods: This is a national long-term follow-up retrospective study to evaluate the natural history of low-grade dysplasia (LGD), high-grade dysplasia (HGD) and CAC in IBD patients in Belgium tertiary referral regional and academic centers within the Belgian Inflammatory Bowel Disease Research and Development group. Clinical, endoscopic and pathological data were retrieved through retrospective electronic chart review. All biopsies and surgical specimen were reviewed by a second independent expert IBD pathologist.

Results: 195 IBD patients (105 CD, 83 UC, and 7 unclassified IBD) with in total 466 lesions (dysplasia/CAC) were identified. From these 466 lesions, 391 were LGD (346 raised, 45 flat), 40 were HGD (35 raised, 5 flat), and 35 were CAC. Median age at IBD diagnosis was 42 years (IQR 29–57). From the 195 affected patients, 161 (83%) had only dysplasia, while 34 (17%) had CAC (26 CD, 8 UC; 20 men, 14 women). Median disease duration was significantly longer in patients with CAC compared to those with dysplasia (13 (IQR 4–27) vs 7 (IQR 1–16) years; $p=0.03$). Overall 11 (7.6%) out of 146 patients with firstly diagnosed LGD have progressed to more advanced neoplasia (6 HGD, 5 CAC) after median follow-up of 43 months (IQR 16–79). 27/34 (79%) IBD patients with CAC were diagnosed with CAC without evidence of prior dysplasia, while 7/34 (21%) developed CAC secondarily. Among them, 4 (57%) had early stage CAC, and 3 (43%) had advanced stage (stages II-IV) at diagnosis, while in patients without prior history of dysplasia, 10 (37%) had early stage at diagnosis. CAC was diagnosed during colonoscopy in 26 patients, and at surgery (performed for pre-existing dysplasia ($n=2$), or for IBD therapeutic management ($n=6$)) in 8 patients.

Conclusions: This is one of the largest cohorts of IBD patients with dysplasia and CAC never described so far. The rate of progression of LGD to advanced neoplasia remains low with the limitation of a retrospective study. CAC diagnosis is mostly done during colonoscopy

with no prior history of dysplasia. CAC was found incidentally at surgery for indications of dysplasia and refractory disease.

DOP070**Endoscopic response to induction therapy with TNF inhibitors is the best predictor of long term mucosal healing in Crohn's disease**

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Background: Identify predictors of therapeutic response is the cornerstone of personalized medicine. The aim of this study was to identify predictors of endoscopic remission in patients with CD at one year of treatment with TNF inhibitors.

Methods: This is a single center prospective study initiated in November 2012. Patients with clinically active luminal CD, with a baseline segmental Crohn's Disease Endoscopic Index of Severity (CDEIS) equal or higher than 10 in at least one segment or presence of ulcerations were included in the study. Patients were treated with anti-TNF therapy for induction of remission, and maintenance. Clinical, biological and endoscopic data were obtained at baseline, week 14 and week 46. Endoscopic response was defined as a decrease of 50% from baseline CDEIS and remission as partial CDEIS lower or equal to 5 (disappearance of mucosal ulcerations) in all segments.

Results: To date, 61 patients have been included, of whom 43 have completed week 46 follow-up. Thirty (49%) are female with a mean disease duration of 9 years. Thirty two out of 61 (52%) received Infliximab and 29 (48%) Adalimumab. At baseline, median CDAI and CDEIS were 181 and 9,07 with a significant reduction after one year of treatment up to 71,2 ($p<0.001$) and 4,2 ($p<0.001$), respectively. At week 14, 64.5% of patients achieved endoscopic response and 37% endoscopic remission. At week 46, percentages of endoscopic response and remission were 56% and 46%, respectively. Demographic or disease characteristics at baseline did not predict endoscopic response to induction or maintenance therapy. Predictors of endoscopic remission at week 46 were the absolute CDEIS value at week 14, percentage of CDEIS reduction from baseline to week 14, and endoscopic remission. Based on the clinical usefulness of the evaluated cutoff values a decrease from baseline CDEIS of at least 80% appeared to be the best discriminative cutoff value to predict endoscopic remission at week 46 with 68% sensitivity and 85% specificity ($p=0.002$).

Conclusions: In patients with CD treated with an anti-TNF a reduction of 80% in CDEIS from baseline to week 14 is a robust predictor of endoscopic remission after one year of treatment. Achievement

Abstract DOP069 – Table 1

Findings on surgery and colonoscopies during follow-up, based on index lesion

Index lesion	Follow-up most advanced lesion (n=number of patients)				Total
	No dysplasia/CAC	LGD	HGD	CAC	
LGD	96 (65.8%)	39 (26.7%)	6 (4.1%)	5 (3.4%)	146
HGD	4 (18.2%)	11 (50%)	5 (22.7%)	2 (9.1%)	22
CAC	21 (77.8%)	4 (14.8%)	1 (3.7%)	1 (3.7%)	27
Total	121 (62.1%)	54 (27.7%)	12 (6.2%)	8 (41%)	195

LGD: low grade dysplasia; HGD: high grade dysplasia; CAC: colitis-associated colorectal cancer

This table shows the most advanced lesion that the patients developed at surgery or during colonoscopies performed during their follow-up after their first lesion was diagnosed (index lesion), according to the grade of this index lesion (LGD, HGD or CAC).

of this endpoint should be considered for optimization of anti-TNF therapy in clinical practice.

DOP071

Comparison of endoscopic responses to adalimumab monotherapy and combination therapy with azathioprine in patients with Crohn's disease: a sub-analysis of DIAMOND trial

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Background: We recently reported the results of a prospective, randomized controlled trial comparing the efficacy of adalimumab (ADA) monotherapy and a combination therapy with azathioprine (AZA) for patients with Crohn's disease (CD), who were naïve to biologics and thiopurines (DIAMOND trial). This sub-analysis aims to evaluate endoscopic response and mucosal healing at week 26 and 52 in patients enrolled for the trial.

Methods: In the preceding DIAMOND trial, 176 patients were randomly assigned to either ADA monotherapy or ADA in combination with AZA. The data for SES-CD were available for 115 patients at week 26 and for 102 patients at week 52. Among 41 patients with adverse events, 25 patients who withdrew the trial due to CD worsening were regarded as endoscopic non-responders (non-responder imputation), while 16 patients who discontinued the study drug were excluded from the analysis. Endoscopic response was defined as a decrease in the SES-CD of at least 8 points from the baseline, or SES-CD ≤ 4 . Mucosal healing was defined as SES-CD ≤ 2 .

Results: Endoscopic response rate at week 26 was significantly higher in the combination group than in the monotherapy group (OR=2.12, 95% CI 1.036–4.323, $p=0.05$), while the rate at week 52 was not different between the two groups (OR=1.50, 95% CI 0.765–2.942,

$p=0.31$). The rate of mucosal healing was different between the two groups neither at week 26 (OR=2.30, 95% CI 0.865–6.128, $p=0.10$) nor at week 52 (OR=1.98, 95% CI 0.795–4.946, $p=0.17$). There were statistically significant associations between mucosal healing at week 26 and CDAI at week 0 (OR=1.01, 95% CI 1.000–1.024, $p=0.05$) and between mucosal healing at week 26 and SES-CD at week 0 (OR=0.80, 95% CI 0.716–0.898, $p<0.01$). Similar trends were also found between mucosal healing at week 52 and CDAI (OR=1.01, 95% CI 1.004–1.024, $p<0.01$) and SES-CD (OR=0.91, 95% CI 0.838–0.980, $p=0.01$) at week 0. The serum ADA concentration at week 26 was significantly higher in patients with endoscopic response than those without at week 26 (8.20 ± 3.55 $\mu\text{g/ml}$ vs. 4.89 ± 3.10 $\mu\text{g/ml}$, $p<0.001$) and at week 52 (8.16 ± 3.68 $\mu\text{g/ml}$ vs. 5.35 ± 3.38 $\mu\text{g/ml}$, $p<0.001$). Among four items belonging to SES-CD, stricture improved less frequently than the other three items at week 26 and at week 52, and there were no difference for this trend between monotherapy group and combination group.

Conclusions: In DIAMOND trial, concomitant AZA had marginal effects on endoscopic response while there was a significant association between ADA concentration and endoscopic response. For patients with CD treated by ADA, the use of concomitant AZA should be optimized on the basis of the clinical course and endoscopic findings especially for stricture.

DOP072

Assessment of the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) using central video review of colonoscopies in paediatric patients with ulcerative colitis: data from the Canadian Children IBD Network

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Background: The Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is a validated endoscopic tool which measures the worst disease activity in the rectosigmoid. This is potentially problematic as paediatric disease is often pancolonic and inflammation can be patchy, especially during active treatment. To date, there are no data evaluating the UCEIS in paediatrics. Using colonoscopy videos performed in patients from the Canadian Children IBD Network, we explored the reliability of the UCEIS when applied to colonic segments proximal to the recto-sigmoid.

Methods: Video recordings of colonoscopies obtained from paediatric patients with UC undergoing endoscopic assessment at Network sites were utilised for the analysis. 4 IBD experts reviewed each video blinded to clinical information. For each anatomic colonic segment data encompassing the 3 elements of the UCEIS (bleeding, ulceration, vascular pattern) were recorded. Total UCEIS scores were calculated for each segment. In addition, the most distal segment with the highest score was identified (UCEIS-max). A global assessment of endoscopic lesion severity for the entire colon (GELS) was also recorded using a visual analogue scale. Inter-rater reliability (IRR) was measured using Intraclass correlation coefficients (ICCs). Correlation between scoring tools was measured using Spearman's test of correlation (r).

Results: There was a broad range of endoscopic severity (median UCEIS 6 (range 3–8)). The IRR for each aspect of the UCEIS are displayed in Table 1. The tool performed well throughout the colon,

Abstract DOP072 – Table 1. Inter-rater reliability for UCEIS variables across anatomical segments

UCEIS Location	UCEIS variables Intra-class Correlation Coefficient (95% CI)			
	Total	Vascular Pattern	Bleeding	Erosions/Ulcers
Standard – Rectosigmoid	0.87 (0.74–0.95) p<0.001	0.80 (0.60–0.91) p<0.001	0.50 (0.11–0.77) p=0.01	0.88 (0.76–0.95) p<0.001
Descending Colon	0.81 (0.73–0.96) p<0.001	0.89 (0.77–0.95) p<0.001	0.61 (0.25–0.82) p<0.001	0.86 (0.71–0.94) p<0.001
Transverse Colon	0.79 (-0.60–0.85) p=0.02	0.90 (0.72–0.98) p<0.001	0.74 (0.26–0.91) p=0.01	0.69 (0.2–0.77) p=0.02
Ascending Colon	0.74 (0.25–0.95) p=0.01	0.85 (0.53–0.97) p<0.001	0.69 (0.25–0.88) p=0.01	0.77 (0.1–0.94) p=0.05

with “bleeding” being the variable demonstrating the most disagreement. When comparing standard UCEIS and UCEIS-max, in 33% of patients the maximally affected segment was proximal to the rectosigmoid. In 10% of these subjects the difference in UCEIS score was greater than 1 point (p<0.001). Correlation with GELS was better for UCEIS-max (r=0.79, p<0.001), than for standard UCEIS (r=0.68, p<0.001).

Conclusions: UCEIS is a valuable tool in the assessment of endoscopic disease severity in paediatric UC. UCEIS, when applied in standard fashion to the recto-sigmoid shows excellent IRR amongst IBD physicians. The tool can be applied across the colon, with only a small decrease in consistency. In this group of patients diagnosed with UC, one third of patients will have the maximally affected area proximal to the rectosigmoid, highlighting the importance of complete colonoscopy in assessing disease activity in UC.

DOP Session 9: New therapies

DOP073

Submucosal injection of the oligonucleotide STNM01 is able to induce clinical remission, mucosal healing and histological response in left-sided ulcerative colitis patients with moderate-to-severe disease

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Background: The extracellular matrix component Carbohydrate sulfotransferase 15 (CHST15) biosynthesizes highly sulfated disaccharide units of chondroitin sulfate (CS), which facilitates mucosal inflammation and the onset of intestinal fibrotic lesions in chronically active ulcerative colitis. We evaluated the safety and efficacy of the double-strand RNA oligonucleotide STNM01 which inhibits the ex-

pression of the CHST15 gene in left-sided ulcerative colitis patients with active mucosal inflammation.

Methods: We conducted a Phase 2a, randomized, multicenter, double-blind, parallel-group, placebo-controlled study of STNM01 in 24 patients with left-sided, refractory ulcerative colitis.

Patients were randomized (1:1:1) to receive a single-dose endoscopic submucosal injection of 25 nM (n=8) or 250 nM (n=8) of STNM01 or placebo (n=8). Submucosal injections were evenly distributed across 8 mucosal sites from 5 cm to 35 cm. The primary endpoint was mucosal healing (Mayo endoscopic sub score ≤1) at day 14 or 28. Secondary endpoints included clinical response (decrease from baseline Mayo score of ≥3 points and ≥30%, plus decrease in rectal bleeding sub score ≥1 or absolute sub score ≤1), histological response (Geboes score) and endoscopic response (UCCIS) within 28 days.

Results: At baseline, 50%–62% of patients had prior anti-TNF exposure across the treatment groups. The primary endpoint of mucosal healing at day 14 or 28 was reached by 62.5% in the STNM01 250 nM (p=0.0183) group vs. 28.6% in the placebo group. If one patient is excluded from evaluation, as his baseline Mayo endoscopic sub score was 1, the rate of mucosal healing increases to 71.4% in the STNM01 250 nM group (per protocol population). Clinical response was shown by 62.5% in the STNM01 250 nM group (p=0.3200) vs. 28.6% in the placebo group. Clinical remission was shown by 50.0% (p=0.0497) in the STNM01 250 nM group vs. 14.3% in the placebo group. UCCIS segmental score and the Geboes score from baseline to either day 14 or day 28 in the STNM01 250 nM treatment group were significantly reduced compared to that in the placebo group (p<0.01). Immunohistochemical analysis revealed statistically significant inhibition of CHST15 expression in the STNM01 250 nM treatment group compared to placebo (p<0.01). Reduced accumulation of mucosal lymphocytes and sulfation of L-selectin ligand on high endothelial venule-like vessels were also demonstrated upon STNM01 treatment. STNM01 application showed a good tolerability and safety profile.

Conclusions: Submucosal injection of STNM01 was well tolerated and able to induce clinical remission, mucosal healing and histological response in left-sided ulcerative colitis patients, who did not respond sufficiently to conventional treatment.

DOP074

Pharmacokinetics and exposure-response of tofacitinib in a Phase 3 maintenance study in ulcerative colitis patients

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Background: Tofacitinib is an oral small molecule Janus kinase inhibitor that is being investigated for ulcerative colitis (UC). A recently completed 52-week (wk) Phase 3 maintenance study (NCT01458574) demonstrated efficacy of tofacitinib 5 and 10 mg twice daily (BID) in patients (pts) with moderately to severely active UC, who achieved clinical response following 8 wks of induction therapy. Here, we characterised the pharmacokinetics (PK) of tofacitinib and the relationships of tofacitinib exposure to efficacy endpoints, using exposure-response (E-R) modeling of data from the Phase 3 maintenance study.

Methods: Plasma samples for population PK analysis were collected from all pts in the maintenance study. PK data from the induction and maintenance studies were pooled, and individual tofacitinib exposure metrics (average concentration [C_{avg}]; trough concentration [C_{trough}]) were derived for pts in the maintenance study. Efficacy endpoints at Wk 24 and 52 were: remission (total Mayo score ≤2, no subscore >1, rectal bleeding subscore of 0), mucosal healing (Mayo endoscopic subscore ≤1), and sustained steroid-free remission. The E-R analysis evaluated linear and non-linear (E_{max}) relationships in a binomial model with Markov dependence, implemented in SAS v 9.2. Maintenance baseline (BL) disease (Mayo score, extent of disease, disease duration), TNF inhibitor (TNFi) failure and prior use of immunosuppressants, BL corticosteroid and aminosalicylate use, age, sex and race were evaluated as covariates.

Results: Individual predicted C_{avg} and C_{trough} did not show significant change over the 52-wk study duration. The PK was linear with a mean estimated clearance of 26.3 L/hr and a volume of distribution of 115.8 L. E-R modeling of remission at Wk 24 and 52 indicated that pts who were not in remission at BL in the study achieved greater incremental benefit with 10 vs 5 mg BID, compared to pts in remission (Figure 1) at BL. Dose-normalised C_{avg} values at each dose level were similar between pts irrespective of remission status. More refractory pts, such as those with higher BL Mayo score, who did not achieve remission during induction, and with previous TNFi failure, showed lower efficacy compared to other pts.

Conclusions: Individual plasma concentrations remained stable through the 52-wk study, and monitoring of plasma tofacitinib concentrations is not needed during maintenance treatment. The incre-

mental efficacy of 10 mg BID relative to 5 mg BID appeared to be more pronounced in pts with refractory disease.

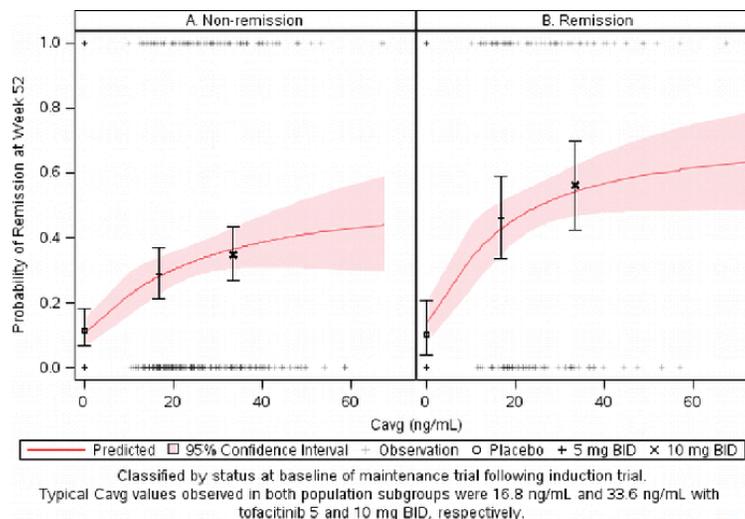
DOP075

Efficacy of filgotinib, a selective JAK1 inhibitor, is independent of prior anti-TNF exposure: subgroup analysis of the phase 2 FITZROY study in moderate-to-severe Crohn's disease

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Background: Filgotinib is an oral, selective Janus kinase 1 (JAK1) inhibitor. This 20-week Phase 2 study evaluated efficacy and safety of filgotinib in patients with active Crohn's disease (CD). The primary endpoint (CDAI remission at Week 10) was met with an acceptable safety profile. Here, an exploratory subgroup analysis of the first 10 weeks, based upon prior exposure to anti-TNF therapy, is presented. **Methods:** 174 patients with moderate-to-severely active CD (CDAI: 220 to 450) and ulcerations confirmed by centrally read endoscopy were randomized 3:1 to receive 200mg filgotinib (FIL) or placebo (PBO) QD for 10 weeks. Immunosuppressants were to be discontinued prior to treatment initiation but corticosteroid-treated patients



Abstract DOP074 – Figure 1. Predicted probability of remission at Week 52 as a function of average tofacitinib concentration (C_{avg}) in patients not in remission (Panel A) or in remission (Panel B) at the start of the maintenance trial.

Abstract DOP075 – Table 1

Variable/unit/population	Anti-TNF naïve		Anti-TNF non-responder	
	PBO=16	FIL=57	PBO=28	FIL=71
Clinical remission (CDAI<150), %, ITT-NRI	13	60	29	37
100-points clinical response (CDAI improvement with ≥100 points), %, ITT-NRI	44	67	39	54
PRO2 score, mean change from baseline, ITT-LOCF (7×(mean daily number of liquid or very soft stools + 7×(mean daily abdominal pain score))	-19.8	-24.8	-13.2	-19.5
PRO2 remission (PRO2 ≤28), %, ITT-NRI	31	61	29	41
CDAI general well-being score, mean change from baseline, ITT-LOCF	-0.78	-1.08	-0.58	-0.90
Total IBDQ score, mean change from baseline, ITT-LOCF	19.7	40.8	16.3	28.2
Overall total histopathology score, mean change from baseline, ITT-LOCF	-0.3	-3.9	-0.7	-3.2
	Anti-TNF naïve		Anti-TNF non-responder	
	PBO=9	FIL=39	PBO=18	FIL=54
Combined clinical-biological response, %, ITT-NRI (CDAI score <150 points and CRP decrease >50% and/or fecal calprotectin decrease >50% from baseline)		36	6	20

CDAI: Crohn's Disease Activity Index; ITT: Intent-to-treat; NRI: Non-responder imputation; LOCF: Last observation carried forward; IBDQ: Inflammatory Bowel Disease Questionnaire; ITT population = 172 patients (2 pts without post-baseline assessments).

remained on stable doses until Week 10. Patients naïve to anti-TNF therapy as well as patients who were previously exposed to anti-TNF with no response or loss-of-response were included. Endpoints include clinical outcome (CDAI), patient-reported outcomes (PRO: CDAI and IBDQ), histopathology (D'Haens score) and combined clinical-biological response (CDAI and biomarkers).

Results: Baseline characteristics were similar in FIL and PBO groups, including mean disease duration (8.3 years), mean CDAI score (293), mean CRP (15.6mg/L, 41%>10mg/L), oral corticosteroids (51%, mean daily dose 20.8 mg/day). 42% of the patients were anti-TNF naïve, 58% were anti-TNF non-responder. Clinical remission (CDAI<150) was induced at Week 10 in 47% of FIL patients versus 23% on PBO (p=0.0077).

CDAI remission and response were higher in the FIL group versus PBO irrespective of prior anti-TNF therapy. PRO measured by changes from baseline in PRO2 score and general well-being (CDAI component), as well as quality of life assessed by IBDQ improved more in both FIL subgroups compared to PBO. A combined clinical-biological response endpoint confirmed these findings in the subgroup with elevated CRP or faecal calprotectin at baseline. Histopathology at Week 10 showed numerically greater effects after FIL treatment versus PBO for both subgroups (Table 1). FIL was safe and well tolerated. Similar incidences in SAEs, TEAEs leading to discontinuation and infections were observed in both anti-TNF subgroups, with a somewhat higher incidence of TEAEs in anti-TNF non-responders.

Conclusions: Efficacy of filgotinib was shown in CD patients independently of their prior anti-TNF exposure, and was consistent across all endpoints. The safety profile was also similar. These data suggest a favourable risk/benefit profile, in both anti-TNF naïves and anti-TNF non-responders.

DOP076

A phase 2B, multicenter, randomized, placebo-controlled dose-ranging trial of peficitinab, an oral JAK inhibitor, in patients with moderately to severely active ulcerative colitis

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Background: Janus kinases (JAK) are intracellular signaling molecules central to immune responses in IBD. We studied efficacy and safety of peficitinib, an oral JAK inhibitor, in moderate-severe UC.

Methods: Eligible patients had a Mayo score of 6–12, including a centrally read endoscopy subscore ≥2, and inadequate response to, or failure to tolerate corticosteroids, 6-MP/AZA, or TNF antagonists. Patients were randomized at wk0 to PBO (n=43), peficitinib 25mg qd, 75mg qd, 150mg qd, or 75mg bid (n=44 per group). Primary endpoint was change from baseline Mayo score at wk8; Multiple Comparison Procedures method was used to analyze dose response for qd regimens. Secondary endpoints (using central endoscopic subscore) were clinical response and remission and mucosal healing at wk8. Safety was evaluated through wk8.

Results: 219 patients were randomized. Baseline characteristics and concomitant medications were generally similar among treatment groups. Primary endpoint of dose response for qd regimens was not met (adjusted p-values for candidate dose response curves were >0.05). Change from baseline in Mayo score at wk 8 was numerically higher for peficitinib doses ≥75mg qd vs PBO (–2.3 [25mg qd], –3.1 [75mg qd], –2.8 [150mg qd], vs –2.4 [PBO]); none reached statistical significance. Trends for efficacy were observed for doses ≥75mg qd based on proportion of patients with clinical response (34.1% [25mgqd], 54.5% [75mg qd], 54.5% [150mg qd], 54.5% [75mg bid] vs 39.5% [PBO]), clinical remission (15.9% [25mg qd], 15.9% [75mg qd], 27.3% [150mg qd], 15.9% [75mg bid] vs 7.0% [PBO]) and mucosal healing (20.5% [25mg qd], 29.5% [75mg qd], 45.5% [150mg qd], 36.4% [75mg bid], vs 18.6% [PBO]). AE rates were higher across peficitinib groups vs PBO through wk8 (45.5% [combined] vs 34.9% [PBO]) mainly occurring in ≥75mg qd dose groups. Most common AEs were UC (5.7% [combined] vs 9.3% [PBO]), CPK increase (4.0% [combined] vs 0.0% [PBO]). Rates of discontinuation due to AE were similar between combined peficitinib groups and PBO (8.0% and 7.0%, respectively). SAEs were uncommon (3.4% [combined] vs 4.7% [PBO]). Incidences of infection were similar (12.5% [combined] vs 14.0% [PBO]). Serious infections were rare. There were modest increases in fasting lipids and CPK for doses of ≥75mg qd.

Conclusions: Peficitinib did not demonstrate dose response based on mean change from baseline Mayo score at wk8 in patients with moderate-severe UC. Trends for greater proportions of patients

achieving clinical response, clinical remission, and mucosal healing were observed at doses ≥ 75 mg qd. The safety profile of peficitinib through wk8 was generally consistent with the known profile of JAK inhibitors.

DOP077
Immunomodulatory effects of etrasimod (APD334), an oral, potent, next-generation, selective S1P receptor modulator

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Background: Etrasimod is an oral potent, next-generation S1P modulator with an optimized S1P receptor activity profile that is currently in Phase 2 clinical development for ulcerative colitis.

Methods: Two randomised, double-blind studies evaluated safety, tolerability and pharmacodynamic (PD) responses of etrasimod, administered orally as single dose (dose-escalation design; 8 subjects/cohort) or repeat once daily (QD) dosing for 21 days (multiple ascending-dose design; 12 subjects/cohort), in healthy adults. PD parameters, including complete blood count (CBC) with differential, platelet count and lymphocyte immunophenotyping, were determined from peripheral blood sampling. Single-dose study assessments were Day -1, pre-dose (Day 1) and pre-specified times post-dose on Day 1, and up until Day 7 (Exit). Multiple-dose study assessments were screening, pre-dose (Day 1) and 4–8 hours post-dose on Days 1, 3, 5, 7, 9, 15, 21, 23 (Exit), and Day 28 (follow-up), with peripheral blood lymphocyte immunophenotyping performed on Days 1 and 21 (2mg cohort only).

Results: In the single-dose study, etrasimod 3mg and 5mg induced a decline in absolute number of B cells, Natural Killer cells, and T cells (absolute and subsets): lower doses (0.1, 0.35 or 1mg) had little or no effect. In the multiple-dose study, lymphocyte lowering was dose-dependent, plateauing at 2mg: median reductions in lymphocyte counts were ~67% with etrasimod 2 and 3mg, returning to baseline within 7 days of discontinuation. Reductions from baseline in T cells (as a % of white blood cell count [WBC] and lymphocytes) were greater with etrasimod (2mg) than placebo. The primary effect of etrasimod was seen in the Thelper and Tnaïve subpopulations, with a lesser extent in Tcentral memory cells (consistent with an expected retention of CCR7+ cells in secondary lymphoid tissue) [1]. Tsuppressor and Teffector memory cells were generally spared. Decreases in neutrophils were not consistently dose responsive: change from baseline in minimal neutrophil count (placebo subtracted) was 0.04–0.65 $\times 10^3$ /UL.

Conclusions: Etrasimod modulates lymphocyte subpopulations believed to be involved in IBD pathogenesis. These findings support further evaluation of this S1P modulator in clinical studies.

References:

[1] Gergely P, et al. *Br J Pharmacol* 2012;167:1035–47.

DOP078
Pharmacology and safety of etrasimod (APD334), an oral, potent, next-generation, selective S1P receptor modulator

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Background: Etrasimod is an oral, potent, next-generation S1P modulator in clinical development for ulcerative colitis.

Methods: *In vitro*, etrasimod potency and selectivity was assessed at mouse, rat, dog and human S1P receptors in intracellular β -arrestin recruitment and cAMP accumulation assays using S1P receptor-expressing cells. *In vivo*, etrasimod (1 and 3 mg/kg, until Day 32) was evaluated in a CD4+CD45RBhigh T cell adoptive transfer model in SCID mice. Chronic toxicology studies of etrasimod once daily (QD) were conducted in rats (≤ 250 mg/kg/day for 26 weeks) and dogs (≤ 15 mg/kg/day for 39 weeks). In healthy adults, two randomised, double-blind studies evaluated safety, tolerability and pharmacology of single or repeat etrasimod QD dosing.

Results: Etrasimod is a potent, full agonist at human S1P1 receptors with a mean EC50 value of 6.10nM. It was selective for S1P1, with 24 fold and 4 fold selectivity versus human S1P4 and S1P5, respectively, and no activity at S1P2 and S1P3 (>1000 fold selectivity). Similar results were found in all species tested. In the T-cell adoptive transfer model, etrasimod (3 mg/kg/day) significantly inhibited weight loss and colon inflammation versus vehicle-treated controls. Chronic administration to rats was well tolerated at ≤ 150 mg/kg/day, but 250mg/kg/day showed significant adverse effects, including mortality. Chronic administration to dogs at ≤ 15 mg/kg/day was well tolerated. The no-observed-adverse-effect level (NOAEL) was therefore 150mg/kg/day for rats and 15mg/kg/day for dogs. Based on these study data, human safety margin for a clinically relevant dose of 2mg etrasimod were 1,068-fold and 402-fold for rats and dogs, respectively. In healthy adults, single doses of etrasimod 0.1–3mg were well tolerated; 4 events (3 subjects) of first/second degree atrioventricular block, with/without bradycardia, were reported in the 5 mg cohort. No other clinically significant safety issues were reported. Etrasimod exposure was dose proportional from 0.1–5mg, with a consistent mean terminal t1/2 (30.7–37.4 hours), and no quantifiable levels in urine analysis. With multiple QD dosing for 21 days, no safety concerns were reported and etrasimod was well tolerated at all doses (0.7–3.0mg). Etrasimod plasma exposure accumulation after 21 days was >2-fold versus single dose administration across all doses: C_{max}: 2.12–2.72; AUC_{0–24}: 2.33–3.03. Etrasimod produced a dose-dependent, sustained decrease in total lymphocyte count, with the maximal effect at the 2mg dose.

Conclusions: The combined preclinical/clinical safety and pharmacology profile of etrasimod provides rationale for further evaluation of this selective S1P modulator in clinical studies.

DOP079
The role of intestinal transplant in patients with complicated inflammatory bowel disease: the Cambridge experience

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Background: A number of patients with inflammatory bowel disease (IBD), despite best medical and surgical interventions, fail to thrive necessitating parenteral nutrition (PN) and in rare cases considera-

tion of intestinal transplant. Some may require other organs transplanted simultaneously for example if they have co-existing severe liver or renal diseases.

Methods: We retrospectively reviewed our database with the aim to study the outcome of IBD patients who were referred for intestinal or multivisceral transplant at our unit between 2008 and November 2016.

Results: Over the last 8 years, 30 patients with IBD were referred for consideration of intestinal transplant. The majority were on PN for a mean of 9.2 years (range 1–30 years) and suffered from PN-related complications (see image). The need for PN stemmed from stricturing or fistulising behaviour of Crohn's disease (CD) while patients with ulcerative colitis (UC) experienced post-colectomy complications such as volvulus or ischaemia rendered them short gut. At the time of referral, most patients (21/30) were no longer on any maintenance drugs for their IBD as they do not have active disease. 43.3% of patients referred (11/24 CD, 2/6 UC) underwent transplant. More than half (8/13) included a liver-containing graft. The indications comprised primary sclerosing cholangitis (PSC) (1), intestinal failure associated liver disease (IFALD) (2), alcohol and non-alcoholic fatty liver disease (1); biliary sepsis (1), and secondary biliary cirrhosis with methotrexate hepatotoxicity (1). 3 patients had kidney and intestine grafts due to concurrent end-stage renal failure. The remaining 2 had intestinal transplant primarily due to loss of vascular access.

Post-transplant, 1 patient required ongoing PN due to severe bowel rejection and 2 required parenteral fluids to maintain their renal function. There was improvement in mean body mass index (from 22.2 to 23.5 kg/m²) and handgrip strength by 7% at median of 12 months post-transplant. To date there is 1 possible but not definite IBD recurrence. During the study period, there were 4 deaths at a mean of 39.3 months (range 16–64.4 months). This is in keeping with our unit's general 5-year survival rate of 55.4% and compared favourably with the international data [1].

Conclusions: PN-related complications are the most common indications for intestinal transplant referral. Concurrent liver disease is common in our studied population with complex IBD resulting in the need for simultaneous liver transplant.

References:

- [1] D. Grant, K. Abu-Elmagd, G. Mazariegos, et al. (2015), Intestinal Transplant Registry Report: Global Activity and Trends, Wiley Periodicals Inc., American Journal of Transplantation, 210–219, 15, <http://onlinelibrary.wiley.com/doi/10.1111/ajt.12979/pdf>, 2016–01–01

DOP080

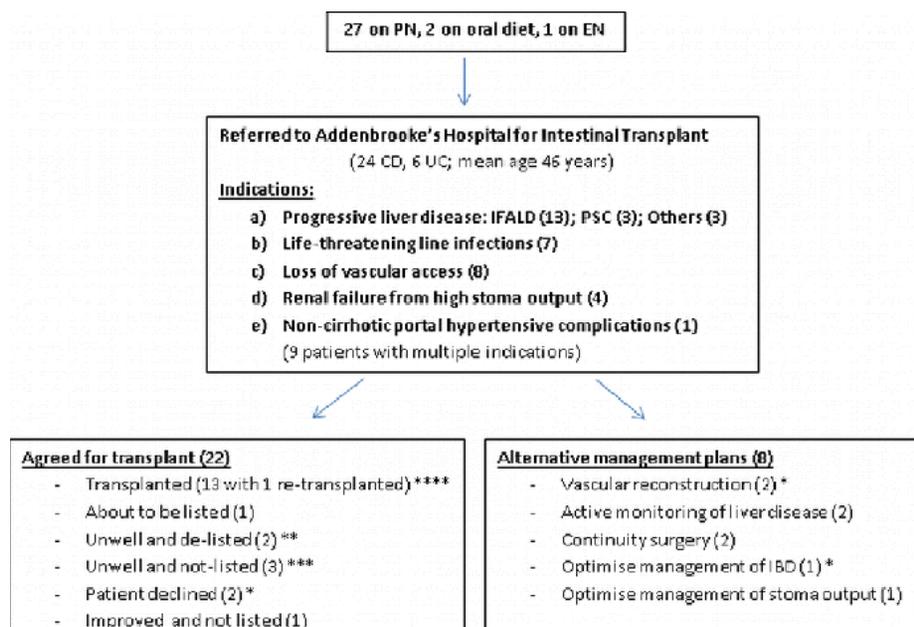
Low viral richness at baseline in ulcerative colitis associated with faecal microbiota transplantation success

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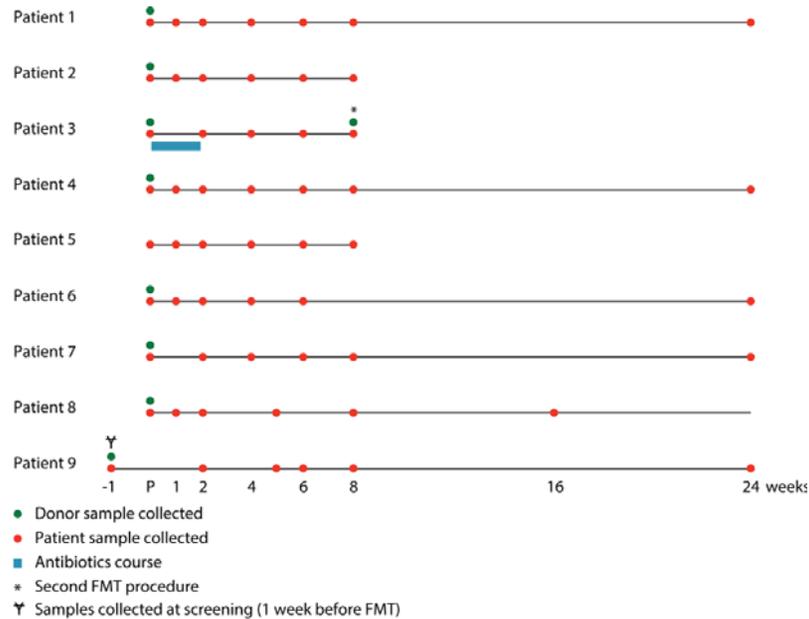
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Background: Faecal microbiota transplantation (FMT) has been seen as a promising tool in inflammatory bowel disease (IBD), but its use remains controversial. Bacteriome dysbiosis in IBD is well established, however the role of viruses is still understudied. Recently, an increased viral richness together with decreased bacterial diversity has been associated with IBD. We accessed the viral longitudinal dynamics in nine ulcerative colitis (UC) patients that underwent FMT (Figure). Of these, two patients (1 and 3, figure) presented endoscopic and long-term (>2-years) remission after FMT. However, the first FMT for patient 3 was followed by pneumonia and a course of antibiotics, and only sample related to the second FMT, of which no follow-up samples were available, were analysed.

Methods: Viral particles were purified from faeces using protocol NetoVIR and subsequently shotgun sequenced on an Illumina platform. Sequences were trimmed, *de novo* assembled, translated and compared to a protein database for taxonomic annotation. Richness and diversity were calculated using the vegan package in R.



Abstract DOP079 – Figure 1. Referral outcome for intestinal transplant (*number of deaths; PN = Parenteral Nutrition; EN = Enteral Nutrition.)



Abstract DOP080 – Figure 1. Overview of the sample collection analysed for the virome dynamics.

Results: A higher viral richness at baseline was observed ($p=0.023$) in patients ($n=9$) when compared to their donors ($n=8$). When comparing all longitudinal samples from FMT responders ($n=7$) and non-responders ($n=43$), a lower richness ($p=0.0005$) was found for the responders. Comparing samples collected before FMT (baseline) from patients based on their outcome showed that responders ($n=2$) already presented a trend towards a lower richness ($p=0.056$) compared to non-responders ($n=7$). Finally, no significant differences could be observed ($p=0.286$) in viral richness of donors and outcome of patients.

Transferred phylotypes were defined as viral genera present in the donor sample and increased in the patient samples post-transplantation. We observed that in the responder with longitudinal data available, 8 viral genera were transferred, while the 6 non-responders, presented on average 32 transferred species. Since no samples post-transplantation were available for patient 3 we could not further verify this observation.

Conclusions: Our data confirms that diseased individuals present a higher viral richness and our study suggests that lower viral richness at baseline is associated with a good FMT outcome. Interestingly, the responder presented less transferred viral genera, in line with previous findings that a lower viral diversity is beneficial, suggesting that pre-screening of patients could lead to an increased success of FMT.

DOP081 Glycosylation of T cells: a novel targeted-specific therapeutic strategy in IBD

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Background: The incidence of Inflammatory bowel disease (IBD) is increasing worldwide and the current therapeutic strategies are limited by reduced effectiveness, high costs, and/or presence of toxic/side effects. We have previously demonstrated that UC patients display a deficiency in the levels of glycosylation of mucosal T cells that was associated with disease severity [1].

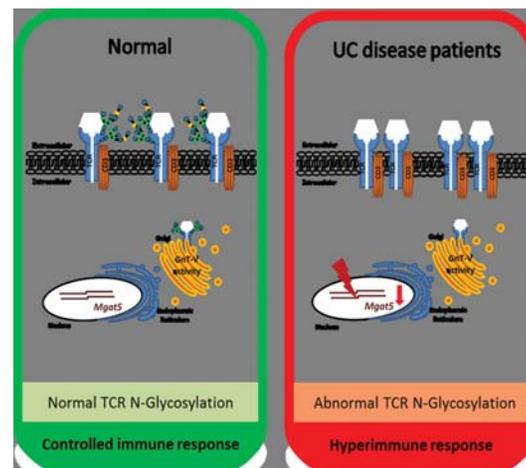


Figure 1. Dysregulation of T cell receptor N-glycosylation: a new molecular mechanism in UC pathogenesis.

However, it remains unknown whether this mechanism can be therapeutically targeted in IBD.

Methods: We conducted *ex vivo* and *in vivo* studies in order to evaluate the impact of glycans supplementation in the regulation of T

cell-mediated immune response. Purified mucosal T cells were obtained from fresh colonic biopsies of 68 Ulcerative Colitis (UC) patients with active disease and the effects of the supplementation with specific glycans in the adaptive immune response were studied by analysing T cell proliferation (by CFSE assay); T cell differentiation and cytokines production (by flow cytometry) and TCR signaling (by western blot). Additionally, we used *in vivo* mouse models of colitis (DSS-induced) as well as transgenic mice with different glycosylation profiles to assess the impact of glycans in the control of disease severity and disease progression.

Results: The results on *ex vivo* T cells cultures revealed that the supplementation with specific glycans is able to enhance the glycosylation of T cells, repairing the previously described deficiency on branched glycans in T lymphocytes [1].

We observed that increasing doses of specific glycans resulted in a significant reduction of T cell proliferation, suppression of Th1 and Th17 response through decreasing the expression of the transcription factors, T-bet and ROR γ t and the respective cytokines production, TNF- α , INF- γ and IL17A. Downstream TCR signaling was also suppressed as observed by the reduction in phosphorylation levels of ZAP70 and LAT. Interestingly, our *in vivo* data reveal that mice with colitis treated with specific glycans exhibited a suppression of disease severity and a delay in disease progression as demonstrated by low disease activity index (DAI) and suppression of Th1 immune response in the gut.

Conclusions: Our data suggest that enhancing the glycosylation of T cells resulted in a significant suppression of T cell mediated-immune response associated with the control of intestinal inflammation and suppression of disease severity and progression. Glycans are thus a novel and promising target-specific immunomodulatory therapy in IBD.

References:

- [1] Dias, AM et al., (2014), Dysregulation of T cell receptor N-glycosylation: a molecular mechanism involved in ulcerative colitis, Human Molecular Genetics

DOP Session 10: Translational IBD

DOP082

Enhanced TH17 responses in patients with IL10 receptor deficiency and history of infantile-onset IBD

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Background: Loss-of-function mutations in the IL10 receptor (IL10R) genes cause severe infantile-onset IBD. Intact IL10R-dependent signals have been shown to be important for innate immune cell function and for regulation of effector and regulatory T cell function in mice. We have previously reported a key role of IL10 is the generation and function of human anti-inflammatory macrophages. Independent of innate immune cell defects, the aim of the current study was to determine the role of IL10R signaling in regulating human CD4⁺T cell function.

Methods: Peripheral blood mononuclear cells and intestinal lamina propria cells were extracted from IL10R-deficient patients and

controls. Frequencies of CD4⁺ T cell subsets, naive T cell proliferation and regulatory T cell (Treg)-mediated suppression and Treg and TH17 generation were determined by flow cytometry. Transcriptional profiling of these populations was performed by quantitative real-time PCR and nanoString platforms.

Results: Analysis of 12 IL10R-deficient patients demonstrated similar frequencies of peripheral blood and colonic lamina propria Tregs, compared to healthy control subjects. Moreover, *in vitro* Treg suppression of naive CD4⁺ T cell proliferation and generation of Treg were not dependent on IL10R signaling. However, IL10R-deficient T naive cells exhibited significantly higher proliferative capacity, a strong TH17 signature and a marked increase in polarization towards TH17 cells, compared to controls. Moreover, the frequency of TH17 cells was increased in the colon of an IL10R-deficient patient vs. controls.

Conclusions: IL10R signaling regulates TH17 polarization and T cell proliferation in humans, but is not required for the generation of Tregs in blood and mucosal compartments, and is dispensable for *in vitro* Treg suppression. Therapies targeting the TH17 axis might be beneficial for IL10R-deficient patients as a bridge to hematopoietic stem cell transplantation.

DOP083

Recombinant subcutaneous human beta-Defensin 2 (hBD2) ameliorates experimental colitis in different *in vivo* models

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Background: In recent years, the significance of antimicrobial peptides for the maintenance of epithelial barriers has been recognized and various diseases have been associated with compromised antimicrobial barrier function. Of note, colonic Crohn's disease has been related to an attenuated induction of human beta defensin 2 (hBD2) in the colon. In addition to their antimicrobial activity, defensins also have important immune-modulatory functions. Here, we screened hBD2 for potency and toxicity and produced this peptide using a microbial expression system. Furthermore, we tested its preclinical efficacy using different *in vivo* models of colitis.

Methods: We established a cellular expression-system, *Saccharomyces cerevisiae*, to produce sufficient amounts of hBD2 for *in vivo* screening and determined its antimicrobial activity *in vitro*. Next, we tested hBD2 for cytotoxicity in human PBMCs and in murine fibroblasts and assessed its anti-inflammatory properties in human PBMCs stimulated with LPS. Finally, we tested hBD2 in different mouse models of colitis using subcutaneous (s.c.) application. We used DSS (dextran sulfate sodium, n=10), TNBS (Trinitrobenzenesulfonic acid, n=15) and T-cell transfer from wild-type into SCID mice to induce colitis (n=11). To test the protective effect of hBD2, animals were treated once a day by s.c. injection of a dose range of 0.1–3 mg/kg.

Results: We obtained a yield of >400 mg/L of hBD2 on a 10 L scale. HBD2 showed antimicrobial activity in radial diffusion assays while we did not find any cytotoxic effect against human PBMCs and murine fibroblasts. Treatment of LPS-activated human PBMCs with hBD2 decreased the release of pro-inflammatory TNF α , IL-1 β and IL-23 while upregulating anti-inflammatory IL-10 and IL-24. In all colitis models tested s. c. application of hBD2 led to a remark-

able improvement of disease at an optimal dose of 0.1 mg/kg (DSS and TNBS) and 1 mg/kg (transfer) on par with anti-TNF α (DSS), prednisolone (TNBS) and dexamethasone (transfer), respectively. In the DSS model hBD2 ameliorated loss of body weight ($p < 0.05$), improved the disease activity index ($p < 0.001$) as well as the histological score ($p < 0.001$), significantly. In the TNBS model the histological score was significantly improved by hBD2 treatment ($p < 0.001$) while in the T-cell-transfer model hBD2 again improved the disease activity index.

Conclusions: We were able to produce and purify hBD2 in relevant amounts. Since hBD2 showed no cytotoxicity, strong anti-inflammatory properties and protected mice from colitis our data provided evidence that hBD2 could be used as potential therapeutic agent in the treatment of inflammatory bowel diseases.

DOP084

Peripheral T cell repertoire reconstitution in Crohn's disease patients undergoing autologous HSCT

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Background: Hematopoietic stem cell transplant (HSCT) is considered a salvage therapy for patients with Crohn's disease (CD) refractory to current pharmacological therapies and in whom surgery is not suitable due to disease location or extension. It has been hypothesized that HSCT induces a "reset" of the immune system, producing a new non-autoimmune repertoire. Accurate and quantitative comparison of the regenerated T cell compartment relative to the baseline repertoire has not been performed in such patients.

Aim: To analyse the changes induced by HSCT in the peripheral blood T cell repertoire.

Methods: Fourteen CD patients were closely monitored at baseline and followed up for 1 year after receiving autologous HSCT. Blood samples were collected at baseline (pre-mobilization) and at 6 months and 1 year after HSCT. Samples from 3 healthy individuals at two different time points were analysed and used as control for TCR stability. We performed high-throughput deep TCR β sequencing to track the presence and frequency of individual T cell clones in each patient across time-points, and to calculate the estimated diversity of the TCR repertoire. We correlated the latter with clinical outcome, and defined response to HSCT as a SES-CD < 7 at 1 year. To quantitatively compare the repertoire similarity at two different time points, we used the Morisita-Horn index (M-H; range 0–1).

Results: Monoclonal expansions in the T cell compartment are present at baseline in CD patients. This fact is associated with overall higher sample clonality compared to healthy individuals (p value = 0.02). Moreover, the number of TCR sequences at baseline is significantly lower in patients that do not achieve remission 1 year after HSCT compared to those that do (p value = 4×10^{-3}). TCR clonality is further increased (p value = 1×10^{-3}) 6 months after HSCT, reflecting the presence of highly expanded clones. The overall similarity between the repertoire at baseline and 6 months after HSCT was low (mean M-H=0.17), whereas a high degree of similarity (mean M-H=0.72) was observed between the repertoire at 6 months and 1 year. Nonetheless, an average of 14% of the clones present at baseline persists (with high frequency) at 6 months and 1 year after-HSCT regardless of response to treatment.

Conclusions: Patients with refractory CD who underwent HSCT present high TCR clonality at baseline compared to controls, suggest-

ing the presence of expanded T cell clones. A lower baseline number of TCR sequences is associated with poor response to HSCT. HSCT induces dramatic changes the pre-existing TCR β repertoire in blood. Nevertheless, a not negligible number of clones persist in the peripheral blood in high frequency following HSCT, regardless of the efficacy of the procedure.

DOP085

Tight NADPH oxidase regulation is a prerequisite for gut health

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Background: Tight control of reactive oxygen species (ROS) production is vital in chronic inflammatory disorders. Overproduction of ROS can lead to oxidative stress, but likewise insufficient ROS compromises the host's antimicrobial defenses, exposing to an increased risk of developing life-threatening infections. ROS deficiency due to phagocytic NOX2 complex loss-of-function mutants is the cause of an inherited immunodeficiency disorder, termed chronic granulomatous disease (CGD). Up to 40% of CGD patients develop severe gastrointestinal complications, such as pancolitis and epithelioid granulomas. Recently, we identified and characterized functionally altered NOX1 and DUOX2 variants in very early onset IBD patients, which were associated with severe intestinal pathology. However, the role of ROS in the maintenance of intestinal homeostasis is still unclear as reduced and increased NADPH oxidase function have been associated with Crohn's disease and ulcerative colitis.

Methods: In order to systemically investigate the role of NADPH oxidase-derived ROS in the regulation of gut pathology, enteric inflammation was studied in a panel of Nox knockout strains. Oral challenge with colitogenic chemicals [(dextran sodium sulfate (DSS) and trinitrobenzene sulfonic acid (TNBS)] or *Citrobacter rodentium* were used to mimic commensal- or pathogen-driven intestinal pathology.

Results: An impairment of ROS production due to discrete deletion (Nox1, Nox2, Nox4) or cumulative inactivation ($p22^{\text{phox}}$) of NADPH oxidases in mice did not affect the severity of DSS-induced colitis. However, mice with limited ROS generation due to partial inactivation of NADPH oxidases showed increased susceptibility to develop severe intestinal inflammation, which compromised their recovery and led to premature death. This pro-inflammatory phenotype was observed in either the DSS or TNBS model of colitis. Mice showed altered mucus production, increased antimicrobial peptides, immune cell infiltration, iNOS overexpression and increased levels of Il6, Inf γ , Il1a, Il17c, and Cxcl1 mRNA. Wild type bone marrow transplantation reduced the DSS-induced inflammation, suggesting that the NADPH oxidase defect responsible of this phenotype resides in the hematopoietic cell compartment. In contrast, limited ROS generation did not impact infectious colitis induced by *C. rodentium*.

Conclusions: Single or cumulative Nox NADPH oxidase deficiency did not affect intestinal pathophysiology, while restricted ROS production in the myeloid cell compartment predisposed to severe chemical-induced intestinal inflammation following epithelial barrier damage. Overall these data suggest that tight NADPH oxidase regulation is a prerequisite to preserve gut homeostasis.

DOP086**Macrophages from Crohn's disease patients showed a defect to control adherent-invasive *Escherichia coli* replication influenced by genetic host factors**

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Background: Adherent-invasive *E. coli* (AIEC) abnormally colonize ileal mucosa from one third of Crohn's disease (CD) patients. AIEC are able to survive within macrophages, which are pivotal cells in eliminating intracellular bacteria. We recently suggested that macrophages from CD patients could have an impaired ability to restrict intracellular AIEC replication.

We aimed to confirm that macrophages from CD patients could have an impaired ability to restrict intracellular AIEC replication compared to ulcerative colitis (UC) patients or healthy volunteers (HV). We also investigated the factors associated with this deficiency and analyzed macrophages behaviour in response to AIEC infection in CD patients.

Methods: Peripheral blood monocyte-derived macrophages (MDM) were obtained from 95 CD patients, 30 UC patients and 15 HV, genotyped for CD-associated polymorphisms implicated in autophagy (ULK, LRRK2, NOD2, IRGM and ATG16L1), ER stress (XBP1), or ubiquitin-proteasome system (CYLD, USP40). The numbers of intracellular bacteria were determined at 1h and 10h post-infection using gentamicin assay. Cytokine secretion was quantified by ELISA, LDH by colorimetry assay and CD163 by western blot.

Results: The AIEC uptake (1h post-infection) within MDM did not differ according to MDM origin. The AIEC survival (10h post-infection) within MDM from CD patients compared to UC patients or HV ($p=0.0019$). In multivariate analysis, AIEC survival within MDM from CD patients was positively correlated with IL1- β secretion ($p<0.0001$) and was decreased in the presence of ULK1 ($p=0.046$), XBP1 ($p=0.014$) and CYLD ($p=0.0008$) mutations. AIEC were able to replicate within MDM from CD patients but not within MDM from UC patients or HV ($p<0.001$). In multivariate analysis, AIEC intracellular replication was increased in CD patients with IRGM mutation ($p=0.045$). AIEC infection leads to specific inflammatory response (increased secretion of TNF- α , IL-1 β and IL-8 compared to UC patients and HV, $p<0.001$ for both) which does not depend on MDM origin but is associated with intestinal inflammation exclusively in CD patients. MDM from CD patients exhibit a specific phenotype at baseline (low LDH secretion, $p<0.001$) compared to UC patients. AIEC infection modified MDM behaviour from CD patients in weakening MDM (increase of LDH secretion, $p<0.05$) and decreasing macrophages activation (decrease of CD163, $p<0.05$).

Conclusions: We confirmed that MDM from CD patients are deficient to control AIEC replication compared to UC or healthy controls and identified the key role of autophagy (especially IRGM), ER stress and ubiquitin-proteasome system genes. We also reported a specific inflammatory response of AIEC-infected macrophages depending on the intestinal inflammation.

DOP087**Microbial colonization at weaning period determines colitis severity in adult mice**

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Background: Evidence for the “hygiene hypothesis” in the etiology of inflammatory bowel diseases (IBD) is not fully established. Epidemiological studies show that children exposed to antibiotics during the first year of life have an increased risk of IBD development. However, underlying cellular and molecular mechanisms remain enigmatic. We aim to determine how perturbations in host-microbial symbiosis during childhood impact intestinal immunity and increase the risk to develop IBD at adult age.

Methods: The impact on the immune system of a decreased exposure to microbiota was assessed during suckling, weaning and adulthood. Dextran sodium sulfate (DSS)-induced colitis was used as the experimental model of IBD. The differential response to DSS in conventional mice treated with a cocktail of antibiotic from birth until 2, 4, 6 or 12 weeks of age was compared to untreated mice. In addition, colitis severity in adult germ-free (GF) mice and in GF mice colonized during the neonatal period or after weaning was compared to conventional mice.

Results: The production of pro-inflammatory cytokines (e.g. TNF- α and IFN- γ) in ileum and in colon was increased around weaning under specific pathogen-free (SPF) but not in germ-free conditions. We show that the gut microbiota produces short chain fatty acids (SCFA) that induce the pro-inflammatory response during the weaning period. Exposition of germ-free mice to SPF conditions only at weaning, but not later, protects the intestine of adult mice from DSS-induced colitis. Conversely, antibiotic treatment during weaning results in increased sensitivity to DSS-induced colitis at adult age. Treatment with selective antibiotics revealed that the protective effect of gut microbiota is associated with the presence of Gram-positive bacteria, probably through the production of SCFA. This protective effect of SCFAs early in life is dependent of regulatory T cells expressing the transcription factor ROR γ t (Retinoid-Acid Receptor-related Orphan Receptor gamma t).

Conclusions: Our study reveals how host-microbial symbiosis early in life determines the colitis severity in adult mice.

DOP088**Somatic and visceral hypersensitivity associated to acute intestinal inflammation are absent in sigma 1 receptor knockout mice**

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Background: Intestinal inflammation is associated to both visceral and somatic hypersensitivity. Several studies show that sigma-1 receptors (σ_1 Rs) are implicated in pain and pain sensitization. We assessed the role of σ_1 Rs on colitis-associated changes in somatic and visceral sensitivity, using a murine model knockout for σ_1 Rs.

Methods: Adult CD-1 male wild type (WT) and σ_1 R knockout mice (σ_1 R KO) were used. Colitis was induced by exposure to a 3% solution of dextran sodium sulfate (DSS) during a 5-day period (experimental days 0 to 5), followed by a 2-day recovery. A von Frey test was used to assess changes in somatic (plantar withdrawal response)

and visceral mechanosensitivity (abdominal withdrawal response). Changes in mechanosensitivity were assessed before (experimental day -1), during (experimental day 3) and after colitis induction (experimental day 7). At termination, colonic expression (RT-qPCR) of several receptors involved in visceral sensitivity, including cannabinoid receptors (CB1, CB2) and μ -opioid receptor (MOR), was assessed.

Results: σ_1 R KO mice showed attenuated clinical signs and colonic inflammation as assessed macro and microscopically. Somatic and visceral mechanosensitivity was similar in WT and σ_1 R KO mice before the induction of colitis (Table 1). In WT mice colitis was associated to a time-related development of somatic and visceral mechanical hypersensitivity (Table). In σ_1 R KO neither somatic nor visceral mechanical sensitivity was altered during inflammation (Table). Basal expression of CB1 and MOR was similar in WT and σ_1 R KO mice, while CB2 was up-regulated in σ_1 R KO mice. Regardless the phenotype considered, CB1 and MOR were down-regulated during colitis, while no changes in CB2 expression were observed.

Table 1. Data are mean \pm SEM, n=6-8 per group. *p<0.05 vs. day -1.

		Day -1	Day 3	Day 7
Somatic sensitivity (g force)				
WT	Control	1.47 \pm 0.03	1.38 \pm 0.08	1.31 \pm 0.07
	DSS	1.49 \pm 0.02	1.07 \pm 0.13 *	0.78 \pm 0.13 *
σ_1 R KO	Control	1.41 \pm 0.07	1.37 \pm 0.08	1.47 \pm 0.03
	DSS	1.46 \pm 0.05	1.49 \pm 0.02	1.49 \pm 0.01
Visceral sensitivity (g force)				
WT	Control	1.16 \pm 0.12	1.34 \pm 0.13	1.13 \pm 0.16
	DSS	1.22 \pm 0.09	0.71 \pm 0.15 *	0.49 \pm 0.15 *
σ_1 R KO	Control	1.06 \pm 0.15	1.06 \pm 0.15	0.92 \pm 0.16
	DSS	1.37 \pm 0.06	1.26 \pm 0.11	1.26 \pm 0.09

Conclusions: Intestinal inflammation-associated visceral and somatic hypersensitivity was absent in σ_1 R KO mice, thus indicating that σ_1 Rs are involved in pain sensitization. Antagonism of σ_1 Rs might represent an attractive pharmacological approach for the treatment of visceral and somatic hypersensitivity.

DOP089

PTPN2 controls intestinal inflammation and promotes colitis-associated tumour formation via control of inflammasome activation and IL-1 α release

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Background: Variants in the gene locus encoding protein tyrosine phosphatase non-receptor type 2 (PTPN2) are associated with Crohn's disease (CD) and ulcerative colitis (UC). We recently found that deletion of PTPN2 in macrophages promotes colitis severity, while protecting from colitis-associated tumours, but the molecular mechanisms underlying this phenotype are still elusive. IL-1 α and IL-1 β exert important, yet distinct, immune-modulatory function in the intestine, but their precise role during intestinal pathologies is still controversial. Here, we investigated whether IL-1 α and/or IL-1 β are involved in enhanced colitis and/or reduced tumour development observed in mice lacking PTPN2 in macrophages (PTPN2-LysMCre mice).

Methods: Colitis was induced in 10-12 week old PTPN2-LysMCre mice and their wild-type (WT) littermates by administration of 2% dextran-sodium sulfate (DSS) for 7 days (acute colitis), or by repeated treatment with 1.5% DSS for 7 days, followed by 10 days normal drinking water (four cycles in total, chronic colitis). For tumour induction, mice were injected with azoxymethan (AOM) at day one of each DSS cycle during chronic colitis induction. IL-1 β and IL-1 α were inhibited using a vaccine-based approach.

Results: *In vitro*, PTPN2-deficient macrophages secreted more mature IL-1 β , and levels of active caspase-1 were enhanced, indicating pronounced inflammasome activity. Responsible for enhanced inflammasome activation was increased phosphorylation of the inflammasome-adaptor molecule ASC. Further, PTPN2-deficient macrophages secreted increased levels of IL-1 α , while surface-associated IL-1 α was markedly reduced. As expected from our previous studies, PTPN2-LysMCre mice suffered from pronounced colitis, but reduced tumour load. In the serum, IL-1 α and IL-1 β levels were enhanced in PTPN2-LysMCre mice upon DSS or AOM/DSS treatment, but surface IL-1 α on macrophages and intestinal epithelial cells was reduced. Inhibition of IL-1 β during colitis induction/tumour formation protected PTPN2-LysMCre mice from pronounced colitis, but re-established the susceptibility to colitis-associated tumours. In contrast, inhibition of IL-1 α did not affect colitis severity, while protecting WT mice from the induction of colitis-associated tumours.

Conclusions: PTPN2 is a crucial regulator of inflammasome activation, and its loss in macrophages has important consequences for intestinal homeostasis. Further, our results demonstrate that the structurally related molecules IL-1 α and IL-1 β exert distinct roles during intestinal inflammation and tumorigenesis, and PTPN2 modulates secretion and surface expression of these two cytokines.

DOP090

The $\alpha 7$ nicotinic acetylcholine receptor agonist GTS-21 attenuate DSS-induced colitis by improving intestinal mucosal barrier function

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Background: GTS-21, a selective $\alpha 7$ -nicotinic acetylcholine receptor ($\alpha 7$ nAChR) agonist, demonstrated to inhibit the inflammation. In this study, we investigate whether GTS-21 can protect against DSS-induced colitis and its potential mechanism.

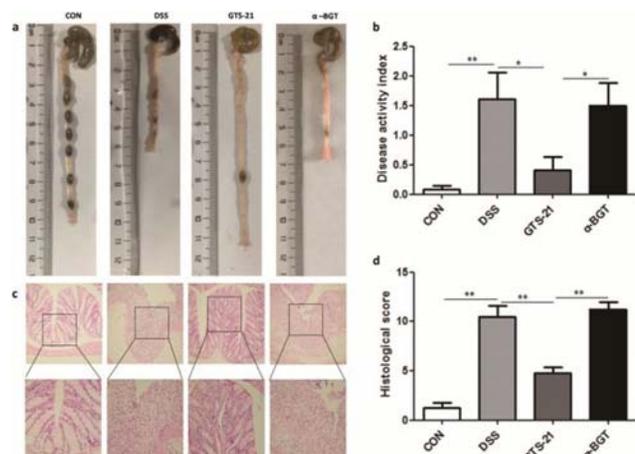


Figure 1

Methods: male BABL/c mice (8-week old) were divided into 4 groups (n=8, each group): control group, DSS group (drank 3.5% DSS), GTS-21 group (drank 3.5%DSS+GTS-21 20mg/kg ip), α -BGT group (3.5% DSS+pre-treated with α -BGT prior to GTS-21). Disease activity index and colonic damage were determined. The intestinal permeability was measured by fluorescein-isothiocyanate-dextran (FITC-Dextran) method. Caco2 cells were used to further investigate the effect of GTS-21 on TJ proteins distribution and NF- κ B activity. Western blot detected the tight junction protein and NF- κ B associated protein expression.

Results: 1. GTS-21 attenuated DSS-induced colitis, while α 7nAChR antagonist α -BGT eliminate protective effects (Fig. 1).
 2. GTS-21 attenuated intestinal permeability ($p < 0.05$), and also reduced intestinal bacterial translocation in DSS-induced mice (Fig. 2).

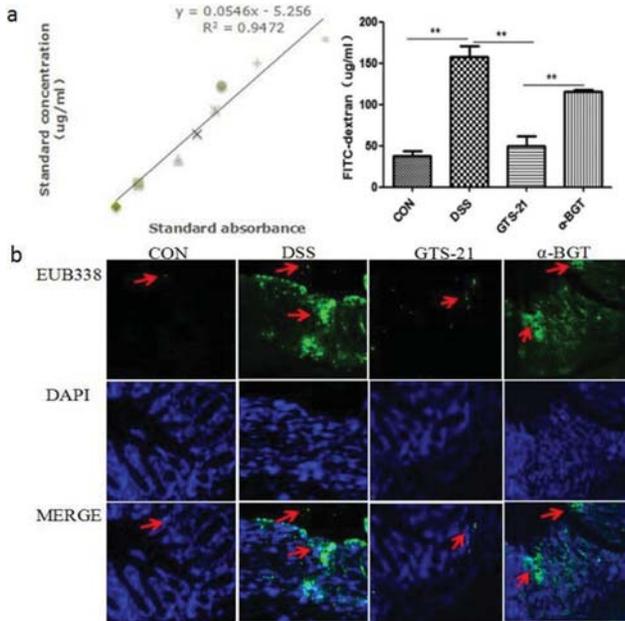


Figure 2

3. The expressions and distribution of tight junction protein were enhanced in DSS-induced mice with GTS-21 treatment (Fig. 3).

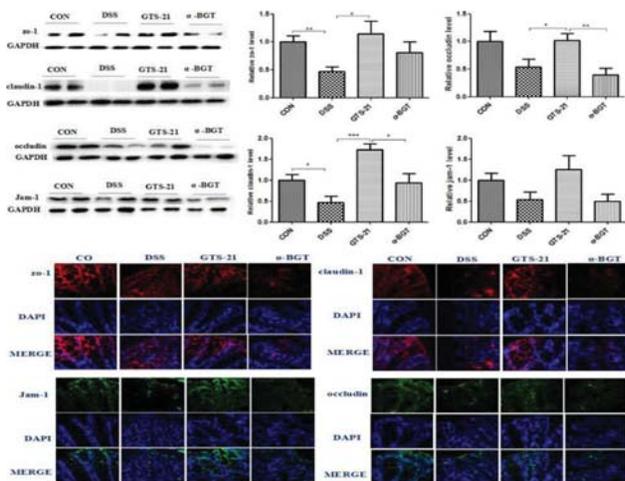


Figure 3

4. GTS-21 decreased the NF- κ B activation, while α -BGT reversed this inhibitory effect (Fig. 4).

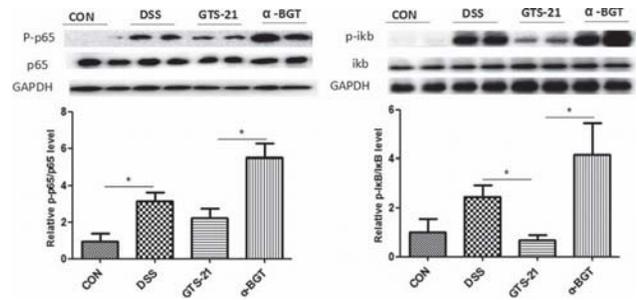


Figure 4

5. GTS-21 improved intestinal epithelial barrier defects (Fig. 5), and reduced nuclear translocation of NF- κ B in Caco2 cells induced by TNF- α (Fig. 6).

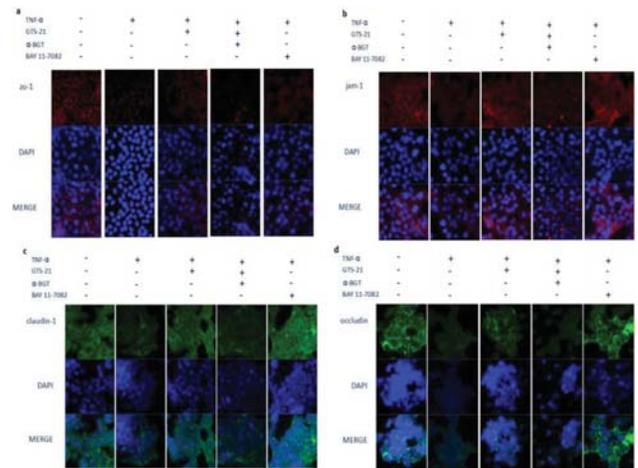


Figure 5

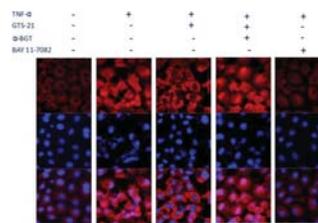


Figure 6

Conclusions: The α 7 nicotinic acetylcholine receptors agonist GTS-21 can attenuate DSS-induced colitis, which might be due to improving intestinal mucosal barrier function.

Poster presentations

Basic science

P001

The biomarker profile of PTG-200, an oral peptide antagonist of IL-23 receptor, tracks with efficacy in a preclinical model of IBD

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Background: The recent regulatory approval of ustekinumab which targets IL-12/IL-23 and clinical data from several anti-IL-23 monoclonal antibodies, MEDI2070, BI655066 and LY3074828, support IL-23 as a therapeutic target for the treatment of inflammatory bowel disease (IBD). We are developing an oral peptide, PTG-200, that would act locally in the gastrointestinal (GI) tissues to block the IL-23 signaling pathway by selectively binding to the IL-23 receptor (IL-23R). In this study, we sought to evaluate the efficacy and associated disease-related and mechanism-specific pharmacodynamic (PD) biomarkers of oral PTG-200 in a preclinical model of IBD.

Methods: Acute colitis was induced in Sprague-Dawley rats by a single intra-rectal instillation of TNBS followed by efficacy analysis at day seven. PD biomarkers were examined using enzyme-linked immunosorbent assay (ELISA), quantitative reverse transcription polymerase chain reaction (qRT-PCR), or immunohistochemistry (IHC) analysis of colon, feces, or serum samples obtained from colitic rats treated with oral PTG-200.

Results: In the TNBS-induced colitis model, oral treatment with PTG-200 resulted in significant dose-dependent improvement in animal body weight, reduction in the colon weight-to-length ratio, and normalization of the macroscopic and histopathological changes in the colon. In the colons of treated animals, the levels of MPO which is an indicator of neutrophil infiltration, the levels of IL-17A and IL-22 which are cytokines downstream of IL-23 signaling, and the levels of pStat3 which is a transcription factor whose phosphorylation status is known to be regulated by IL-23, were significantly reduced and correlated to dose titration of PTG-200. In the feces collected from the colons of treated animals, the levels of MPO and lipocalin 2 (LCN2), which is a neutrophil anti-bacterial protein over-expressed in the inflamed colonic epithelium, were significantly downregulated. LCN2 was also found to be significantly decreased in the serum.

Conclusions: Blockade of IL-23R-mediated signaling by oral treatment with PTG-200 significantly improved disease outcomes in a TNBS-induced rat model of IBD through specific inhibition of the IL-23 pathway. Moreover, we identified additional inflammatory markers from feces as well as a non-invasive marker for colitic activity in the serum, that were responsive to PTG-200 treatment. Finally, we showed that responses from these biomarkers tracked with effects of PTG-200 on disease parameters. These data support the poten-

tial value of the profiled PD biomarkers in translating preclinical efficacy to clinical proof-of-concept for PTG-200, a potential first-in-class oral peptide therapeutic targeting IL-23R for the treatment of IBD.

P002

Inhibition of Axl signaling by BGB324 reduces fibrogenesis in human intestinal cells and human intestinal organoids

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Background: In Crohn's disease, fibrosis is the final common pathway to intestinal failure. Fibrostenotic disease is the primary cause of obstruction and reason for surgical intervention in these patients. Currently no medical therapies exist to treat intestinal fibrosis.

We found that Axl is induced in both *in vitro* and *in vivo* models of intestinal fibrosis. Axl is a tyrosine kinase targeted for the treatment of acute myeloid leukemia (AML). Inhibition of Axl signaling has been shown to reverse epithelial-mesenchymal transition, sensitize cells to apoptosis, and reduce liver fibrosis via hepatic stellate cell inactivation. BGB324 is an orally available tyrosine kinase inhibitor that is highly selective for Axl. We evaluated the effect of BGB324 on pro-fibrotic gene expression in three *in vitro* models.

Methods: We assessed Axl gene expression in strictured human intestine vs. unaffected margin from human Crohn's patients and in 5 models of Crohn's disease. These included the fibrotic vs. unaffected intestine in rat TNBS, mouse salmonella, CCD18Co substrate stiffness, CCD18Co TGF- β (fibrogenic cytokine), and human intestinal organoid (HIO) TGF- β models of fibrosis. We then treated our three *in vitro* models with BGB324, assessing for reduction in pro-fibrotic gene expression of collagen 1A1 (COL1A1), fibronectin 1 (FN1), myosin light chain kinase (MYLK), and smooth muscle actin (ACTA2) using real-time PCR.

Results: In strictured intestine vs. unaffected margin from Crohn's patients, Axl expression was increased approximately 5 fold. Axl induction was also observed in the fibrogenic state in all 5 models of intestinal fibrosis. In rat TNBS and mouse salmonella models, Axl expression increased 1.8 and 2 fold respectively. In CCD18Co cell cultures, pathological substrate stiffness and TGF- β models caused 1.4 and 1.7 fold increases respectively. In HIO, TGF- β increased Axl by 1.8 fold.

BGB324 abrogated expression of COL1A1 in the CCD stiffness model as well as the CCD TGF- β model. Similar results were obtained when analyzing FN1, MYLK, and ACTA2.

In the TGF- β HIO model, BGB324 reduced pro-fibrotic gene expression. Random-effects meta-analysis of multiple biologic replicates demonstrated reduction in pro-fibrotic gene. Individual fold reductions and 95% CI for MYLK, FN1, COL1A1, and ACTA2 were 3.87 [1.58, 6.17], 3.17 [1.55, 4.79], 2.24 [0.91, 3.57], and 1.37 [0.27, 2.46] respectively.

Conclusions: Axl signaling appears to be an important pathway in intestinal fibrosis. BGB324 is being actively investigated in clinical trials for AML, and thus far appears safe for human use. The use of potent Axl inhibitors including BGB324 represents a therapeutic avenue for the treatment of intestinal fibrosis that warrants further testing.

P003

Abstract has been withdrawn

P004

Stimulation of CYP450-mediated ω -3 docosahexaenoic acid metabolism via MFSD2A as a novel therapy for inflammatory bowel disease

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Background: New evidences indicate that defects in pro-resolving pathways might underlie the pathogenesis of IBD. The resolution process is regulated by lipid mediators, such as those derived from the ω -3 docosahexaenoic acid (DHA), whose esterified form is transported by the Major Facilitator Superfamily Domain containing 2A (MFSD2A) through the endothelium of brain, retina, and placenta. We investigated if and how MFSD2A may modulate the lipid metabolism of gut endothelial cells, thus promoting the resolution of intestinal inflammation.

Methods: Lipidomic analysis was performed by Liquid chromatography–mass spectrometry on both mucosal biopsies and primary human intestinal microvascular endothelial cells (HIMEC) isolated from surgical specimens of active, drug-induced resolving patients and healthy non-IBD subjects. Using a lentiviral strategy, healthy HIMEC were transduced with a lentivirus carrying GFP-tagged MFSD2A overexpressing vector (MFSD2A-OE), and assayed for their angiogenic properties and response to an inflammatory stimuli. Adoptive transfer of human circulating endothelial progenitor cells (ECFCs), genetically engineered to overexpress MFSD2A, was performed in CD1 nude colitic mice, along with orally administered DHA.

Results: The lipidomic analysis revealed a reduced percentage of pro-resolving metabolites derived from Cytochrome P450 epoxygena-

tion of DHA in the inflamed mucosa, when compared with samples from healthy and resolving tissues ($1.40 \pm 0.09\%$ vs $0.85 \pm 0.15\%$ over total fatty acids; $p < 0.05$). Interestingly, we found that reduced level of epoxy-DHA derivatives in active tissues correlated with lower amounts of MFSD2A compared to resolving mucosa (2 ± 0.3 vs 1 ± 0.1 ; $p < 0.01$). MFSD2A, found exclusively expressed by gut endothelium, exerted pro-resolving effects in HIMEC in terms of reduced pro-inflammatory markers and anti-angiogenic functions. Transplantation of engineered human MFSD2A-OE ECFCs in DHA-fed colitic mice, resulted in amelioration of intestinal inflammation, through stimulation of docosanoids production in the inflamed mucosa. These pro-resolving effects of MFSD2A were completely abolished by CYP2C inhibitor both *in vitro* and *in vivo*, demonstrating that protective functions exerted by MFSD2A depends on epoxy metabolites of DHA.

Conclusions: Our study provides not only important insights into the molecular mechanisms regulating resolution of intestinal inflammation, but also a strong rationale for the development of novel therapeutic strategies to treat IBD. Our cell-based therapeutic approach may help a selective cohort of non-responding patients, with the potential advantage of avoiding immune suppression, and using natural endogenous pathways to resolve inflammation.

P005

Establishing a porcine model to translate anorectal stem cell organoid models to elucidate the aetiology of perianal Crohn's fistulae

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Background: Perianal fistulising Crohn's disease remains an extremely challenging medical problem as many fistulas do not respond to available treatments. A regenerative medicine approach is showing promise: injecting allogeneic adipose-derived mesenchymal stem cells in and around complex fistulas improves healing similar to surgery in a recent Phase 3 randomised trial (TiGenix, Cx601) [1].

Organoid-based technologies may expand the understanding of ineffective endogenous stem cell response to tissue damage in Crohn's fistulas and offer a range of new therapeutic targets. Organoids are *in vitro* 3D cellular structures derived from primary tissue stem cells and capable of self-renewal and self-organization [2]. Anorectal organoids provide accessible and physiologically relevant models to elucidate the inherent properties of stem cells outside a tightly regulated *in vivo* environment [3]. In this study, we used the porcine model to establish anorectal organoid methodology.

Methods: Anal tissue, including the anorectal transition zone (ATZ), was resected from healthy Landrace/Cross pigs (females, aged 4–6 months) within one hour of termination. Biopsies taken from anal, ATZ and rectal tissue were transferred to petri-dishes, where they were washed/minced. Stem cells were isolated from tissues using a modified protocol developed for mice [4]. Tissues were exposed to enzymatic digestion (collagenase/dispase, Sigma) at 37C for 1–2 hours on a shaker to release non-adherent cells from the mucosal tissue layer; tissue fragments were then removed by sequential filtering and centrifugation. Porcine cells were cultured in human organoid medium [5].

Results: Ring structures, characteristic of developing 3D *in vitro* organoid were derived from anal, ATZ and rectal tissue over period of 7–14 days. Rectal organoids formed crypt-like structures, similar to the phenotype of small intestine organoids. In contrast, non-adherent cells were produced by organoids derived from anal and ATZ derived tissues and formed a monolayer in culture. All anorectal organoids can be serially passaged for extended periods for characterisation.

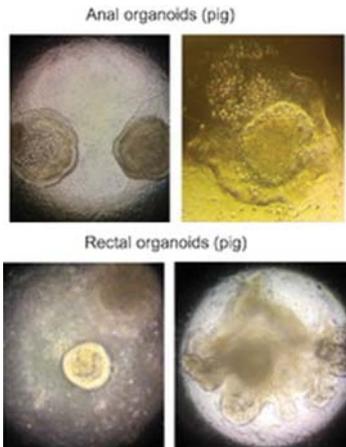


Figure 1. Anorectal tissue cell production in 3D *in vitro* organoids.

Conclusions: Here we describe for the first time the ability to establish porcine anorectal organoid models using modifications of established techniques. The porcine model provides a valuable model to establish methodologies and characterise anorectal organoid biology to translate to Crohn's patients

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P006

Transcriptomic profiling of intestinal macrophages isolated from patients reveals a profound gene expression reprogramming underlying IBD pathogenesis

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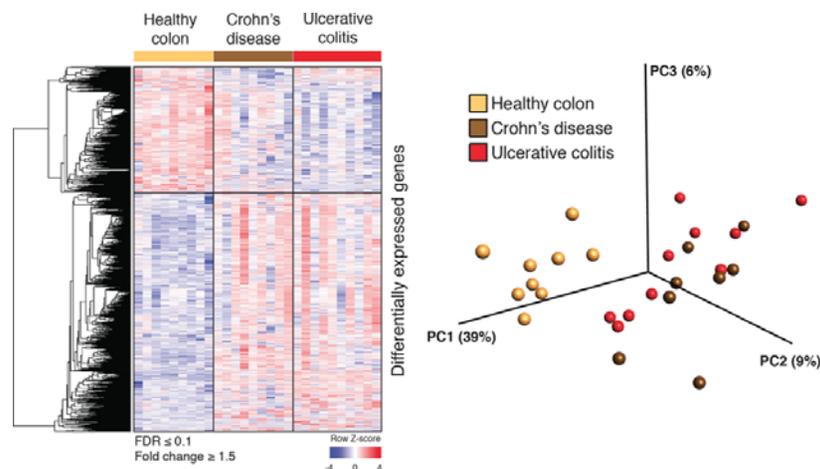
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Background: Macrophages play a major role as effector cells of the innate immune system and are vital for intestinal tissue homeostasis. An altered function of intestinal macrophages may contribute to the development and propagation of intestinal inflammation in IBD. However, all data available come from mouse models, human whole tissue or *in vitro* derived macrophages from blood monocytes. We have isolated intestinal macrophages from patients and healthy subjects and analysed their transcriptome in order to study the intrinsic role that macrophages play in the pathogenesis of IBD.

Methods: Fresh colonic mucosal tissue biopsies from 10 CD patients, 10 UC patients and 10 healthy controls were disaggregated to cell suspensions and sorted using fluorescence-activated cell sorting. RNA from intestinal macrophages, identified as CD163+CD14+CD3- population, was extracted and subjected to RNA sequencing. Differential Gene Expression analysis and pathway analysis were performed between the groups.

Results: The transcriptomic analysis revealed that the gene expression profile of the intestinal macrophages from IBD is dramatically reprogrammed. Differential Gene Expression analysis revealed 1287 DEGs between macrophages from UC patients and healthy controls; 840 DEGs between macrophages from CD patients and healthy controls and 20 DEGs between macrophages from UC and CD patients (1.5 fold change and FDR <0.1).

Conclusions: This is the first study to describe the transcriptome of



Abstract P006 – Figure 1. Differential gene expression analysis and principle component analysis.

intestinal macrophages from active lesions of patients with IBD by high throughput RNAseq. We show that the transcriptome of these macrophages is profoundly different from those taken from healthy subjects. These results suggest that macrophages play an important role in the propagation of inflammation and we have identified a number of molecules that should be investigated as potential therapeutic targets.

P007

Oral tyrosine kinase 2 inhibitor ameliorates T cell transfer colitis

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Background: Several Janus Kinase (JAK) inhibitors selectively targeting one JAK-family member are currently under development for the treatment of inflammatory bowel diseases (IBD). Tyrosine Kinase 2, one of the JAK family members, mediates signalling of pro-inflammatory cytokines involved in the pathogenesis of IBD including IL6, IL12, IL23 and interferon gamma (IFN γ). The aim of this study was to investigate the potency of an oral TYK2 inhibitor (TYK2i) *in vivo* in a murine colitis model.

Methods: T cell transfer colitis was induced by adoptive transfer of wild type CD45RBhigh T lymphocytes into RAG1KO mice. After onset of endoscopic disease (day 36), animals were administered with placebo or TYK2i (10, 30, 70 mg/kg/day) daily by oral gavage. Upon sacrifice, colon weight, colon length and disease activity index (DAI, consisting of diarrhoea, oedema and occult blood, score 0–7) were recorded. Colon tissue was analysed by histology (score 0–12) and protein and transcriptional analyses of various cytokines were performed.

Results: In the T cell transfer colitis model, daily administration of TYK2i prevented loss of bodyweight at all doses tested. Both endoscopic and clinical disease activity were decreased by TYK2i in a dose-dependent manner, with animals receiving 70mg/kg displaying disease activity comparable to healthy controls (median activity 0, 1.75 and 0 for healthy controls, placebo and 70mg/kg respectively). Histologically, animals receiving 70 mg/kg showed significantly decreased colitis when compared to placebo treated animals, although some residual inflammation was apparent (median score 1, 5.25 and 1.5 for healthy controls, placebo and 70mg/kg respectively). Analysis of the affected colon revealed decreased expression of IFN γ and IL6 both at the mRNA and protein level, as well as decreased protein expression of TNF α .

Conclusions: Our results show that oral administration of a TYK2 inhibitor ameliorates the course of T cell transfer colitis, suggesting TYK2 as a potential therapeutic target in the treatment of IBD.

P008

Common and different inflammatory features in inflammatory bowel disease and colon cancer

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Background: The etiology of Inflammatory Bowel Disease (IBD) is complex and still, for the most part, obscure. Although the adaptive immune response has classically been considered to play a major role in the pathogenesis, there are evidence for involvement of tissue resident cells such as ILC, T gamma-delta and MAIT cells. The inflammatory response also plays an important role in CRC development. Since inflammation-associated tumorigenesis can rely on the interaction of pathogens and inflammatory cells, triggering the release of inflammatory cytokines and recruitment of other pro-inflammatory cells, in this study we wanted to understand how in IBD treated patients, innate immune response can drive toward tumor evolution.

Methods: The identification of tissue resident immune cells was performed by flow cytometry after isolation and digestion of fresh intestinal biopsies, evaluating the frequency and the effector functions of ILC1, ILC3, MAIT and gamma-delta T cells. We analyzed a total of 52 samples: IBD at onset (n=12), IBD after therapy with Infliximab and Adalimumab (n=13), CRC (n=21), and healthy donors (n=6).

Results: IFN gamma-producing ILC1 accumulated in IBD patients at onset, after treatment and in CRC. As expected TNF alpha-producing ILC1 were more abundant in IBD at onset and CRC. ILC3 producing IL17 but not IL22 accumulated in treated IBD patients and CRC but not in IBD at onset. Gamma-delta T cells with a predominantly effector phenotype were increased in IBD and in CRC. In particular, in CRC patients both gamma-delta T cells subsets were present, while in IBD patients the Vdelta1 subpopulation was more represented at onset but the Vdelta2 subset in treated patients. IL17 producing Vdelta1 cells accumulated in CRC but not in both IBD groups. Finally, MAIT cells were more represented in both groups of IBD than in CRC.

Conclusions: Our results, albeit preliminary, suggest that the innate immune system participates to gut inflammation and colorectal cancer, suggesting the intriguing possibility that certain inflammatory responses can be common to both pathologies and contribute to the development of chronic inflammation associated cancer.

P009

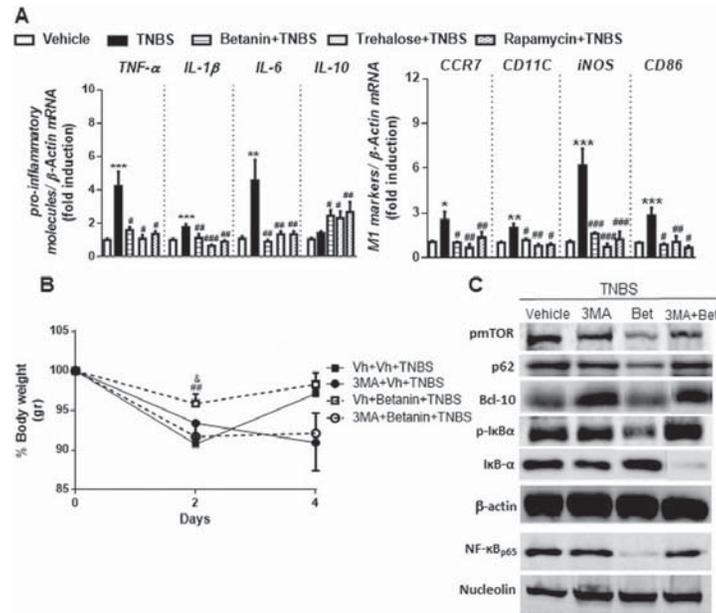
Autophagy stimulation reduces mucosal NF- κ B protein levels and ameliorates murine colitis

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Background: A defective autophagy is involved in the pathogenesis of inflammatory disorders such as IBD. Cross talk interactions between autophagy and inflammation have been reported and we analyse the effects of autophagy stimulators on murine colitis.

Methods: Mice were treated with intrarectal administration of TNBS (3.5 mg/20 mg mice) and body weight was measured every day (and expressed as a percentage of starting weight), and histological damage score analysed two or four days after treatment. Some mice received trehalose (3% in drinking water three weeks before TNBS administration) or a daily administration of rapamycin (1.25 mg/kg,



Abstract P009 – Figure 1

i.p.), betanin (1g/kg, i.p.) or betanin + 3MA (10mg/kg, i.p.). Mucosal protein levels of p-mTOR, p62, LC3, BCL10, NF- κ B, I κ B α and p-I κ B α were determined by WB and mRNA expression of TNF α , IL1 β , IL6, IL10, COX2, CCR7, CD11c, iNOS and CD86 by qRT-PCR.

Results: An impaired autophagy associated with body weight loss and intestinal damage was detected in the mucosa of TNBS-treated mice. Administration of trehalose, rapamycin or betanin prevented the impaired autophagic flux induced by TNBS and decreased the expression of pro-inflammatory cytokines and M1 macrophage markers (Fig. 1A) and mucosal protein levels of BCL10, p-I κ B α and NF- κ Bp65. Blockade of the autophagosome formation by treatment of mice with 3MA prevented the reduction in both body weight loss (Fig. 1B) and protein levels of p62, BCL10, p-I κ B α and NF- κ Bp65 (Fig 1C) induced by betanin in TNBS-treated mice and weakened the protective effects of betanin on murine colitis.

Conclusions: Our results demonstrate that pharmacological stimulation of mucosal autophagy reduces intestinal inflammation and ameliorates murine colitis.

P010

Effects of cigarette smoke on the DSS-induced colitis model in C57Bl/6 mice

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Background: Inflammatory bowel disease (IBD) is a chronic inflammatory disease affecting the gastrointestinal tract, which consists of two major forms: Crohn's disease (CD) and Ulcerative Colitis (UC). The impact of cigarette smoking on IBD has been well established by a large number of epidemiological studies in which exposure to cigarette smoke was associated with a higher risk of developing CD and with an increased severity in CD patients. By contrast, cigarette smoking was shown to be protective against UC. The incidence of UC is 2.5 times less frequent in smokers, and, after disease onset, it

has been reported that smoking improves the course of the disease, decreases the frequency of flare-up episodes, decreases the need for steroid administration, and decreases the colectomy rate. It has also been established that smoking cessation improves CD and worsens UC. While there are numerous descriptive and epidemiological publications about cigarette smoking and IBD, few mechanistic studies have explored the effect of cigarette smoke exposure on intestinal inflammation.

Methods: This study evaluated the impact of mainstream cigarette smoke (CS) on the severity of dextran sulfate sodium (DSS)-induced UC in C57Bl/6 female mice. UC-like symptoms were induced using DSS administered through drinking water at a concentration of 5.0%. Three groups of animals, low, medium, and high exposure groups, were exposed to CS to a target concentration of 750 μ g/l total particulate matter for 1, 2, and 4 h per day, respectively. A 2-week CS pre-exposure period (including a 6-day concentration adaptation to the target CS concentration) was included to acclimatize the animals to the target CS concentration. This was followed by an 8-day CS treatment combined with DSS or control (drinking water only), after which the animals were evaluated for the progression and severity of UC symptoms.

Results: Using a comprehensive profiling approach (transcriptomics and proteomics) together with classical endpoint analysis (body weight, cytokine release assays), we were able to show a protective CS-related effect on the development of UC. Interestingly, although a reduction in the inflammatory state of CS-exposed mice was observed, different molecular processes were activated depending on CS exposure timing and colon localization.

Conclusions: The current study enables the investigation of possible molecular mechanisms responsible for the attenuation of UC by CS exposure.

P011

Evaluation the intestinal barrier function patients with inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD) characterized by increased intestinal permeability (IP). This leads to bacterial translocation and systemic endotoxemia, which cause immuno-inflammatory response.

Aim: to evaluate the intestinal barrier function in patients with IBD. **Methods:** We prospectively included 119 patients with IBD – 80 patients with ulcerative colitis (UC) and 39 patients with Crohn's disease (CD) and 20 healthy controls. All included into the study had assessment of passive IP – the level of systemic endotoxemia using the Limulus Amebocyte Lysate (LAL) test. 60 patients with IBD (33 UC and 27 CD) went through evaluation of active IP – triple sugar test using the high performance liquid chromatography. Small bowel IP was assessed by lactulose/mannitol ratio, colonic permeability – levels of sucralose in urine.

Mean age in UC was 38.03±1.14 years, CD – 34.7±1.5 and in control group – 30.13±1.5. Severity of UC was assessed by Mayo score and in CD by CDAI.

Results: Increase of endotoxin level was observed during in exacerbation of CD (0.065±0.04 EU/ml; p<0.01), remission (0.012±0.01 EU/ml; p<0.05) comparing with healthy controls (0.00038±0.0003 EU/ml). There was increasing of small bowel IP and colonic permeability – levels of lactulose/mannitol ratio in active CD was higher (0.042 [0.021; 0.077]) than in remission (0.009 [0.006; 0.01]) (p<0.01) and in healthy controls (0.011 [0.009; 0.017]) (p<0.001). There was the relationship with disease severity and location of CD. There was tendency to increasing of colonic permeability in group of patients with colitis of CD.

Analysis of IP in UC had revealed an increase of endotoxin level in active stage (0.014±0.006 EU/ml; p<0.05) remission (0.0019±0.001EU/ml; p<0.05) comparing with control group (0.00038±0.0003 EU/ml). Small IP in exacerbation of UC 0.021 [0.014; 0.034] was higher than in remission (0.006 [0.005; 0.01]) (p<0.01) and in healthy (0.011 [0.009; 0.017]) (p<0.01). Colonic permeability in active UC (1600 [700.8; 2185.6] nmol/l) was increased compared with remission UC (374.4 [267.2; 481.3] nmol/l) (p<0.01) and healthy (819.2 [521.6; 1044.8] nmol/l) (p<0.01). There was the relationship with disease severity and lesion extending of UC. Endotoxemia was higher in colonic lesions than the small intestinal. Endotoxin level in colitis of CD and UC was higher than in ileitis of CD. Level of endotoxin in blood increased with increasing of sucralose level in urine in UC (r=0.54; p<0.05) and in CD (r=0.28; p<0.05).

Conclusions: Patients with IBD had an increased IP with a predominant increase of small IP in CD and more pronounced changes of IP in UC. There was found increased systemic endotoxemia, more pronounced in patients with CD and with colonic lesions of IBD.

P012

Ral activation exacerbates colonic inflammation through the impairment of intestinal barrier function in experimental murine colitis

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Background: Ral, a small GTPase of the Ras subfamily protein, has various biological functions such as cell proliferation, exocytosis, and actin organization through the downstream of Ras signaling pathway. Also, Ral is considered to be involved in inflammation, but its role of intestinal inflammation remains unclear. The aim of this study is to investigate the involvement of Ral activation in intestinal inflammation of experimental murine colitis using RalGAPα2, inhibitory molecule of Ral activation, knockout (KO) mice.

Methods: We assessed the difference of Ral activation in the colonic tissues under steady-state condition between RalGAPα2 KO and wild type (WT) mice using pull-down assay. To compare the phenotype of the colonic tissues under steady-state condition between RalGAPα2 KO and WT mice, we evaluated the histologic findings of their colonic tissues by hematoxylin and eosin staining and immunohistochemistry (IHC) over time. We also assessed the gene expression of inflammatory cytokines in the colonic tissues of both mice. Moreover, we examined the expression of the colonic tight junction molecules in both mice by IHC and western blotting (WB). Next, to investigate a role of Ral activation on colonic inflammation, we compared the histologic findings and the gene expression of inflammatory cytokines in the colonic tissues of murine dextran sodium sulfate (DSS)-induced colitis between RalGAPα2 KO and WT mice. Moreover, we compared the difference of intestinal epithelial permeability in DSS-induced colitis of both mice using fluorescein isothiocyanate (FITC)-dextran permeability assay.

Results: Under steady-state condition, pull-down assay showed more Ral activation in the colonic tissues of RalGAPα2 KO mice compared to WT mice. RalGAPα2 KO mice did not develop spontaneous colitis. However, IHC revealed that the number of CD11b positive cells in the colonic tissues of RalGAPα2 KO mice was significantly higher compared to WT mice. Additionally, RalGAPα2 KO mice showed significant increased gene expression of TNF-α, IL-12p40, and IL-1β compared to WT mice. Furthermore, decreased expression of ZO-1 in the colonic tissues of RalGAPα2 KO mice was found by IHC and WB. On the other hand, under inflammatory condition caused by DSS-induced colitis, RalGAPα2 KO mice showed more severe colitis and significant increased gene expression of TNF-α and IL-1β compared to WT mice. Moreover, RalGAPα2 KO mice showed more increased epithelial permeability compared to WT mice in the FITC-dextran permeability assay (1017±250 vs 405±38 ng/ml, p<0.05).

Conclusions: Our data indicate that RalGAPα2 KO mice showed more susceptible to DSS-induced colitis. Ral activation might be involved in the colonic inflammation through the impairment of intestinal barrier function.

P013

Decreased fibrogenesis in CH25H knockout mice in a mouse model of intestinal fibrosis

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Background: Long-term treatment of inflammatory bowel disease (IBD) remains an ongoing challenge and intestinal stenosis or fibrosis are common complications during the course of Crohn's disease (CD). Anti-inflammatory strategies, such as anti-tumor necrosis factor (TNF) antibodies or immunosuppressants, are only partially effective in preventing fibrosis and surgery often does not provide a

definite solution. Thus, anti-fibrotic therapy approaches are still an unmet clinical need. Oxysterols are oxidized derivatives of cholesterol which play an important role in a spectrum of biological activities. Cholesterol 25-hydroxylase (CH25H) mediates enzymatic conversion of cholesterol to 25-hydroxycholesterol (25-HC), which modulates immune responses and oxidative stress. In vitro analysis of human fetal lung fibroblasts demonstrated 25-HC to promote alpha-smooth muscle actin (alpha-SMA) expression and collagen production, to augment the release of matrix metalloproteinases and stimulate transforming growth factor (TGF)-beta release. We characterized the role of CH25H in the development of intestinal fibrosis.

Methods: Sections of small intestine from a donor mouse, either wildtype or CH25H knockout, were transplanted subcutaneously into the neck of a recipient mouse of the same genotype. Seven days after surgery the intestinal grafts were isolated and examined for collagen layer thickness and mRNA expression of fibrosis mediators.

Results: In our *in vivo* fibrosis model, mice deficient for the CH25H enzyme developed a thinner collagen layer compared to wildtype controls. Reduced collagen deposition in CH25H knockout animals was confirmed by automated image analysis. Furthermore, concentration of the collagen metabolite hydroxyproline was significantly decreased in CH25H knockout intestinal transplants. mRNA expression of fibrosis mediators including lysyl oxidase-like 2, collagen type 1 and type 3 was decreased in CH25H knockout mice compared to wildtype controls as confirmed by qPCR.

Conclusions: Our findings indicate an involvement of CH25H in the pathogenesis of intestinal fibrosis. CH25H deficiency partially prevented collagen deposition, pointing to oxysterols as a potential new treatment option for CD associated fibrosis. Further mechanistic and therapeutic studies will be necessary.

P014

Mucosal lymphocyte subsets in ulcerative colitis at diagnosis and during follow-up

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Background: The initial immunologic processes that occur in the inflamed mucosa of patients with Ulcerative Colitis (UC) remain largely unclear. We aimed to investigate different mucosal lymphocyte subsets in UC patients at diagnosis and during follow-up to study the changes that might occur in different phases of disease activity (remission/exacerbation).

Abstract P014 – Table 1. Flow cytometry results of colonic lymphocyte subsets in healthy controls and patients with ulcerative colitis at baseline and during follow-up (either in remission or during exacerbation)

Lymphocyte subsets, median % (interquartile range)	Healthy controls (n=7)	Ulcerative Colitis – baseline (n=35)	Follow-up – remission (n=8)	Follow-up – exacerbation (n=11)	p-value between follow-up groups
T cells (CD3 ⁺)	58 (40–61)	57 (48–69)	54 (48–78)	48 (39–62)	0.247
CD4 ⁺ T cells (CD3 ⁺ CD4 ⁺)	40 (33–57)	74 (66–83) ^a	54 (40–70)	80 (75–87) ^a	0.001
CD8 ⁺ T cells (CD3 ⁺ CD4 ⁺)	52 (33–55)	21 (16–29) ^a	37 (24–54)	13 (10–22) ^a	0.002
Mucosal T cells (CD3 ⁺ CD103 ⁺)	40 (32–60)	12 (6–18) ^a	36 (14–57) ^b	7 (2–15) ^a	0.004
Regulatory T cells (CD3 ⁺ CD4 ⁺ CD25 ^{high} FoxP3 ⁺)	8 (3–12)	10 (8–14)	7 (3–10)	11 (8–16)	0.055
Naive T cells (T _N , CD3 ⁺ CD27 ⁺ CD45RA ⁺)	13 (10–24)	21 (12–30)	8 (5–15)	18 (14–34)	0.013
T effector memory cells re-expressing CD45RA (T _{EMRA} , CD3 ⁺ CD27 [–] CD45RA ⁺)	2 (1–6)	4 (2–8)	4 (2–7)	3 (3–4)	0.165
Central memory T cells (T _{CM} , CD3 ⁺ CD27 ⁺ CD45RA [–])	30 (21–36)	50 (39–58) ^a	25 (10–44)	55 (50–77) ^a	0.005
Effector memory T cells (T _{EM} , CD3 ⁺ CD27 [–] CD45RA [–])	52 (39–58)	21 (12–29) ^a	56 (23–80) ^b	11 (5–21) ^a	0.003

^ap<0.05 compared to healthy controls by Mann-Whitney U Test, ^bp<0.05 compared to baseline values by Wilcoxon signed ranks test.

Methods: A total of 35 newly diagnosed untreated adult UC patients and seven healthy controls (HC) were prospectively included. Colonic biopsy specimens of the inflamed areas were collected at diagnosis and, from the same colon segment, during follow-up. Flow cytometry was used to analyse lymphocyte subsets in the colonic biopsy specimen as defined in Table 1.

Results: At diagnosis UC patients displayed higher percentages of CD4⁺, T_{CM} and lower percentages of CD8⁺, T_{EM} and mucosal T cells compared to HC (Table 1 and Figure 1, see p. S87). Compared to diagnosis, a statistical significant increase of mucosal T cells and T_{EM} cells was found in patients colon during remission at follow up (median time to follow-up 20 months, IQR 16–30). No differences compared to baseline percentages were observed in patients with an exacerbation at follow-up (26 months, 19–54, p=0.238) (Table 1 and Figure 1).

UC patients in remission at follow-up had comparable lymphocyte subsets to HC (P values all >0.05), while patients with an exacerbation at follow-up had comparable findings to baseline and the same statistical significant differences in lymphocyte subsets were observed compared to HC.

Conclusions: Mucosal inflammation was associated with increased percentages of CD4⁺ T cells and T_{CM} cells and decreased percentages of (mucosal) CD103⁺ T cells, CD8⁺ T cells and T_{EM} cells. A trend towards normalization of the colonic T cell profile, with increase of CD103⁺ and T_{EM} cells, is seen during remission; suggesting a positive role for these mucosal T cell subpopulations. These observations could question the efficacy of anti-CD103 treatment in UC patients. More research is needed to elucidate the pathological and regulatory effects of the different lymphocyte subsets, as well as their potential predictive role for response to therapy.

P015

Wnt10b promotes fibrosis in murine colitis

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Background: Intestinal fibrosis is a common complication of IBD. We have recently reported in STAT6 knockout mice treated with TNBS that intestinal fibrosis is associated with up-regulation of M2c macrophages which express high levels of Wnt10b. The aim of the

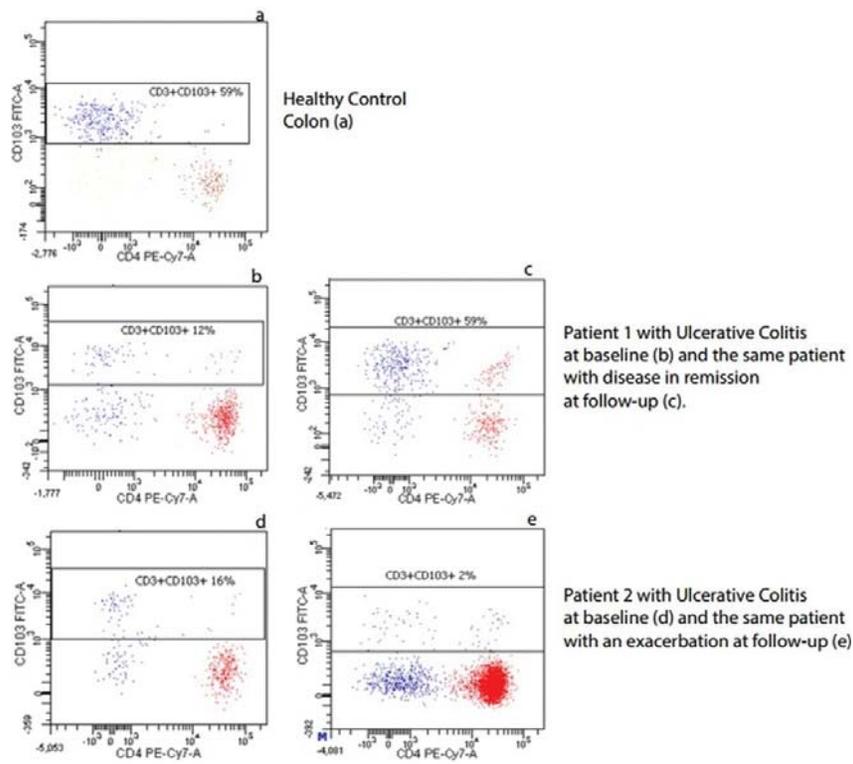


Figure 1. Representative flow cytometric dot plots showing mucosal CD103+ cells within CD3+ T cells in a healthy control (a) and in two patients with ulcerative colitis at baseline (b, d) and during their follow-up in remission (c) and during an exacerbation (e).

Abstract P014 – Figure 1

present study is to analyze the direct effects of Wnt10b in fibrosis development in a murine model of colitis.

Methods: Balbc mice were given TNBs (0.5, 0.5 mg, intrarectally) or saline weekly and received a single administration of Wnt10b (1ug/mice) or its vehicle, daily until sacrifice, 2 weeks after the first TNBs administration. Body weight was recorded daily and the mRNA expression of collagens (Col1a, Col3a and Col4a), fibrosis markers (TIMP1, MMP2) and cellular markers (Vimentin, FSP1, E-Cadherin and αSMA) in the intestinal mucosa was analyzed by quantitative PCR. Results are expressed as fold induction vs control mice. Collagen deposition was quantified by the Sircol assay and the expression of β-catenin was analyzed by immunohistochemistry in the intestinal mucosa, 2 weeks after the first TNBs administration. Data are expressed as Mean ± SEM with n≥3 in all groups (*p<0.05 vs vehicle; #p<0.05 vs TNBS).

Results: The systemic administration of Wnt 10b: a) did not significantly alter the body weight loss in TNBS- or vehicle-treated mice; b) significantly increased the amount (μg/mg wet weight) of collagen in TNBS-treated mice (Sircol quantification; TNBS: 0.75±0.08 and TNBS+Wnt10b: 1.39±0.06*#) while it did not significantly modify it in vehicle treated mice (vehicle: 0.85±0.18 and vehicle+Wnt10b:

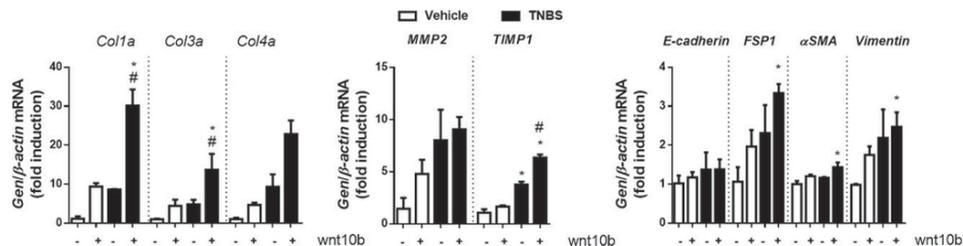
1.07±0.10); c) significantly increased the mRNA expression in collagen (Col1a and Col3a) and fibrosis markers (TIMP1, FSP1, αSMA and Vimentin) in TNBS-treated mice while it failed to induce a significant increase in the expression of these genes in vehicle-treated mice; d) increased the expression of nuclear β-catenin in cells located at the base of the crypt and cells in the lamina propria.

Conclusions: Wnt10b increase deposition of collagen and promotes intestinal fibrosis in TNBS-treated mice through the activation of myofibroblasts likely through canonical Wnt signaling pathway.

**P016
Pregnancy in IBD: direct effect of sex-hormones on epithelial barrier function**

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Background: Inflammatory bowel disease (IBD) is a chronic inflammatory diseases of the gastrointestinal tract. The epithelial barrier is known to be compromised in active IBD. Previously we have



Abstract P015 – Figure 1. mRNA expression.

demonstrated that some of the patients can stop maintenance therapy during pregnancy without a disease relapse. While pregnancy is an immune-tolerant state, the direct effect of pregnancy hormones on epithelial barrier cells is unknown but might play an important role in the favorable disease course during pregnancy. We aimed to study the direct effect of pregnancy hormones on barrier cells and their function.

Methods: The effect of progesterone and estrogen on intestinal epithelial cell barrier functions was investigated using human colonic adenocarcinoma cell lines (CACO2 and HCT116) as model system. Endoplasmic reticulum (ER) stress (earlier shown to induce epithelial cell death, barrier dysfunction and pro-inflammatory responses in IBD) was induced by treatment of cells with tunicamycin, followed by Western blot analysis of the ER stress marker GRP78. Epithelial barrier function was analyzed by transepithelial electrical resistance measurement (TEER), wound healing was determined by scratch assay, and cell viability was measured by MTT assays. IL-8 production by CACO2 cells was determined by enzyme-linked immunosorbent assay (ELISA).

Results: Progesterone and estrogen were able to reduce tunicamycin-induced ER stress in intestinal epithelial cells. This effect was dependent on the amount of ER stress induced and GRP78 reduction was most efficient in CACO2 cells (progesterone $p=0.029$, estrogen $p=0.02$). Scratch assays showed a faster wound closure in the presence of pregnancy hormones (estrogen and progesterone double treatment, $p=0.034$ for CACO2 cells and $p=0.019$ for HCT116 cells). This was not due to increased proliferation, as determined by MTT assay. Barrier function as determined by TEER measurement improved in the presence of estrogen and progesterone. IL-8 cytokine production by CACO2 cells increased in the presence of progesterone alone and in combination with estrogen.

Conclusions: Our study shows that estrogen and progesterone alleviate ER stress, increase IL-8 production, stimulate wound healing and increase barrier function of epithelial cells, thereby suggesting that in toto these pregnancy hormones can have beneficial effects on disease activity by positive modulatory action on the intestinal epithelial lining.

P017 OGR1 (GPR68) expression is increased in intestinal inflammation and correlates with disease activity in patients with IBD

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Background: A family of pH-sensing G-protein coupled receptors (GPCRs), including ovarian cancer G-protein coupled receptor 1 (OGR1), T-cell death-associated gene 8 (TDAG8 or GPR65) and G-protein coupled receptor 4 (GPR4) play an important role in physiological pH homeostasis. Gut-wall inflammation in both forms of inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC), is associated with extracellular tissue acidification. Recent studies reported a link between IBD and this family of pH-sensing receptors. TDAG8 has been identified as an IBD-risk gene. We previously reported that OGR1 is strongly regulated by TNF via a NF- κ B dependent pathway and is essential for intestinal inflammation and fibrosis. We showed that genetic ablation of OGR1

and GPR4 ameliorates colitis in different murine models. Further, we demonstrated that OGR1 regulates barrier function and epithelial restoration, and that OGR1 expression is enhanced by hypoxia.

Methods: Expression of OGR1 in surgical specimens from non-IBD (n=5), CD (n=10) and UC (n=10) patients was determined by immunohistochemistry, RT-qPCR and Western blotting. Clinical disease activity was assessed by the Harvey Bradshaw Index and the Modified Truelove and Witts activity index (MTWAI) for CD and UC patients, respectively. Nonparametric Spearman's rank correlation analysis was performed.

Results: OGR1 immunostaining of human surgical samples from non-IBD patients revealed OGR1 expression mainly in lamina propria cells, with weaker staining in epithelial cells. OGR1 staining in IBD patients was stronger compared to controls; however, in IBD patients OGR1 is highly expressed in both epithelial cells and cells in the lamina propria. Further, paired samples taken at the same time, from non-inflamed and inflamed intestinal tissue from IBD patients showed stronger OGR1 staining in the inflamed mucosa compared to the non-inflamed mucosa. Accordingly, mRNA and protein expression of OGR1 was significantly increased in patients with IBD compared to non-IBD patients. Additionally, a significant positive correlation was observed between OGR1 expression and the clinical score in both the non-inflamed (rs 0.7311, $p=0.0069$) and the inflamed mucosa (rs 0.7698, $p=0.0034$).

Conclusions: The expression of OGR1 is significantly increased in patients with IBD. OGR1 expression correlates with IBD disease activity, suggesting an active role of OGR1 in IBD pathogenesis.

P018 Complete metabonomic and microbiota profiling identifies biomarkers for anti-TNF therapy response

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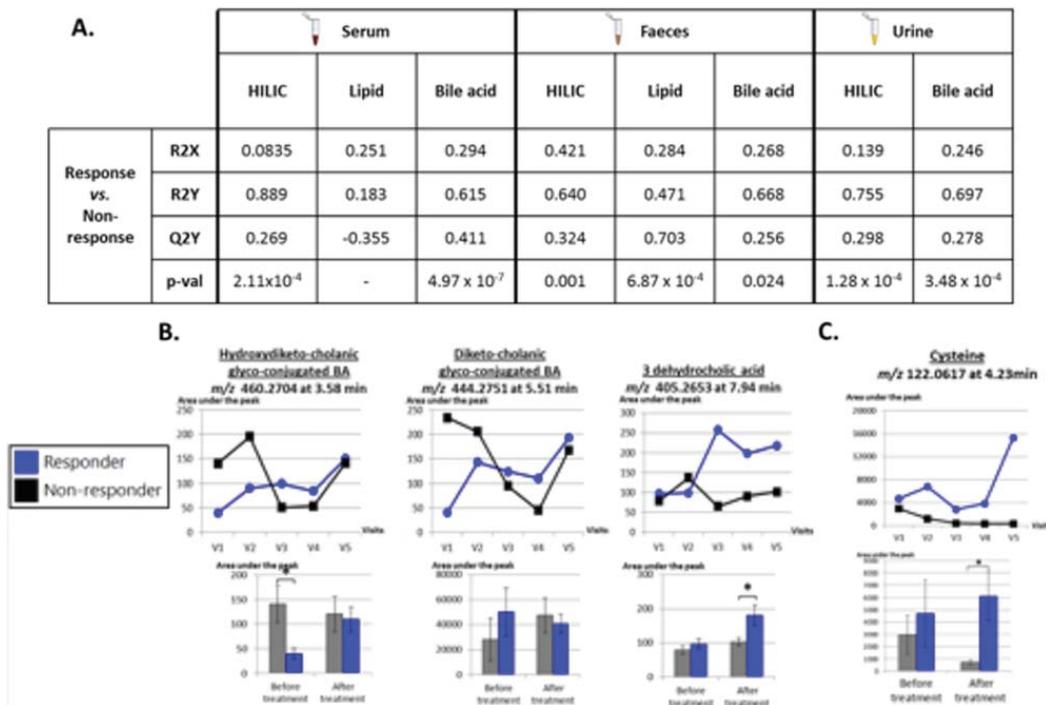
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Background: Anti-TNF therapy forms the backbone for treatment in moderate to severe Crohn's disease (CD). Metabonomic approaches to profiling Crohn's disease has led to numerous discoveries in disease pathogenesis. We aim to use metabonomic and microbiome profiling to identify predictive biomarkers of anti-TNF response.

Methods: CD patients commencing anti-TNF had 3 monthly visits for 12 months with collection of biofluids (urine, faeces and serum) and disease assessment with biochemistry and faecal calprotectin or mucosal healing. A response index combining biochemistry (decrease in FC or CRP) and mucosal healing was used to define therapeutic response in the presence of adequate drug level.

We collected 179 urine, 210 serum and 168 faecal samples from 68 anti-TNF naive CD patients (luminal phenotype undergoing anti-TNF therapy without surgical resections) and 20 healthy controls. Liquid-Chromatography Mass Spectroscopy using Waters[®] instruments with lipid, bile acid (BA) and polar molecule (HILIC) profiling of metabolites and multivariate analysis compared to response index on SIMCA software was undertaken. 16SrRNA extraction using Powerlyzerkit[®], sequencing with MiseQ illumina[®] and processing using Mothur was performed.

Results: There were 18 non-responders and 9 responders to anti-



Abstract P018 – Figure 1. OPLS-DA models created for response vs. non-response (A) with biomarkers from serum bile acid profiling (B) and urine HILIC profiling (C).

TNF therapy according to our strict criteria for response. Multiple biomarkers were identified across assays to be significant for predicting anti-TNF response to therapy across all visits (Fig. 1).

The strongest models were from serum bile acid (R2X 0.29, Q2Y 0.41, $p=4.97 \times 10^{-7}$) and urinary HILIC (R2X 0.14, Q2Y 0.30, $p=1.28 \times 10^{-4}$) (Fig. 1A). Serum BA profiling analysis identified 2 conjugated and 1 unconjugated BAs (Fig. 1B) while urinary HILIC profiling identified cysteine as biomarkers (Fig. 1C) creating a model allowing prediction of anti-TNF response, with levels being significantly different between non-responders and responders (Fig. 1).

On 16SrRNA, lactobacillus is higher in responders while clostridiales were lower in abundance for non-responders. The quantities of species did not alter significantly over time nor with therapy. Lactobacillus is known to synthesise cysteine from serine and for expansion in gut microbiota.

Conclusions: This prospective, longitudinal cohort study of microbiome and metabolomic analysis demonstrates that there are predictive biomarkers involved with bile acid and inflammatory pathways. The microbiome of patients with Crohn's disease does not alter significantly despite anti-TNF therapy response which allows for prediction of therapeutic outcome.

P019

Anti-TNF-alpha therapy induces microbial and immunological changes in dextran sodium sulphate chronic colitis

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Background: Anti-TNF alpha represent the best therapeutic option to induce mucosal healing and clinical remission in patients with moderate-severe Ulcerative colitis. On the other side gut microbiota plays a crucial role in pathogenesis of ulcerative colitis but few information exists on how microbiota changes following anti-TNF-alpha therapy and this role in mucosal healing. Evaluate gut microbiota changes and adaptive immune system response to anti TNF-alpha therapy in murine DSS colitis.

Methods: C57BL/6 mice were fed for 5 days with 3% Dextran-sodium sulphate (DSS) in drinking water. At day 3 of DSS treatment, a group of mice received intravenous administration of infliximab (IFX) (5 mg/Kg) or placebo. Further 2 groups of mice received IFX or placebo without DSS. Disease severity was scored daily using the four points Disease Activity Index (DAI). At the moment of sacrifice, serum, colon, feces and mesenteric lymph node (MLN) were collected from each animal. *Bacillus fragilis*, *Clostridium scindens*, *Fecalibacterium prausnitzii* and *Escherichia coli* were assessed by qPCR, following bacterial DNA extraction from feces.

Results: Anti-inflammatory species increased in fecal samples of colitis mice treated by IFX, compared to control mice, and in particular *B. fragilis*, *F. prausnitzii* and *C. scindens*. Furthermore, in colitic mice treated with IFX, microbial changes are associated to an initial increase (day 5 of the colitis) in T reg cells and Th1 cells, followed by a consequent decrease (day 14 of the colitis) in Treg, Th1, Th2 and Th17. Similar results, with different absolute values, were found in mice treated with IFX in absence of DSS induced colitis.

Conclusions: IFX therapy is associated with measurable microbial and immune cells changes in DSS colitis. These preliminary data open the scenario to the possibility that the translocation of microbial products, especially from anti-inflammatory species, could influenced the plasticity of T cells from Th1 to iT regs. Further analysis on immune cells within mucosa will be necessary.

P020

Wnt5b could contribute to regeneration of the epithelium in inflammatory bowel disease by potentiating epithelial mesenchymal transition

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Background: In active inflammatory bowel disease (IBD), the intestinal epithelium undergoes a process of regeneration to re-establish homeostasis at the site of injury. Transforming growth factor beta (TGF- β)-dependent epithelial mesenchymal transition (EMT) has been postulated to contribute to this regenerative process. Emerging evidence indicates that non-canonical Wnt5b could play a role in EMT. Our hypothesis is that Wnt5b could be expressed in the intestinal mucosa and contribute to the regeneration of IBD epithelium through EMT. In order to demonstrate this, we aimed to: 1) localize the areas of expression of Wnt5b in healthy gut mucosa; 2) evaluate Wnt5b expression differences in tissue samples from non-IBD controls and IBD patients; and 3) investigate Wnt5b's effects on primary intestinal epithelial cells.

Methods: Human tissue samples were used for *in situ* hybridization (RNAScope) and RNAseq to characterize Wnt5b expression in the intestine of non-IBD controls and Crohn's Disease (CD) and ulcerative colitis (UC) patients. Human intestinal tissue specimens were then used to generate *ex vivo* epithelial organoid cultures (EPOCs). EMT was assessed by stimulation of EPOCs with Wnt5b, TGF- β or the TGF- β -neutralizing antibody 1D11. Total RNA was isolated for transcriptional analysis. A migration assay (xCELLigence RTCA System) was performed to functionally check Wnt5b-induced migration changes in dissociated EPOCs.

Results: Wnt5b was found to be expressed in both the lamina propria and epithelial crypts of non-IBD intestinal samples. Transcription of Wnt5b was increased in active CD and UC colonic tissues throughout the mucosa. In EPOCs, Wnt5b addition promoted changes that closely resembled the TGF- β -induced phenotype. These included a transition towards a fibroblast-like phenotype and a significant up-regulation of EMT markers (e.g., Vimentin, Fibronectin) and other TGF- β targets (e.g., CDKN2B, Serpine1). Moreover, the addition of Wnt5b significantly increased expression of Wnt5b and TGF- β by EPOCs. In agreement with a suggested role for TGF- β in driving this Wnt5b-induced phenotype, 1D11 antibody fully suppressed the Wnt5b-mediated changes. Of note, Wnt5b stimulation promoted a migratory phenotype in dissociated EPOCs compared to un-stimulated cultures.

Conclusions: Wnt5b could contribute to epithelial regeneration in both forms of IBD by amplifying the TGF- β -dependent EMT process.

P021

Utility of therapeutic anti-TNF drug monitoring in hospitals with different degree of experience in the treatment of inflammatory bowel disease

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Background: Therapeutic drug monitoring (TDM) of anti-TNF in patients with inflammatory bowel disease (IBD) is an innovative practice used to support clinical decisions. First data on its usefulness in clinical practice has been obtained by Centres with much-experienced IBD-focused professionals. Is it possible that TDM might be more useful for decision making to less-experienced more-generalist GIs? To address this question we aimed to: a) determine concordance between foreseen selected treatment decision by physician's criteria and that selected according to TDM in two hospitals with different degree of experience on IBD; b) patient's clinical evolution according to the TDM-based management.

Methods: A prospective multicentre study (in two hospitals A and B) for a period of one year in patients with Crohn's disease (CD) or ulcerative colitis (UC) under treatment with infliximab or adalimumab and which need to modify their treatment.

It has been defined a different degree of experience (A more/B less) based on: a) years of clinical experience on IBD by involved professionals (A >10/B <10), counting on a specific IBD Unit (A Yes/B No) and number of patients visited on each centre (A 83/B 35).

The assessed variables were: drug levels plus anti-drug antibodies in blood, Harvey-Bradshaw index [HB \geq 5 active disease (AD), <5 clinical remission (CR)] and simple clinical colitis activity index (\geq 3 AD and <3 CR) at T0 (before treatment modification) and T1 (at six months)

Results: 34 patients, 50% men, 26 with CD and 8 with UC. Mean age: 48,8 years. Mean duration of anti-TNF treatment: 44,6 months. Concordance between regimen selected according physician's criteria and that selected after TDM was 74% at hospital A vs 54% at hospital B.

In 32% (11/34) of the cases there was not any concordance between physician's criteria and TDM. According to levels based management, the following decisions were taken:

Intensification or switch (6/11): AD 100% at T0 – 50% at T1; CR 0% at T0 – 50% at T1.

De-escalation o maintenance (5/11): AD 20% at T0 – 20% at T1; CR 80% at T0 – 80% at T1.

In 68% (23/34) of the remaining cases (with concordance):

Intensification or switch (5/23): AD 80% at T0 – 40% at T1; CR 20% at T0 – 60% at T1

De-escalation, maintenance or cession (18/23): AD 11% at T0 – 11% at T1; CR 89% at T0 – 89% at T1.

Conclusions: Determination of anti-TNF drug levels in patients with IBD can improve the effectiveness of those treatments by helping on physician's decision making. It looks TDM is an especially useful tool for hospitals with lower degree of experience on IBD.

More studies should take into consideration TDM use on clinical practice in hospitals with less experienced GIs that actually accounts for a high rate of the real-life clinical practice on IBD throughout Europe.

P022

MET deletion in MRP8+ neutrophils is protective during DDS-induced colitis via Th17 pathway

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Background: During intestinal inflammation, neutrophils aid in the recruitment of other immune cells and facilitate the immune response

in the gut. However, during chronic inflammatory conditions, such as Inflammatory Bowel Disease (IBD), excessive neutrophil accumulation can lead to tissue damage, delayed tissue repair and loss of homeostasis. Thus, we aim to identify the role and function of neutrophils in the pathogenesis of colitis.

Methods: To block neutrophil chemoattraction and cytotoxicity in response to its ligand hepatocyte growth factor, we used the neutrophil-specific Mrp8-Cre line backcrossed with Metfl/fl. Acute and chronic colitis were induced in MRP8Cre/WT METfl/fl (KO) mice and MRP8WT/WT METfl/fl littermate controls (WT) by 1 or 3 cycles of 2.5% dextran sodium sulfate (DSS) in drinking water for 5 days followed by 2 weeks of water. Disease progression was assessed via a standardized disease activity index (DAI). Colonic immune cells were assessed by flow cytometry. Data are expressed as mean \pm SEM; t-test was performed; $p < 0.05$.

Results: During the third cycle of chronic DSS colitis, KO mice displayed a decreased DAI ($p < 0.01$) and body weight loss ($p < 0.05$) compared to WT mice. Moreover, flow cytometric analysis revealed a reduced amount of ROS⁺ neutrophils (WT; $3.17 \pm 0.84 \times 10^5$, KO; $0.69 \pm 0.26 \times 10^5$, $p < 0.05$), eosinophils (WT; $3.00 \pm 0.62 \times 10^5$, KO; $0.80 \pm 0.20 \times 10^5$, $p < 0.05$), and macrophages (WT; $9.98 \pm 0.59 \times 10^5$, KO; $6.46 \pm 0.73 \times 10^5$, $p < 0.05$), implying a protective effect of MET deletion in MRP8⁺ neutrophils during chronic intestinal inflammation. In addition, KO mice subjected to acute DSS colitis showed an improved disease course with reduced body weight loss and DAI and a comparable decrease in the amount of neutrophils, eosinophils and macrophages. Moreover, the percentage of FoxP3⁺ T regulatory cells was increased in KO mice compared to their WT counterparts (WT; $29.27 \pm 2.14\%$, KO; $41.05 \pm 2.11\%$, $p < 0.05$), pointing towards a return to homeostasis in the KO colon. Strikingly, analysis of CD3⁺ CD4⁺ T cells showed a predominant decrease of the percentage IL17A⁺ Th17 (WT; $26.87 \pm 1.85\%$, KO; $14.19 \pm 2.11\%$, $p < 0.01$) and IL17A⁺ IFN γ ⁺ Th1-like Th17 (WT; $10.62 \pm 0.50\%$, KO; $4.70 \pm 1.51\%$, $p < 0.01$) in KO mice compared to WT mice, while no differences were observed in the percentage of IFN γ ⁺ Th1 cells (WT; $12.03 \pm 0.61\%$, KO; $12.03 \pm 3.00\%$, ns).

Conclusions: In the present study, we showed that MET is required for neutrophil chemoattraction and cytotoxicity during colitis. In addition, MET deletion in neutrophils was associated with a specific reduction of Th17 cells. Further understanding the mechanisms underlying neutrophil function during colitis will aid in the development of novel therapeutic strategies to treat IBD patients.

P023

Fatigue in quiescent inflammatory bowel disease is associated with low GM-CSF levels and metabolomic alterations

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Background: Fatigue is common in patients with inflammatory bowel disease (IBD: Crohn's disease (CD), ulcerative colitis (UC)) with profound impairment of health-related quality of life. While active disease and nutritional deficiencies contribute to fatigue in some patients, up to 40% of patients with quiescent IBD report significant fatigue in the absence of overt causes. We examined whether subclinical

inflammation or metabolomic abnormalities contribute to fatigue in a prospective cohort.

Methods: This prospective study enrolled patients with quiescent CD and UC defined as clinical remission and a colonoscopy within 1 year which demonstrated no active disease. Fatigue was assessed using the Multidimensional Fatigue Inventory (MFI) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores. A FACIT-F score < 43 indicated significant fatigue. Serum samples from each parent were analyzed for a panel of 25 inflammatory cytokines and targeted metabolomics.

Results: Our study included 87 IBD (58 CD, 29 UC) patients in remission with a mean age of 40 years and disease duration of 13.6 years. The mean MFI was significantly higher (56 vs. 34) and FACIT lower (31 vs. 48) in patients with significant fatigue ($p < 0.0001$). Those with significant fatigue reported lower SIBDQ scores (50 vs. 63) and greater anxiety (53 vs 43), depression (49 vs 43) and disturbed sleep t-scores (50 vs 43) compared to those without ($p < 0.001$). There were no differences in disease related characteristics, demographics, or medication use between the two groups. Analysis of the log-transformed cytokine levels demonstrated significantly lower G-CSF ($p = 0.02$), GM-CSF ($p = 0.003$) (Fig. 1), and lymphotoxin α ($p = 0.069$) in patients with fatigue. On metabolomic profiling, 15 metabolites were significantly different between those with and without fatigue (4 down-regulated, 11 up-regulated) (Table 1).

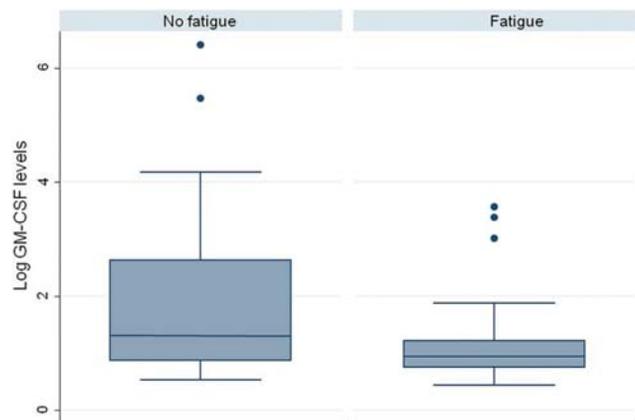


Figure 1. Comparison of log GM-CSF levels between IBD patients with fatigue and those without.

Table 1. Altered metabolites found in fatigue IBD patients with quiescent disease

Metabolite	P-value
Downregulated in fatigue	
Glycerate	0.0020
p-aminobenzoate	0.0043
Citraconic acid	0.0308
2-isopropylmalic acid	0.0423
Upregulated in fatigue	
Cytidine	0.0032
Deoxyadenosine	0.0034
Allantoin	0.0116
N-carbamoyl-L-aspartate	0.0171
Oxaloacetate	0.0270
dTMP-nega	0.0301
2-ketohexanoic acid	0.0308
Indole-3-carboxylic acid	0.0406
Orotate	0.0441
Arginine	0.0450
Phenylpropionic acid	0.0460

Key differences were identified in three pathways – pyrimidine metabolism, branched chain amino acid biosynthesis (valine, leucine, isoleucine), and glyoxylate and dicarboxylate metabolism.

Conclusions: Fatigue in IBD patients in remission is not due to a subclinical pro-inflammatory state. Rather, more complex immune dysregulation and metabolomic abnormalities contribute to this disabling symptom and could be therapeutic targets.

P024

Stratification of ulcerative colitis patients according to distinctive tissue cytokine profiles

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Background: A personalized approach to therapy has great promise to improve disease outcomes. Selection of patients as candidates for the early introduction of highly effective therapy can both maximize treatment efficiency and prevent long-term complications. Ulcerative Colitis (UC) has been associated with an atypical Th2 cell response mediated inflammation, but recent findings showed that Th17 response also participates in the inflammatory process. Although some evidences provided a proof-of-concept that IL-13 is an effector cytokine in UC, administration of anti-human IL-13 neutralizing monoclonal antibody, did not significantly improve clinical response vs placebo in UC patients. However, in the same study, the proportion of patients who achieved clinical remission was statistically significantly higher in the anti-IL13 treated group compared with the placebo group, suggesting that UC patients' subgroups might exist. We hypothesize that UC patients might be stratified according to distinctive cytokine profiles

Methods: We analyzed tissue cytokine in endoscopic biopsies of 40 UC outpatients (27 males, 13 females, disease duration 117±95.61 (mean±SD) months; median: 108 (range 0–384) months) undergoing colonoscopy for clinical relapse. At the time of endoscopy patients Mayo endoscopic score was 2.07±0.74 and 2 (1–3); mean±SD and median (range), respectively. We quantified by RT-qPCR TNF- α , IFN- γ , IL-17 and IL-13 and analyzed the results by r square of the k means four cluster solution.

Results: Only IL-13 and IL-17 mRNA tissue content showed discriminatory ability. A subset of patients (17.5%) showed low IL-13 and IL-17 mRNA tissue content. The remaining patients (82.5%) was distributed in two different clusters characterized by high and low IL-13 mRNA expression in the context of high mRNA IL-17 expression. Patients with low IL-17 and IL-13 mRNA expression showed a shorter disease duration and a lower Mayo endoscopic score when compared to patients with high IL-17 mRNA expression. High IL-13 expression was significantly associated ($p < 0.05$ by Fisher's exact test) with extensive colitis.

Conclusions: Data suggest that the majority of UC patients might be classified into two different groups according to the tissue content of IL-13. Disease extension is differently associated with IL-13 mRNA tissue content.

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P025

Transcriptional and molecular pathways activated in mesenteric adipose tissue and intestinal mucosa of Crohn's disease patients

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Background: Crohn's disease (CD) is a chronic inflammatory disorder, characterized by cytokine imbalance and transcription signaling pathways activation. In addition, increase of mesenteric adipose tissue (MAT) near the affected intestinal area is a hallmark of CD, and its role has been studied. Therefore, we evaluated the transcription signaling pathways and cytokines expression in intestinal mucosa and MAT of active CD patients.

Methods: Ten patients with ileocecal CD and eight with non-inflammatory diseases were studied. Histological analysis was performed by Haematoxylin-eosin staining (H&E). The biopsies of intestinal mucosa and MAT were snap-frozen and proteins expression were determined by immunoblotting. RNA levels were measured by qPCR.

Results: H&E showed crypt distortion, ulcers and inflammatory infiltrate in intestinal mucosa and reduced adipocyte size in MAT. The p-I κ B/I κ B ratio and TNF α level were significantly higher in intestinal mucosa of CD when compared to controls. However, STAT-1 expression was similar between intestinal mucosa of CD and controls. Considering the MAT, the p-I κ B/I κ B ratio was significantly lower and anti-inflammatory cytokine IL-10 was significantly higher in CD when compared to controls. Additionally, no differences was observed in TNF α , IL6, IL8, IL23, IL10 and STAT1 gene expression in MAT of CD patients compared to controls. Finally, the protein content of p-STAT1 was higher in MAT of CD compared to controls. **Conclusions:** These findings reinforce the predominance of the pro-inflammatory NF- κ B pathway in CD intestinal mucosa. For the first time, we showed the activation of STAT1 pathway in MAT of CD patients, which may help to understand the physiopathology of this immune mediated disease.

P026

The role of fibrocytes in mesenteric Crohn's disease

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Background: The mesentery in Crohn's disease frequently displays disease manifestations, such as mesenteric thickening and fat wrapping. Fibrocytes are a precursor cell type that can differentiate into fibroblasts or adipocytes [1]. They have previously been identified in the mesentery in inflammatory conditions such as mesenteric panniculitis [2]. This study aimed to investigate the role of fibrocytes in Crohn's mesenteric disease manifestations.

Methods: Ethical approval and informed consent were obtained from the HSE Mid-Western Regional Hospital Research Ethics Committee. Circulating and mesenteric fibrocytes were identified and enumerated by flow cytometric and immunohistochemical analysis. Mesenteric disease was quantified using a novel disease activity index. Disease was graded based on the presence and extent of mesenteric thickening and fat wrapping. The relationship between circulating fibrocytes and mesenteric disease was investigated. Serologic cytokine levels were assessed by cytokine array technology in Crohn's disease patients (n=9) and healthy controls (n=4).

Results: Circulating fibrocytes were increased in Crohn's disease (n=20) when compared with healthy controls (n=16) (8.0 ± 5.64 vs. $2.6 \pm 1.68\%$, $p=0.003$, independent t-test). Fibrocytes were also increased in Crohn's disease mesentery but were not identified in normal mesentery. They were normally found in clusters at the intestinal surface and adjacent to the blood vessels. Levels of circulating fibrocytes increase as mesenteric disease scores increase, i.e. as severity of disease increases ($r=0.81$, $p<0.0001$). The circulating cytokine profile in Crohn's disease was pro-fibrotic and pro-inflammatory. Several cytokines associated with fibrocyte migration and differentiation were elevated in Crohn's disease, such as TGF- β 1 ($p<0.01$), Eotaxin-2 and RANTES.

Conclusions: Fibrocytes were increased in Crohn's disease, both systemically and within the mesentery. An increase in circulating fibrocytes was associated with increased mesenteric disease severity. Cytokines involved in fibrocyte recruitment are elevated in Crohn's disease.

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P027

Comparing the immunological signatures of inflammatory diseases

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Background: Inflammatory bowel disease (IBD), ankylosing spondylitis (AS), psoriasis (Ps) and psoriatic arthritis (PsA) are chronic inflammatory diseases with overlapping symptoms, which are associated with similar genetic polymorphisms. We aimed to increase our understanding of the cellular pathways involved in these conditions. Using multi-parameter flow cytometry, we have characterised disease associated immunological signatures of patients with IBD, AS, Ps and PsA. These data can now be used to identify both common and unique immune pathways affected by these diseases and will be fundamental in identifying therapeutic targets in future.

Methods: 25–38 blood samples were collected from patients with IBD, AS, Ps, PsA and healthy volunteers (HC). Patients receiving biologic therapy were excluded from the study.

Immunophenotyping was performed using multi-parameter flow cytometry, focussing on T cells, monocytes and dendritic cells.

Results: We have collected samples from a total of 156 individuals

(31 HC, 38 Ps, 32 AS, 30 PsA and 25 IBD). All samples have been analysed by high-density flow cytometry, generating data on 74 pre-defined cell populations for each sample. Analysis of this dataset is ongoing, though preliminary analysis has already revealed 3 parameters that differed significantly between HC, AS and Ps cohorts.

Conclusions: Analysis of the dataset is continuing, and is being integrated with the clinical data from the donors. We anticipate that this will reveal more of the cell populations, and important cellular activation pathways that are involved in the pathogenesis of these chronic inflammatory conditions.

P028

Oligonol attenuates dextran sulfate sodium-induced colitis and reduces flare-UP in mice by enhancing host defense mechanism

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Background: Oxidative injury plays a role in the pathogenesis of inflammatory bowel disease (IBD). Oligonol, oligomerized low molecular weighted-polyphenols, have been demonstrated anti-oxidative and anti-inflammatory properties. We investigated anti-inflammatory effects of oligonol in 2 protocols of a dextran sulfate sodium (DSS)-induced colitis mouse model independently: acute colitis and repeated colitis.

Methods: DSS-induced colitis male C57BL/6 mice were made following pretreatment with different dosages of oligonol for 7 days (acute colitis model). In the second protocol, once the acute colitis had been induced with 3% DSS, sham water, oligonol (50mg/kg), and sulfasalazine (30mg/kg) were given during 2 weeks after the first DSS administration in each group. Then, 3% DSS was given again after the first DSS administration. Colitis was evaluated with macroscopic and microscopic findings.

Results: In the acute colitis model, pretreatment of 10, 50, 100mg/kg oligonol po reduced total pathologic scores significantly ($p<0.05$). Along with gross and pathological improvement, oligonol decreased the levels of interleukin (IL)-1, IL-6, and tumor necrosis factor- α as well as NF- κ B, c-Fos, and c-Jun. Also, oligonol enhanced the expression of heme oxygenase (HO)-1 and NADH: quinone oxidoreductase-1 (NQO-1), and increased total antioxidant concentration significantly ($p<0.005$). In repeated colitis model, oligonol ameliorated exacerbations of colitis, whereas sulfasalazine did not ($p<0.01$). The level of COX-2, TNF- α were much lower, and induction of HO-1 and NQO1 were increased significantly in oligonol group, compared with in sulfasalazine group.

Conclusions: These results suggest that oligonol could be possibly protective against experimentally induced colitis through enhancing host defense mechanism. Thus, oligonol may be useful for the treatment of human IBD.

P029

Azelnidipine, a novel calcium channel blocker, ameliorates severity of colitis in DSS induced colitis in mice possibly by modulating tissue levels of TNF-alpha and IL-6

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Background: Inflammatory mediators play an important role for the development inflammatory bowel disease (IBD). Regulation of these mediators is essential in the treatment of IBD, for which immune suppressants and biologics are used with the risk of suppressing the immune response. Azelnidipine is a novel calcium channel blocker (CCB) introduced for the treatment of hypertension however, growing body of evidence supports that this CCB has some anti-inflammatory properties. The aim of this study was to determine whether Azelnidipine could suppress the inflammation in DSS colitis model in mice

Methods: Six week old mice were randomized into four groups; sham, Azelnidipine control, DSS control and DSS + Azelnidipine. Mice that were exposed to 3% DSS for 7 days developed acute colitis. At the end of experiment period all of the mice were sacrificed, blood sample was taken, whole colon was excised, and distal colon segment of at least 1 cm were resected and cut into half for histopathology examination, determination tissue and serum levels of TNF alpha, VCAM and IL-6 levels.

Results: Serum levels of TNF alpha, VCAM and IL-6 levels were not different between groups ($p > 0.05$) However, tissue levels of TNF alpha ($p = 0.05$) and IL-6 ($p < 0.05$) were significantly different in DSS control group. There is no difference between DSS + Azelnidipine and control or sham groups regarding tissue levels of examined cytokines. Azelnidipine attenuated the histological damage compared to DSS control ($p = 0.05$).

Conclusions: Azelnidipine exerted a beneficial effect in acute DSS induced colitis by modulating the tissue levels of TNF alpha and IL-6. A change in experimental design would yield more valuable effect in chronic colitis model. Modulation of tissue levels of cytokines, not the blood levels, support that Azelnidipine has anti-inflammatory effect at the damaged tissue. We believe this is a noteworthy observation of inflammatory response modulation by a calcium channel blocker in colitis model.

P030 Inhibitory activity of 6-amino-2,4,5-trimethylpyridin-3-ols against inflammatory cell adhesion and recruitment to colon epithelium

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Background: The pathogenesis of inflammatory bowel disease (IBD) is complex, and a useful therapeutic marker has not been proposed, yet. The role of PI3K/Akt pathway, however, is highlighted and suggested as a target for IBD therapy. Previously, we showed that 6-amino-2,4,5-trimethyl-pyridin-3-ols significantly inhibited angiogenesis induced by VEGF and serotonin. The structure-activity relationship and dose-dependency in antiangiogenic activity of the pyridinol derivatives clearly suggest that the compounds inhibit the common target molecule involved in both VEGF and serotonin signaling such as phosphoinositide-3-kinase (PI3K)/Akt. In the present study, we examined whether 6-amino-2,4,5-trimethyl-pyridin-3-ols suppress intestinal inflammation.

Methods: Based on the notion that IBD is of complex etiology, we tried a phenotype-based primary screening to inhibit the pathological action of TNF- α , instead of conducting a specific target-based approach to directly target TNF- α molecule. The anti-inflammatory activity *in vitro* was measured as an inhibitory activity against TNF- α -induced adhesion of monocytes to HT-29 human colonic epithelial

cells. In order to demonstrate *in vivo* efficacy, some compounds were tested in the rat model of 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis, a widely used animal model of IBD.

Results: We synthesized 6-amino-2,4,5-trimethylpyridin-3-ols and tested them in colitis models *in vitro* and *in vivo* as surrogate conditions of IBD. Compared to the activity of 20 mM 5-aminosalicylate (5-ASA), an active metabolite of sulfasalazine (SSZ), showing 53% inhibition against TNF- α -induced U937-HT29 adhesion, fifteen 6-aminopyridin-3-ol derivatives at 1 μ M concentration inhibited the adhesion over 50%. In the IC₅₀ measurement, 5-ASA showed 18.1 mM, some selected 6-aminopyridin-3-ol derivatives showed IC₅₀s ranging from 0.28 to 1.47 μ M. The results indicate N-p-alkylphenyl analogues showed superior inhibition to 5-ASA against TNF- α -induced adhesion of monocytes to colon epithelial cells at three orders of magnitude lower concentration. Among the analogs, oral administration of four compounds showed potent alleviation of TNBS-induced rat colitis (67~95% of colon weight recovery and 49~82% of body weight recovery at 1 mg/kg dose) compared to SSZ (70% of colon weight recovery and 51% of body weight recovery at 300 mg/kg). As low as 1 mg/kg of the compounds showed comparable recovery activities to 300 mg/kg SSZ in those profiles, demonstrating its remarkable potency.

Conclusions: The *in vitro* and *in vivo* results strongly suggest that 6-amino-2,4,5-trimethylpyridin-3-ol can be an excellent anti-IBD scaffold.

P031 Identification of alternative splicing in transcript isoforms in patients with ulcerative colitis: effects of disease duration

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Background: Patients with long duration ulcerative colitis (UC) patients have high risk of developing colitis-associated cancer (CAC). Chronic diseases including various types of cancer have been associated with aberrant alternative splicing (AS). However, data on AS in chronic IBD such as UC and CAC is still lacking. Aberrant alternative splicing (AS) has been linked with various types of cancer but its association with CAC has not been well defined. This study aimed to determine the crucial genes that are differentially spliced within the UC susceptibility loci in long duration UC as compared with short duration UC.

Methods: To date, a total of 15 patients (11 with short duration <5 years and four with long duration >20 years) were recruited. During routine colonoscopy procedure, the inflamed colonic tissues were biopsied and RNA was extracted and hybridised to the Affymetrix GeneChip[®] Human Transcriptome Array 2.0. Affymetrix Transcriptome Analysis Console was used to identify AS events (splicing index >|1.5|, ANOVA $p < 0.05$, false discovery rate <0.05). KOBAS 2.0 was used for KEGG and Gene Ontology analysis.

Results: A total of 2,443 genes exhibited differential splicing between long duration UC and short duration UC. Alternate 3' acceptor, alternate 5' donor, cassette exon and intron retention events were reported. Both negative (range -1.51 to -143.98) and positive (range 1.51 to 204.48) splicing indexes were reported. Among these, 11 genes were IBD susceptibility loci (REL, STAT1, ERAP2, TRAF3IP2,

PHACTR2, CNTF, VDR, RPS6KB1, CD226, HCK and TNFRSF6b) and three genes were UC-specific (NFKB1, SLC9A3 and HNF4A). The KEGG pathway and Gene Ontology analysis showed enrichment for immune regulatory and CAC pathways ($p < 0.05$). Among all, JAK/STAT signalling pathway was the most prominent pathway which contains genes that were differentially spliced between long duration UC compared to short duration UC.

Conclusions: This is the first study that has successfully discovered alternative splicing events in the crucial genes that possibly involved in the transformation of long duration UC to colitis associated cancer. Further validation is essential to confirm the alternative splicing events in order to understand the potential mechanisms in carcinogenesis derived from chronic ulcerative colitis.

P032

The pharmacological profile of TOP1288, a narrow spectrum kinase inhibitor in clinical development as an anti-inflammatory treatment for ulcerative colitis

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Background: Intracellular kinase activation plays a key role in inflammation and kinase inhibitors have been proposed as potential therapy for chronic inflammatory disorders such as ulcerative colitis. Selective kinase inhibitors have proved disappointing, particularly in the treatment of rheumatoid arthritis and inflammatory bowel disease (IBD). In a strategy to improve efficacy through multi-kinase inhibition, a series of narrow spectrum kinase inhibitors (NSKIs) have been developed. The activity of TOP1288, an NSKI in clinical development, has been compared to selective kinase inhibitors (BIRB-796, dasatinib and BAY-61-3606) in a range of innate and adaptive inflammatory cell assays. In addition, TOP1288 has been assessed as an inhibitor of inflammatory cytokine release from inflamed biopsies and myofibroblasts from ulcerative colitis (UC) patients.

Methods: Activity of compounds as inhibitors of purified kinases was assessed using ZLYTETM assays. Anti-inflammatory effects of TOP1288 or selective kinase inhibitors were assessed by measurement of pro-inflammatory cytokine release from peripheral blood mononuclear cells (PBMCs) from healthy donors, primary macrophages and HT29 cells. Similarly, TOP1288 was assessed in inflamed colonic UC biopsies and myofibroblasts isolated from colonic mucosa by measuring spontaneous or TNF α induced cytokine release.

Results: TOP1288 potently inhibited P38 α , Src and Syk kinase activity with IC₅₀ values of 116nM, 24nM and 659nM respectively. Similarly, TOP1288 demonstrated efficacious and potent inhibition (IC₅₀ values ranging from 0.6–77 nM) of pro-inflammatory cytokine release from PBMCs from healthy donors, primary macrophages and HT29 epithelial cells. In each cell type, TOP1288 achieved complete inhibition, regardless of the cytokine measured or stimulus used. Generally, the selective kinase inhibitors showed much more limited efficacy and weaker potency in the cellular assays compared to TOP1288. TOP1288 down regulated spontaneous release of IL-1 β , IL-6 and IL-8 release from inflamed colonic UC biopsies with an efficacy similar to or greater than prednisolone. Similarly, TOP1288 potently inhibited IL-6 and IL-8 release from TNF α stimulated myofibroblasts isolated from inflamed colonic UC mucosa.

Conclusions: Targeted, multi-kinase inhibition using the NSKI TOP1288 leads to an efficacious and broad inhibitory profile in UC tissues and across a range of cell types including epithelial cells, innate and adaptive immune cells. TOP1288, which is in clinical development, may provide significant advantages over existing selective kinase approaches, and potentially offers a much improved therapeutic benefit in IBD

P033

DSS-induced colitis is attenuated in sigma-1 receptor knockout mice

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Background: Sigma-1 receptors (σ_1 Rs) have immunomodulatory properties and have been shown to modulate gene expression of several proteins related to inflammation. Indeed, σ_1 R modulation has been suggested to be potentially useful in pathologies where pro-inflammatory cytokines are involved. Here we assessed the potential implication of σ_1 Rs on colitis using a murine model knockout for σ_1 Rs.

Methods: Adult CD-1 male wild type (WT) and σ_1 R knockout mice (σ_1 R KO) were used. Colitis was induced by exposure to a 3% solution of dextran sodium sulfate (DSS) during a 5-day period, followed by a 3-day recovery. Body weight and clinical signs were assessed on a daily basis. At termination, colonic inflammation was assessed macro and microscopically (Stress 2008,11:348–62). Colonic expression of pro- (Interferon -INF-, IL-1, IL-6, IL-18 and IL-12p40) and anti-inflammatory cytokines (IL-10) was also determined (RT-qPCR).

Results: During colitis induction, body weight loss and clinical signs were attenuated in σ_1 R KO vs. WT animals. At necropsy, colonic inflammatory score, changes in colon length and relative weight and colonic histopathological scores were also attenuated in σ_1 R KO mice (Table 1). Improvement in histopathological scores was due mainly to a reduction in submucosal edema. Basal expression of cytokines was similar in WT and σ_1 R KO mice, except for IL-12p40 which was up-regulated by 4-fold in σ_1 R KO mice ($p < 0.05$ vs. WT). During colitis, INF, IL-1 and IL-6 were up-regulated in WT mice (all $p < 0.05$ vs. non-inflamed WT), while only minor expression changes were observed in KO animals (all $p > 0.05$ vs. non-inflamed σ_1 R KO mice). IL-12p40 showed a selective down-regulation in colitic σ_1 R KO mice while IL-18 showed minor, non-significant, changes. Regardless the phenotype considered, no changes in IL-10 expression were detected. Expression of σ_1 Rs was detected in the colon of WT mice, but not in KO animals. In WT mice, σ_1 R expression was reduced by 28% ($p < 0.05$) during colitis.

Table 1

		Macroscopic score (0–12)	Microscopic score (0–12)	Colon length (cm)	Colon relative weight (mg/cm)
WT	Water	0±0	1.29±0.22	11.09±0.26	26.45±0.75
WT	DSS	4.18±1.05*	7.73±0.62*	9.09±0.44*	53.82±3.30*
KO	Water	0±0	1.33±0.24	11.22±0.33	25.60±1.03
KO	DSS	0.08±0.08	4.77±0.51*#	10.83±0.28#	32.50±1.69*#

Data are mean \pm SEM, n=12–13 animals per group. * $p < 0.05$ vs. respective water-treated group; # $p < 0.05$ vs. WT-DSS group.

Conclusions: Lack of functional σ_1 R resulted in an attenuated in-

flammatory and immune response in the DDS-induced colitis model in mice. These results indicate that σ_1 Rs are implicated in the modulation of intestinal inflammation. Antagonism of σ_1 Rs might represent a pharmacological approach for the treatment of intestinal inflammation.

P034

Altered microbiota and host-bacterial interactions during the spontaneous development of colitis in IL-10 knockout mice

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Background: Dysbiosis and altered host-bacterial interactions are a common feature of intestinal inflammation. Spontaneous colitis in Interleukin 10 knockout (IL-10 KO) mice seems to be associated to the presence of dysbiosis. We assessed changes in gut commensal microbiota (GCM) and host-bacterial interaction systems (toll like receptors – TLR – and antimicrobial peptides – AMP) during colitis development in IL-10 KO mice.

Methods: Wild type (WT) and IL-10 KO mice were bred under barrier conditions; at 4-wk of age animals were moved to a conventional facility for an additional 8-wk period. Colitis and GCM were assessed in 4-wk-old (WT, n=5; KO, n=6) and 12-wk-old animals (WT, n=4; KO, n=5). GCM was evaluated from stools (pyrosequencing of 16S rDNA). Expression of pro-inflammatory markers (INF- γ , IL-12p40, TNF- α and iNOS), AMPs (regenerating islet-derived 3 γ – Reg3 γ – and defensin α 6/24 – Def α 6/24) and TLR2/3/4/5/7 was assessed by RT-qPCR.

Results: In 4-wk-old mice no signs of colitis were observed. GCM was similar in IL-10 KO and WT mice; with a predominance of Firmicutes (WT: 80%, IL-10 KO: 73%) and Bacteroidetes (WT: 17%, IL-10 KO: 25%). 12-wk-old IL-10 KO mice showed signs of colitis (increased relative colonic weight and histopathological scores; 100% incidence) and an up-regulation of pro-inflammatory markers vs. 10-wk-old WT mice. At this time, WT and IL-10 KO mice showed similar adaptive changes of their GCM (Firmicutes: 46% in WT, 30% in IL-10 KO; Bacteroidetes: 50% in WT, 68% in IL-10 KO). However, Verrucomicrobia (genus *Akkermansia*) increased significantly in IL-10 KO mice (95-fold vs. 3-fold in WT). Similarly, the genus *Alistipes* (phylum Bacteroidetes) appeared in the WT at detectable levels and increased by 50-fold in IL-10 KO mice. Verrucobacteria ($p < 0.001$) and *Alistipes* ($p < 0.01$) proportions correlated positively with histopathological scores. 12-wk-old IL-10 KO mice showed a general down-regulation of TLRs (50–75% vs. WT, $p < 0.001$ in all cases), an up-regulation of the AMP Reg3 γ (12-fold vs. WT, $p < 0.001$) and a down-regulation of Def α 6/24 (0.8-fold vs. WT; $p < 0.05$).

Conclusions: When moved to standard conditions, similar adaptive changes of GCM were observed in WT and IL-10 KO mice, although only IL-10 KO mice developed colitis. Increased proportions of Verrucobacteria and *Alistipes* were observed in IL-10 KO mice with colitis. Colitic IL-10 KO mice showed also alterations in host-bacterial interaction systems. These observations support the implication of Verrucobacteria and *Alistipes* in intestinal inflammation, although the cause-effect relationship remains unclear. Dysbiosis and altered host-bacterial interactions might contribute to the development and maintenance of intestinal inflammation.

P035

TNF-driven pathways are increased at baseline in Crohn's disease patients not responding to infliximab

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Background: Anti-TNF therapy (infliximab, IFX) is effective for treating Crohn's Disease (CD) but 15–25% of patients fail to respond.

Pathophysiological understanding of primary response (R) and non-response (NR) to IFX might help to predict who will benefit most from it. Additionally, it may highlight other potential therapeutic targets in non-responders.

Methods: Inflamed colonic mucosal biopsies from 17 CD patients (11 R and 6 NR, median age 31.8 years) before first IFX infusion were studied. Total RNA was analysed for whole genome expression via Affymetrix Human Genome U133 Plus 2.0 Arrays, followed by a Weighted Gene Co-expression Network Analysis [1]. A false discovery rate < 0.1 was considered biologically significant. Gene set enrichment and upstream regulation analyses were performed with Ingenuity Pathway Analysis. Mann-Whitney U-test or Fisher's exact test were used, when appropriate.

Results: Network analysis identified 70 gene clusters of which 4 (including 2179 probe sets) were correlated with (N)R to IFX. Consensus clustering using these identified probe sets perfectly discriminated R from NR. Although disease activity and CRP were not significantly different between R and NR at baseline, pathway analysis showed increased (a)granulocyte adhesion and diapedesis, TREM-1 signalling, IL-6 signalling, inhibition of matrix metalloproteases and NF- κ B signalling at baseline in NR. Upstream regulation analysis identified TNF and TGF β 1 as the strongest upstream regulators. Also TREM-1 was identified as a potential upstream regulator. Interestingly, the previously identified top 5 differentially expressed genes between IFX R and NR [2], are regulated by TNF and/or TGF β 1 and TREM-1. Colonic mRNA levels of TNF, TGF β 1 and TREM-1 showed a significantly higher expression in IFX NR vs R. Finally, we hypothesized that NR with increased TNF-driven pathways at baseline may need more TNF-blockade. We therefore retrospectively reviewed the need for dose escalation within the first year after IFX induction and found that 50.0% of NR received dose escalation, all successfully leading to R.

Conclusions: At baseline several inflammatory pathways differ between IFX R and NR. TNF was the strongest predicted upstream regulator and colonic TNF mRNA levels were significantly higher in IFX NR, suggesting that local cytokine production is (partially) driving these upregulated pathways. These patients may benefit from a higher dose of anti-TNF to neutralise gut inflammation. Additionally, therapy directed against TREM1, a triggering receptor ex-

pressed on myeloid cells, may also be a potential treatment strategy in these patients.

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P036

Human peripheral blood monocytes and intestinal macrophage populations activate transforming growth factor beta via expression of the integrin alpha v beta 8

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Background: Intestinal immune cells must be poised to clear invading pathogens while remaining tolerant to the trillions of commensal bacteria present in the gut, with perturbations in this process implicated in development of inflammatory bowel disease (IBD). The cytokine transforming growth factor beta (TGF β) is a key factor in regulating intestinal immunity, but is secreted as an inactive complex that requires activation to function. Although recent data have established important ways that TGF β activity is controlled in the mouse, the pathways present in humans remain unclear. Here we aimed to identify mechanisms regulating TGF β activity in the human immune system, and establish the functional importance of TGF β activation in intestinal homeostasis.

Methods: Healthy human peripheral blood mononuclear cells, monocyte-derived macrophages (MDMs), and colonic lamina propria cells from control and IBD patients were analysed by flow cytometry. Cells of interest were co-cultured with an active TGF β reporter cell line to determine TGF β activation.

Results: Here, we show that human CD14⁺ blood monocytes activate high levels of TGF β , which is not apparent with the equivalent murine monocytes. Mechanistically, we show that activation of TGF β by CD14⁺ monocytes requires expression of the integrin, alpha v beta 8 (α v β 8). When monocytes are differentiated to MDMs, expression of α v β 8 and TGF β activation was observed on MDMs cultured with M-CSF, which are proposed to represent a more anti-inflammatory macrophage population. In addition, integrin α v β 8 expression was increased on these cells by exposure to IL-10, TLR-4 and -7/8 ligands. In contrast, MDMs cultured with GM-CSF expressed lower levels of the integrin and activated minimal amounts of TGF β . In the intestine, integrin α v β 8 is highly expressed on CD64⁺ macrophage population expressing CD163 and CD206, which are proposed to represent a more regulatory phenotype, and are decreased in patients with active Crohn's disease.

Conclusions: Our results suggest that expression of integrin α v β 8 by CD14⁺ monocytes may play an important role in the induction and function of anti-inflammatory macrophages in the intestine via TGF β activation. Further work will provide important new insights into how myeloid cells regulate immune responses in the human intestine to maintain homeostasis and prevent IBD.

P037

MDR1-deficiency unmasks mitochondrial dysfunction as a pathogenic mechanism in IBD

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Background: The multidrug-resistance-1 (MDR1) gene encodes an ATP-dependent efflux transporter that is highly expressed in the colon. In mice, loss of MDR1 function results in colitis with similarities to human IBD. Recently, we observed a marked accumulation of dysmorphic mitochondria within the *mdr1a*-deficient colonic epithelial cells (CEC) using electron microscopy (EM). We hypothesise that loss of MDR1 results in intestinal mitochondrial dysfunction, a relevant process which drives the development of colitis in IBD.

Methods: We characterised mitochondrial function in *mdr1a*-deficiency mouse model and in shRNA-knockdown of MDR1 in T84 CECs. *In vivo*, we tested if induced gut mitochondrial dysfunction can potentiate colitis, by using direct colonic administration of rotenone and MitoQ₁₀ (mitochondrial reactive oxygen species, mtROS inducer and inhibitor respectively) in *mdr1a*^{-/-}; and in acute + recovery DSS-colitis. Furthermore, we generated a novel mouse model with intestinal-epithelial specific deletion (IEC Δ) of superoxide dismutase-2 (SOD2) gene responsible for mtROS detoxification to directly test the role of mitochondria in CECs. Finally, we analysed current GWA datasets (42 992 IBD/53 536 controls) to determine the clinical significance of mitochondrial homeostasis in IBD.

Results: Damaged mitochondria accumulate in *mdr1a*^{-/-} CECs vs. ileum/liver/lung; and vs. wild-type and *il-10*^{-/-} CECs. *Mdr1a*^{-/-} CECs have increased expression of p62, LC3 (general autophagy), PINK (specific mitophagy) and SOD2 protein expressions and impaired cellular energetics with reduced baseline respiration. Isolated *Mdr1a*^{-/-} mitochondria have lower threshold to induced damage and produced more mtROS, which are replicated *in vitro* in T84 shMDR1 CECs. *In vivo*, colonic rotenone accelerated spontaneous *mdr1a*^{-/-} colitis, increased the severity of acute DSS-colitis in *mdr1a*^{-/-} and in WT mice. Inhibition of mROS using MitoQ₁₀ attenuated the severity and promoted the recovery from DSS colitis. SOD2-IEC Δ mice displayed analogous dysmorphic mitochondria in CECs and are highly susceptible to DSS colitis. We showed that 29 (5.0%) of 574 IBD susceptibility genes ($p < 5 \times 10^{-8}$) have direct roles in mitochondrial function (GO term: 0005739). MDR1 and SOD2 genes showed associations with $p = 3.19 \times 10^{-3}$ and 3.04×10^{-3} respectively.

Conclusions: MDR1 has an important protective role for the mitochondria in the colon. Given that many IBD susceptibility genes are involved in the regulation of mitochondrial health, our findings suggest that mitochondrial toxin + genetic susceptibility interaction leading to mitochondrial dysfunction is a novel pathogenic mechanism that could offer many new therapeutic opportunities for IBD.

P038

Tissue differences in the pro-inflammatory activation of ER stress of patients with Crohn's disease

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Background: Crohn's disease (CD) is a chronic inflammatory disorder characterized by a transmural granulomatous inflammation. The prevalence of CD is increasing worldwide and arises as a complex interplay between genetic and environmental components. CD can affect any part of the gastrointestinal tract, especially the ileum and/or colon. Besides, an increased mesenteric adipose tissue (MAT) is observed near the affected intestinal area named creeping fat, suggested to be the hallmark of the disease. Recent evidences suggest a link between CD and the endoplasmic reticulum (ER) stress. ER organelle is crucial for synthesis, folding and processing of secreted and membrane proteins and lipid. The accumulation of unfolded proteins in the ER lumen activates the unfolded protein response (UPR), which resolves the protein-folding defect and restores ER homeostasis. Here we tested the hypothesis that ER stress plays a role in the pathophysiology of CD and investigated the activation of this pro-inflammatory pathway in intestinal mucosa and MAT of CD patients.

Methods: To test this, intestinal and MAT biopsies were collected from CD patients (CD group) and from patients with no endoscopic alterations (CTR group).

Results: We first evaluated the IRE1/sXBP1 pathway. Our results show an increased expression of sXBP1 in the intestinal mucosa of CD patients compared to controls ($p=0.018$). The second ER stress signaling investigated was PERK/EIF2alpha pathway. Here we show an increased expression of PERK gene in intestinal mucosa of CD patients ($p=0.025$), as well as EIF2alpha protein expression ($p=0.0031$) and pEIF2alpha/EIF2alpha ratio. However, no differences in gene and protein expression were observed in MAT tissue. By qPCR we observed an increase in the cleaved/activated form of ATF6 protein in the intestinal mucosa of CD patients ($p=0.0327$), however, this increase does not translate in protein content augmentation. Also, no differences were observed in ATF6 gene expression in MAT. Additionally, we observed an increased expression of genes related to ER stress activation in intestinal mucosa of CD patients, like ATF3 ($p=0.0226$), DNAJC3 ($p=0.044$), CALR ($p=0.0021$), STC2 ($p=0.0027$) and the chaperones GRP94 ($p=0.0277$) and GRP78 ($p=0.082$). No differences were observed in ATF3, DNAJC3, CALR and STC2 genes in MAT, however, we found an increased gene expression of GRP94 ($p=0.0087$) and a decrease in the chaperone GRP78 ($p=0.0017$) in MAT of CD patients.

Conclusions: Our results demonstrate the activation of the three branches of ER stress in the intestinal mucosa of CD patients, while no activation in MAT. Thus, ER stress is an important pro-inflammatory mechanism of CD, specifically in intestinal mucosa, and may be an attractive therapeutic target.

P039

Suppression of phospholipase A2 of intestinal microbiota by the phospholipid-bile acid conjugate ursodeoxycholate-lysophosphatidylethanolamide ameliorates mucosal inflammation in a genetic mouse model of ulcerative colitis

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Background: The mucosal attack by commensal microbiota is one component for induction of inflammatory episodes in ulcerative colitis (UC). Previously we could show that in UC the mucus layer is

intrinsically devoid of phosphatidylcholine (PC) resulting in low hydrophobicity which facilitates bacterial invasion. Ectophospholipase carrying bacterial strains are most likely candidates to break the PC mucus barrier.

Our aim of this study was to evaluate the effect of phospholipase A₂ (PLA₂) inhibitors on prevention of inflammation in a genetic UC mouse model.

Methods: As PLA₂ inhibitor we applied the bile acid-phospholipid conjugate ursodeoxycholate-lysophosphatidylethanolamide (UDCA-LPE). The tamoxifen-sensitive, intestinal specific kindlin 2 knockout mouse was used as a genetic model for UC. During 3 days of i.p. tamoxifen application to induce the UC phenotype, the control and experimental group were orally gavaged and a 100 µl bolus of 5% Tween80 or 100 mM UDCA-LPE in Tween80 was applied, respectively. At the 4th day the animals were sacrificed and analyzed in regard to the degree of mucosal inflammation as well as the change of colonic microbiota.

Results: Luminal UDCA-LPE reduced the PLA₂ activity in stool by 36±8%. Concomitantly no inflammatory phenotype was observed when compared to kindlin 2^(-/-) mice not treated with UDCA-LPE. The improvement was documented in regard to calprotectin in stool levels, endoscopic as well as histologic features. The pattern of colonic microbiota distribution obtained in the UC phenotype mice was reversed by UDCA-LPE to the control mice pattern.

Conclusions: The inhibition of the bacterial ectophospholipase A₂ activity improves mucosal inflammation in a genetic mouse model of UC. It is assumed that the remaining mucus PC shield is better preserved when luminal PLA₂ is suppressed.

P040

Intestinal EP4 receptor is required for homeostasis of the colon in mice

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Background: Prostaglandin E2 plays an important role in inflammation and cancer. Prostaglandin E2 acts on the PGE receptors (EP), including EP1, EP2, EP3, and EP4. EP4 is expressed in the colorectal epithelium. Recent studies showed that EP4 agonists ameliorate colitis in experimental murine models by inhibiting the production of chemokines and cytokines from immune cells. Furthermore, in a clinical trial, administration of EP4 agonist was effective in treating patients with mild-to-moderate ulcerative colitis (UC) who were refractory to 5-AZA therapy. Therefore, administration of EP4 agonists may be a therapeutic strategy for the management of UC. However, the functional role of intestinal EP4 in homeostasis of the colorectal epithelium in a normal condition is not fully understood. The aim of this study is to elucidate the functional role of intestinal EP4 in homeostasis of the colon.

Methods: We generated Villin-Cre mice (control) and Villin-Cre; EP4 flox/flox mice (EP4 cKO) and assessed the colorectal epithelium at the age of 8–9 weeks. In EP4 cKO mice, EP4 was deleted exclusively in the intestinal epithelium from an embryonic stage. Colonic epithelium was evaluated in terms of morphology, apoptosis, cell proliferation, differentiation, and signaling pathways by hematoxylin and eosin staining, immunohistochemistry and quantitative RT-PCR analyses. Furthermore, to induce experimental colitis, 2% of DSS was administered for 7 days and mice were analyzed histologically.

Results: EP4 cKO mice were born according to the Mendelian frequencies. The length of crypts in the distal colon was significantly

shorter in EP4 cKO mice relative to control mice. Apoptosis and cell proliferation were markedly increased within the crypts in EP4 cKO mice. In terms of differentiation, secretory lineages including goblet cells, tuft cells, and entero-endocrine cells were significantly decreased in EP4 cKO mice. Furthermore, ectopic Paneth cells were observed in EP4 cKO colons, whereas they were not observed in controls. Moreover, colonic epithelial cells expressing Muc2 and Cdx2 were markedly decreased in EP4 cKO mice. Notably, instead of decreased number of cells expressing Muc2 and Cdx2, colonic epithelial cells expressing Notch1IC, Hes1 and Sox9 were significantly increased and distribution of these cells was extended from the bottom to the more upper regions of the crypts in EP4 cKO mice, suggesting that Notch signaling was more broadly activated in EP4 cKO mice. Additionally, in a DSS-colitis model, colitis was more severely exacerbated in EP4 cKO mice.

Conclusions: Intestinal EP4 receptor is required for homeostasis of the colon in mice, which appears to be mediated by Notch signaling pathway.

P041

C-jun n-terminal kinase 2 promotes enterocyte survival and goblet cell differentiation in the inflamed intestine

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Background: c-Jun N-terminal kinases (JNKs) contribute to immune signalling but their functional role during intestinal mucosal inflammation has remained ill defined

Methods: Using genetic mouse models we characterized the role of JNK1 and JNK2 during homeostasis and acute colitis. Epithelial apoptosis, regeneration, differentiation and barrier function were analysed in intestinal epithelium-specific (Δ IEC) or complete JNK1 and bone-marrow chimeric or complete JNK2 deficient mice as well as double knockout animals (JNK1 ^{Δ IEC}JNK2^{-/-}) during homeostasis and acute dextran sulfate sodium (DSS)-induced colitis. Results were confirmed using human HT-29 cells and wildtype (WT) or JNK2 deficient mouse intestinal organoid cultures.

Results: We show that non-hematopoietic JNK2 but not JNK1 expression confers protection from DSS-induced intestinal inflammation reducing epithelial barrier dysfunction and enterocyte apoptosis. JNK2 additionally enhanced Atonal homolog 1 (Atoh1) expression, goblet cell and enteroendocrine cells differentiation and mucus production under inflammatory conditions.

Conclusions: Our results identify a protective role of epithelial JNK2 signalling to maintain mucosal barrier function, epithelial cell integrity and mucus layer production in the event of inflammatory tissue damage.

P042

Expression of IL-38 and their antagonists in patients with inflammatory bowel disease

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Background: Recently, has been demonstrated the role of IL-36 cytokines in chronic inflammatory diseases. Phenotypic characterization of IL-36 family members, IL-38 and IL-36Ra producing cells and gene expression is poorly described in patients with inflammatory bowel disease (IBD). Thus, the aim of this study was to characterize tissue expression of IL-38 and their antagonist (IL-36Ra) producing cells regarding to clinical activity in patients with Ulcerative Colitis (UC) and Crohn Disease (CD).

Methods: This is a cross-sectional and comparative study that included 30 active UC, 20 remission UC, 10 active CD, and 10 remission CD and 30 normal controls. Gene expression of IL-38 and IL-36Ra were measured by real-time polymerase chain reaction (RT-PCR) after total RNA extraction and complementary DNA was synthesized by PCR. Protein expression was detected by double-staining immunohistochemistry. Statistical analysis was performed using the SPSS 19 program by the Kruskal-Wallis One Way Analysis of Variance on Ranks Data were expressed as the median, range and mean \pm SE. A P value \leq 0.05 was considered as significant.

Results: The gene expression of IL-38 was increased in colonic tissue from patients with inactive UC when compared with active UC and control group (p=0.009 and p=0.008, respectively). The gene expression of IL-36Ra was significantly higher in colonic tissue of patients with active UC when compared with remission UC and non-inflamed control group (p=0.006 and p=0.007). CD14+/IL-36Ra+ pDCs were determined on higher number on submucosa, muscular, and adventitia from active CD patients compared with active UC patients and non-inflamed control tissue. A small number of epithelial cells from mucosa and perivascular lymphocytes synthesized the IL-36Ra. The IL-38 expression in tissue from patients with UC and CD was mostly by epithelial and connective tissue cells. Nevertheless, some perivascular inflammatory CD123- cells that expressed this cytokine. In addition, there were a small subpopulation of CD123+/IL-38-producing cells distributed along serosa, muscular, submucosa and mucosa. The IL-38-expressing cells were plentiful in serosa, muscular and submucosa from active UC compared to active CD and non-inflamed control tissue. The protein expression of IL-38 was higher in mucosa from IBD patients compared to other layers.

Conclusions: The IL-38 and IL-36Ra were increased in patients with IBD. These cytokines might represent novel therapeutic targets in patients with IBD.

P043

Ulcerative colitis is characterised by an exaggerated onset of acute inflammation with delayed resolution

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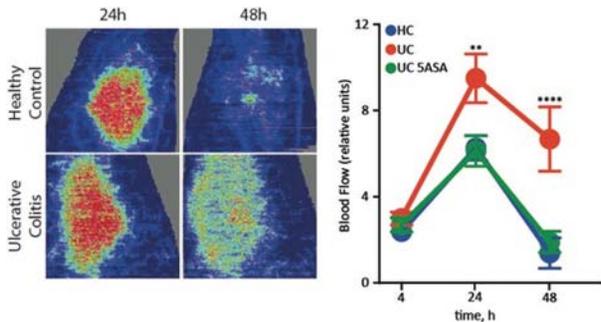
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ogy, London, United Kingdom; ³University of Manchester, Division of Pharmacy and Optometry, Manchester, United Kingdom; ⁴University College London, Clinical Pharmacology, London, United Kingdom

Background: The early inflammatory response in ulcerative colitis (UC) has been shown to be protracted. We used an *in vivo* bacterial challenge model to determine the cellular and molecular determinants and consequences of this perturbed acute inflammatory response in patients with UC.

Methods: Acute inflammation was provoked in 26 UC patients off treatment or on 5-aminosalicylates, and 17 healthy controls (HC), by intradermal injection with UV-killed *E. coli* or *S. pneumoniae*. The local vascular reaction was quantified using laser Doppler imaging. The early and resolving inflammatory exudates were sampled by raising suction blisters over inoculation sites after 4h or 48h. Cells were characterised by polychromatic flow cytometry; cytokines by multiplex array; and lipid mediators by mass spectrometry. *In vivo* findings were confirmed by *in vitro* stimulation experiments on cultured peripheral blood-derived neutrophils and macrophages.

Results: UC patients off treatment demonstrated enhanced local blood flow within 24h of bacterial exposure, with impaired resolution, to both Gram-negative and Gram-positive bacteria ($p=0.01$).



Legend. Left: Doppler images showing enhanced blood flow 24h post-inoculation, and delayed resolution at 48h, in UC. Right: summary results showing exaggerated response in UC and normalisation in patients taking 5-aminosalicylates; $P<0.01$, $**P<0.0001$.

Neutrophil accumulation within 4h of inoculation was almost double that of HC (115,217 vs 67,760 cells/blister, $p=0.04$). This was associated with elevated PGE2 production ($p=0.02$), and did not appear to be a cytokine-driven phenomenon. At 48h, the excess of neutrophils in UC persisted (5,402 vs 494 cells, $p=0.001$), accompanied by T lymphocytes (7,713 vs 3,670 cells, $p=0.03$) of an effector memory phenotype. The exaggerated onset was normalised in UC patients taking 5-aminosalicylates; these individuals had greater numbers of macrophages present at 48h (5,044 vs 1875 cells, $p=0.03$), consistent with their role in inflammation resolution and tissue healing. Excess PGE2 production and normal cytokine secretion were replicated in cultured UC macrophages stimulated with *E. coli* *in vitro*, supporting the primary impact of these abnormalities in the generation of the excessive acute inflammatory response.

Conclusions: The acute inflammatory response to bacteria in UC is exaggerated, and slow to resolve, with immunological findings mirroring those seen in acute disease flares. This phenomenon was not restricted to Gram-negative bacterial stimuli, and is associated with abnormalities in inflammatory lipid mediators. 5-aminosalicylates normalise this process, likely through harnessing novel pro-resolution mechanisms. This method also provides a platform to investigate disturbed inflammation in UC, and the impact of novel therapies on this.

P044

Therapeutic effects of mesenchymal stem cells induced regulatory dendritic cells on chronic colitis model in mice

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Background: Mesenchymal stem cells (MSCs), emerging cell therapeutics for inflammatory bowel disease (IBD), have demonstrated immunomodulatory effects by interactions between T cells and dendritic cells (DCs). In this study, we investigated whether MSCs could differentiate mature DCs (mDCs) into a distinct regulatory DCs and these DCs could alleviate inflammation through a T cell modulation in DSS induced chronic colitis mouse model.

Methods: DCs were derived from mouse bone marrow and different subsets of DCs were characterized by fluorescence-activated cell sorting (FACS). Quantitative polymerase chain reaction (q-PCR) for anti-inflammatory (interleukin (IL)-10 and transforming growth factor (TGF)- β) and pro-inflammatory cytokines (interferon (IFN)- γ , tumor necrosis factor (TNF)- α and IL-6) were performed in both *in vitro* DC subsets and *in vivo*. Using splenocytes co-cultured with MSC induced DCs, q-PCRs for CD4, CD8, CD25 and Foxp3, and Western blotting for Foxp3 were performed to measure the expression of regulatory T (Treg) cell markers *in vitro*. *In vivo* dextran sulfate sodium (DSS) chronic colitis model, Expression of IL-10, TGF- β , STAT3 and Foxp3 were compared among 5 groups (control, DSS-colitis, immature DCs only, MSCs, and MSC-induced DCs).

Results: MSC-induced DCs expressed CD11c+ CD80lo CD86lo cell surface marker. These DCs secreted high levels of anti-inflammatory cytokines, whereas production of pro-inflammatory cytokines were diminished *in vitro*. Also, the levels of mRNA and protein of Foxp3+, CD4+ and CD25+ were increased in splenocytes co-cultured with MSC-induced DCs. In addition, intraperitoneal injection of MSC induced DCs significantly increased anti-inflammatory cytokines at both m-RNA and protein level and enhanced differentiation of FOXP3+ Treg cells, resulting in considerable amelioration of chronic colitis and improvement of survival in DSS treated mice.

Conclusions: These results showed that MSCs induced DCs alleviated chronic colitis by promoting Treg cells differentiation and the secretion of anti-inflammatory cytokines, providing potential application of MSC-induced DCs in the treatment of IBD.

P045

5-Aminosalicylates promote inflammation resolution in ulcerative colitis through generation of anti-inflammatory hydroxy fatty acids

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Background: 5-aminosalicylate (5-ASA) drugs constitute a major therapeutic option for ulcerative colitis (UC), but their mechanism

of action remains incompletely understood. We employed an *in vivo* model of acute inflammation in humans both with and without UC to elucidate the functional impacts of 5-ASAs on the acute inflammatory response.

Methods: Acute inflammation was provoked by intradermal injection of killed *E. coli* (EC) in 26 UC patients and 23 healthy controls (HC), with individuals in both cohorts either on no immunomodulatory treatment or on 5-ASAs. Inflammatory exudates were sampled at 4h and 48h by raising suction blisters over the inoculation sites. Cells were characterised by polychromatic flow cytometry; and lipid mediators by mass spectrometry. The impact of lipid mediators on macrophage pro-inflammatory cytokine secretion was determined by ELISA following *in vitro* stimulation of peripheral-blood monocyte-derived macrophages with killed EC.

Results: An excessive inflammatory reaction clinically observed in UC was normalised in patients taking 5-ASA therapy. This enhanced resolution was associated with increased concentrations of the hydroxy fatty acids 9-oxo-octadecadienoic acid (OxoODE) and 13-OxoODE. To characterise the effect of these novel mediators, cultured macrophages were co-incubated with EC, in the presence of increasing concentrations of either 9-OxoODE or 13-OxoODE. 9-OxoODE led to a dose-dependent suppression of both TNF- α ($p=0.0001$) and MIP-1 β secretion ($p=0.002$), and 13-OxoODE inhibited TNF- α secretion ($p=0.01$), at concentrations reflective of those detected in the *in vivo* model.

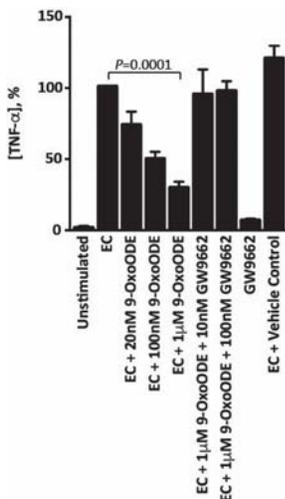


Figure 1

9-OxoODE was more potent than 13-OxoODE for TNF- α inhibition, with an IC₅₀ of 100nM. These effects were completely reversed by GW9662, an antagonist at the PPAR- γ receptor ($p=0.006$). Notably, the *in vivo* profile of lipid mediators in HC treated for 5 days with 5-ASAs differed from that seen in UC, associated with subtle differences in the resolving cellular inflammatory infiltrates and cytokine milieu. This has important implications for understanding the generation of hydroxy fatty acids *in vivo* in patients.

Conclusions: We have uncovered an important novel pathway through which 5-ASAs normalise the overly exuberant acute inflammatory response in UC, by generation of hydroxy fatty acids that harness a previously unexplored pro-resolution pathway. These exert anti-inflammatory actions through the PPAR- γ receptor, providing potential new drug targets in this disease.

P046

Starch consumption is associated with serologic responses in patients with ulcerative colitis and an ileo-anal pouch

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Background: Serologic markers are associated with complicated Crohn's disease (CD). Ulcerative colitis (UC) patients after proctocolectomy with ileo-anal anastomosis (pouch surgery) often develop *de-novo* small intestinal inflammation (pouchitis). Serologic responses against sugar moieties (glycans) in pouch patients have similarities with those observed in CD. We hypothesized that serologic responses may reflect consumption of dietary sugars, specifically starch.

Our aim was to correlate anti-glycan serologic responses and dietary sugars and starch consumption in UC patients with a pouch, and its evolution over time.

Methods: UC pouch patients were recruited and serum was evaluated for the presence of the anti-glycan antibodies anti-chytobioside (ACCA), anti-laminaribioside (ALCA), anti-mannobioside (AMCA) antibodies, and anti-Saccharomyces cerevisiae (ASCA) using ELISA. Food-frequency questionnaires (FFQ) were filled. Correlation between dietary sugars and starch consumption and anti-glycan serologic responses was assessed.

Results: Seventy five pouch patients were recruited: 38 (50.7%) women, average age 45.2 \pm 14 and pouch age 9.8 \pm 6.7 years. The rate of seropositivity against any anti-glycan was 26 patients (34.7%) of which 11 (14.7%), 8 (10.7%), 13 (17.3%) and 2 (2.7%) patients were positive for ACCA, ALCA, AMCA and ASCA, respectively. In a multivariate analysis, higher starch consumption was associated with higher titers of AMCA and ACCA antibodies, with an increase of 4.08% {(0.8–7.4), $p=0.014$ } and 4.8% {(0.7–9.1), $p=0.007$ } for each 10 grams of dietary starch, respectively. In a subgroup analysis of 21 patients with longitudinal follow-up of 9.1 \pm 5 months, AMCA and ACCA increased in correlation with starch consumption, with an increase of 6% {(1.2–11.2), $p=0.015$ } and 6.2% {(1.8–10.8), $p=0.006$ } for each 10 grams increase of dietary starch. ASCA or ALCA levels did not correlate with starch consumption.

Conclusions: Starch consumption is associated with increased serologic responses against glycans, specifically ACCA and AMCA. This may suggest that an increased intake of dietary polysaccharides may trigger a specific immune response in patients with IBD. Further dietary modification is being evaluated.

P047

Therapeutic dosing of filgotinib (GS-6034, GLPG0634) is efficacious in the mouse DSS model of colitis

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Background: Janus kinase (JAK) family proteins, JAK1, JAK2, JAK3, and TYK2, are key non-receptor tyrosine kinases, activated by common gamma chain cytokines, interferons, and other growth factors. Filgotinib (GS-6034) is a selective JAK1 inhibitor. Recently completed clinical phase 2 trials in RA and Crohn's disease demonstrated clinical benefits in patients with an acceptable safety profile relative to pan-JAK inhibitors. Previously, preclinical benefits of GS-6034 were demonstrated in a preventive mode in a murine model of dextran sulfate sodium (DSS)-induced colitis. Here, we evaluated preclinical benefits of therapeutic dosing of GS-6034 in the DSS-induced colitis model.

Methods: Colitis was induced in female C57BL/6 mice (n=15/group) by 4% DSS in drinking water for 7 days. GS-6034 (30, 10, and 3 mg/kg) was orally administered once daily beginning on Day 5, once disease had been established, until Day 14 at study completion. Efficacy was assessed via disease activity index (DAI: stool consistency, hemocults, and body weight change) and histopathological measures (inflammation, gland loss, erosion, and hyperplasia), both accepted metrics of colitis.

Results: All animals were included in the evaluation. 30 mg/kg of GS-6034 demonstrated efficacy in all measures including body weight change, stool consistency, hemocults, colon length and weight, and histopathological assessment. 10 mg/kg of GS-6034 demonstrated efficacy in some measures including body weight change and colon length and weight. Disease-induced body weight loss was improved in 30 and 10 mg/kg of GS-6034 groups (37% and 28%, respectively; vehicle as 0%; sham as 100%; $p < 0.05$ to vehicle). DAI score was lower in 30 mg/kg of GS-6034 group (67% to vehicle as 100%, $p < 0.05$ to vehicle) and showed a trend of reduction in 10 mg/kg of GS-6034 group. Normal stool consistency was well maintained in 30 mg/kg GS-6034 group throughout the study period (185% to vehicle as 100%, $p < 0.05$ to vehicle). None of animals in 30 mg/kg GS-6034 group showed diarrhea throughout the study period. The median ratio of colon weight/ length (mg/ cm) was 34 in 30 and 10 mg/kg of GS-6034 groups vs. 45 in vehicle group ($p < 0.05$ to vehicle; 22 in sham group). The sum of histopathology measures was 3.9 in 30 mg/kg of GS-6034 group vs. 6.8 in vehicle group ($p < 0.05$ to vehicle).

Conclusions: Therapeutic dosing of GS-6034 dose dependently slowed disease progression and demonstrated efficacy in all measures of disease activity.

P048

Decreased expression of aquaporins in colonic biopsies from collagenous colitis patients. A novel diarrhoeal pathomechanism?

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Background: Collagenous colitis (CC) is an inflammatory bowel disease and common cause for watery diarrhoea. The diarrhoeal mechanisms in CC are poorly understood as well as the mode of action how budesonide effectively reduces stool frequency and improves stool consistency. Aquaporins are water channels responsible for absorption and water balance in the colon as well as water homeostasis inside cells. We therefore investigated aquaporins expression in colonic biopsies of CC patients with active disease and in clinical remission under budesonide therapy.

Methods: The aquaporin expression was assessed using qPCR on colonic biopsies. The aquaporins investigated were AQP1, AQP3, AQP4, AQP6, AQP7, AQP8, AQP9, AQP10 and AQP11. We also investigated the sodium/ hydrogen exchanger 1 (NHE1). Further investigation with immunohistochemistry is ongoing.

Results: qPCR analysis of the colonic biopsies revealed a significant decrease in the mRNA expression of AQP1, AQP8, AQP11 and NHE1 in CC-patients compared to healthy controls. Under budesonide therapy which led to clinical remission in all patients, we observed an increase in the expressions of all AQPs, especially significant for AQP8 and NHE1 compared to prior treatment.

Conclusions: CC patients showed a decreased expression level of AQP1, 8, 11 and NHE1 compared to healthy controls. During budesonide treatment the expression was re-established for AQP1 and 11 and significantly increased for AQP8 and NHE1 indicating an involvement of AQPs in CC. AQP dysregulation could be a novel pathomechanism to explain the watery diarrhoea in CC and budesonide might have anti-diarrhoeal properties via AQP upregulation.

P049

Lewis score: a useful tool for the diagnosis but not for the definition of prognosis in suspected Crohn's disease

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Background: Small bowel capsule endoscopy (SBCE) is currently the most sensitive diagnostic technique to detect early small bowel inflammation. Previous reports showed that the application of Lewis Score (LS) ≥ 135 as the cutoff value for the presence of significant inflammatory activity in patients undergoing SBCE for suspected Crohn's disease (CD) may be useful to establish the diagnosis of CD. Our aim was to evaluate the diagnostic and prognostic accuracy of the LS in patients with suspected CD undergoing SBCE.

Methods: Retrospective single-center study including patients who underwent SBCE for suspected CD between January 2010 and June 2015. Inflammatory activity was assessed with the LS. Patients were grouped according to the criteria of the International Conference on Capsule Endoscopy (ICCE) for the definition of suspected CD (Group 1: patients not fulfilling ICCE; Group 2: patients with ≥ 2 ICCE criteria). Subsequent diagnosis of CD was established according to international guidelines. All patients were followed for at least 12 months. **Results:** 193 patients (61% women, mean age 39 ± 13 years) were included. SBCE detected significant inflammatory activity (LS ≥ 135) in 82 patients (43%): 24 patients from Group 1 (32%) and 58 patients from Group 2 (50%) ($p = 0.012$). During follow-up, a CD diagnosis was established in 61 patients (32%): 56 patients with LS ≥ 135 (68%) and 5 patients with LS < 135 (5%) ($p < 0.001$).

The LS showed good diagnostic accuracy with AUROC of 0.93 ($p < 0.001$) (Fig. 1). Considering a cutoff of 135, this score had a sensitivity, specificity, positive predictive value, and negative predictive value for the diagnosis of CD of 92%, 80%, 68%, and 96%, respectively. Two (4%) patients from Group 1 with a LS < 135 and 44 (76%) patients from Group 2 with LS ≥ 135 had CD diagnosis on the follow-up ($p < 0.001$). During the first year after diagnosis there was no significant association of LS with the need of immunomodulatory therapy, biological therapy, bowel resection surgery or hospital admission due to CD flair.

Conclusions: The LS (cutoff ≥ 135) is very useful in the diagnosis of

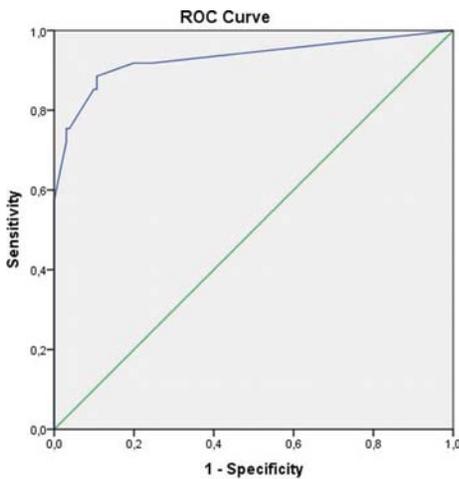


Figure 1. Receiver operating characteristic curve for LS for the diagnosis of CD.

CD in patients undergoing SBCE, with a very high negative predictive value. Applying the ICCE criteria for the definition of suspected CD may improve the diagnostic accuracy of LS. However, this score was not associated with prognostic variables.

P050
Centrally-determined standardization of flow cytometry methods reduces inter-laboratory variation in a prospective multicenter study

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Background: Flow cytometry (FC) of mucosal biopsy and peripheral blood samples from patients with inflammatory bowel disease aids

Abstract P050

Table 1. Comparison of inter-laboratory coefficients of variation

Parameter	Within cell population	Condition	Mean proportion, % (SD)	CV, % (SD)			p-value*
				LGLS	LGCS	CG	
% CD3+	Lymphocytes	US	74.0 (6.7)	5.1 (1.8)	29.2 (9.1)	2.6 (0.5)	0.004
% CD4+	CD3+ αβ T cells	US	67.6 (4.1)	11.3 (4.0)	10.9 (2.6)	2.1 (0.3)	0.011
% CD8+	CD3+ αβ T cells	US	30.0 (6.9)	74.1 (6.8)	20.4 (7.9)	5.4 (0.2)	<0.001
% IL-17A+	CD4+ CD3+ αβ T cells	S	2.3 (0.5)	21.0 (1.4)	47.7 (12.0)	14.1 (4.5)	0.007
% IFNγ+ CD4+	CD4+ CD3+ αβ T cells	S	19.9 (3.9)	21.4 (1.4)	24.1 (9.1)	7.9 (2.0)	0.034
% IL-17A+ IFNγ+CD4+	CD4+ CD3+ αβ T cells	S	0.4 (0.1)	44.0 (7.5)	65.6 (3.4)	20.9 (8.1)	0.001
% IFNγ+ CD8+	CD8+ CD3+ αβ T cells	S	60.0 (12.8)	34.7 (8.1)	15.7 (4.0)	7.4 (4.9)	<0.001

*Between-strategy comparisons were made using a two-way ANOVA (adjusting for donor) CV, coefficient of variation; SD, standard deviation; LGLS, local gating, local strategy; LGCS, local gating, central strategy; CG, central gating; US, unstimulated; S, stimulated

in characterization of cellular and molecular factors involved in the pathologic immune response in these diseases. This technique has potential to facilitate early drug development and elucidate mechanisms of action of prospective therapies. Lack of standardized methods and variation in FC outcomes across laboratories hamper its use in multicenter clinical trials. We compared the variation in 3 FC strategies among international laboratories.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from buffy coats from 3 healthy volunteers, cultured in a cocktail +/- phorbol 12-myristate 13-acetate and ionomycin at a central laboratory, and then fixed, frozen, and shipped on dry ice to 7 international laboratories. Permeabilization and staining of PBMCs was performed at each laboratory in triplicate using a common protocol and centrally-provided reagents. Gating was performed according to 3 strategies: local gating with a local strategy, local gating with a central strategy, and central gating. A range of cell populations, with high or low event numbers and in stimulated and unstimulated conditions was chosen for analyses. Mean cell proportion was calculated across triplicates and within donors, conditions and strategies. The coefficient of variation (CV) for each FC parameter was calculated across laboratories. Among-strategy comparisons were made using a two-way ANOVA, adjusting for donor.

Results: Mean inter-laboratory CV ranged from 2.1%–74.1% depending on cell population and gating strategy (5.1%–74.1% for local gating with a local strategy, 10.9%–65.6% for local gating with a central strategy, and 2.1%–20.9% for central gating [Table 1]). For each FC parameter, mean-inter laboratory CV differed significantly across gating strategies and variability was consistently lower with central gating, which reduced mean inter-laboratory CV by 3%–67%, depending on cell population.

Conclusions: Flow cytometry can be performed by multiple international laboratories with reasonable precision using a common protocol for permeabilization and staining, and centrally-performed gating. Central gating was the only strategy with mean CVs consistently lower than 25%; a proposed standard for pharmacodynamic and exploratory biomarker assays [1]. Our results suggest that gating is a major source of variability in FC.

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[1] O’Hara DM et al, (2011), Recommendations for the validation of flow cytometric testing during drug development: II assays, J Immunol Methods, 120

P051
Use of digital technology to boost patient recruitment in inflammatory bowel disease clinical trials

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Background: The weakest link in the long and expensive clinical trial process for the treatment of Inflammatory Bowel Disease (IBD) and other disabling chronic diseases is the patient recruitment. It has been estimated that insufficient patient enrollment in clinical trials can double the clinical development time and in certain cases cause premature termination of clinical trials [1]. As a leading academic research group, GETAID created CT-SCOUT™ platform, a software for clinicians to pre-screen candidates for trials which are actively recruiting in their center without requiring any prior knowledge of the ongoing trials.

Methods: A prospective, single center, open-labelled and observational pilot study was conducted with the objective to evaluate the benefits of implementing CT-SCOUT™ platform for patient enrollment into clinical trials within a tertiary-care center. All physicians in contact with IBD patients were asked to use the CT-SCOUT™ platform to evaluate whether patients were eligible for either academic or industry-sponsored trials. The primary endpoint was the patient randomization rate per month. The 21-month intervention period (Apr 2014 – Dec 2015) was compared with the previous 21-month reference period (Jul 2012 – Mar 2014) using Wilcoxon's matched-pair signed-rank test. Logistic regression analysis was performed to determine predictors of patient enrollment.

Results: After implementing CT-SCOUT™, the inclusion (i.e. defined as informed-consent form signature) and randomization rate increased from 1.7±1.4 to 4.7±3.1 (p=0.001), and from 1.2±1.2 to 3.5±2.8 (p=0.005) patients per month, respectively. During the 42-month study period, IBD patient population grew in terms of both consultations (from 219±48 to 270±57, p=0.002) and days hospitalizations (from 139±25 to 189±32, p=0.001), while the number of IBD hospitalizations, study coordinators and ongoing trials remained stable.

CT-SCOUT™ platform acted as predictor for higher patient randomization in clinical trials (OR =25.28; IC95% [5.26–1 032.77], p=0.002) as well as the monthly rate of IBD consultation >200/month (7.32; [0.95–386.45], p=0.05).

Conclusions: CT-SCOUT™ has multiplied the patient recruitment rate by a three-fold in clinical trials, regardless of increasing IBD patient cohort of the center. This application appears to be an easy-to-use solution to the global issue of patient enrollment in clinical trials.

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P052

The role of TDAG8 in intestinal inflammation

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Background: Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are typically associated with a decrease in local pH. Genome-wide association studies (GWAS) revealed a strong genetic impact on IBD, identifying over 200 non-overlapping single-nucleotide polymorphism (SNP) genetic risk loci

for IBD. G-protein-coupled receptor (GPCR) T-cell death associated gene 8 (TDAG8 or GPR65) has been identified found to be a genetic risk gene factor for IBD in recent GWASs. TDAG8 belongs a family of proton-sensing GPCRs, which consists of OGR1, TDAG8 and GPR4. Therefore, we aim to investigate the role of TDAG8 in a murine IBD models.

Methods: Chronic colitis was induced in WT and TDAG8^{-/-} mice with 4 cycles of 2% DSS in drinking water for 7 days followed by 10 days of regular drinking water. Colon specimens were obtained for haemalaun and eosin, mRNA, Immunohistochemistry (IHC). Peritoneal macrophages (MΦs) from WT and TDAG8^{-/-} mice were isolated. Cells were treated with pH 6.8 serum free RPMI to activate TDAG8 using pH 7.6 as negative controls. After 24 h RNA was collected and transferred for sequencing.

Results: In the chronic colitis model weight changes, colonoscopy scores, colon lengths and spleen weights, MPO activity and histological scores did not show any statistically significant differences between WT and TDAG8^{-/-}. In DSS challenged mice mRNA expression of IFN γ , TNF α , IL6, iNOS was increased in the TDAG8^{-/-} group. No significant differences for mRNA expression of IL17a, Gata3, Foxp3 and RORc were detected. IHC staining revealed that DSS-treated TDAG8^{-/-} specimens showed increased immunoreactivity of MΦ marker F4/80 compared to WT and water controls. Protein staining of T cell marker CD3 showed no difference between WT and TDAG8^{-/-} mice. Interestingly, mRNA and protein expression of OGR1 were downregulated in TDAG8^{-/-} colon tissue. To further examine the role of TDAG8 in MΦs, we performed RNA-sequencing after pH shift from pH 7.6 to pH 6.8. Pathways in mouse MΦs, mediated by TDAG8, were positively enriched for regulation of lymphocyte and leukocyte activation, apoptosis, M1 regulation. Conversely, pathways in TDAG8-deficient MΦs were upregulated for cytokine production involved in inflammatory response and M2 regulation. Moreover, expression of OGR1 was significantly downregulated in TDAG8^{-/-} MΦs.

Conclusions: Although, TDAG8 does not play an important role in murine chronic colitis model, it seems to be relevant in the inflammatory response of macrophages.

P053

Circulating non-classical monocytes are reduced in patients with active IBD but increase after vedolizumab: a role for $\alpha 4\beta 7$ in myeloid cell recruitment to the inflamed intestine

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Background: Monocyte derived cells populate the intestine and contribute to inflammation in IBD. Circulating human monocytes comprise classical, intermediate and non-classical subsets which likely represent a differentiation pathway. The expression and role of $\alpha 4\beta 7$ signalling on human myeloid cells is not known. Our aim was to test the hypothesis that $\alpha 4\beta 7$ contributes to monocyte trafficking to the human intestine and investigate whether vedolizumab impacts this pathway.

Methods: 9 patients and 7 healthy controls were recruited (mean age = 28.9 years; 7M:2F; CD:UC=5:4. Six patients were bled pre and post (2–6 wks) infusion. Classical (CD14+CD16-), Intermediate

(CD14+CD16+) and non-classical (CD14-CD16+) HLA-DR+ monocytes were identified by antibody labeling. $\alpha 4\beta 7$ was defined by the presence on $\beta 7$ in the absence of CD103 (αE). Cell numbers were determined by simultaneous acquisition of Flow Count beads.

Results: Non-classical monocytes were a numerically small population in all subjects and significantly reduced in patients with active IBD ($n=9$ $p=0.0052$ Mann-Whitney U -test). In contrast numbers of intermediate monocytes and the predominant classical population did not differ in disease. Reduced non-classical monocytes may reflect depletion as the result of recruitment of these cells, or their precursors, to the intestine in a manner similar to CD4+CD45RA- effector T cells which were also reduced in active IBD patients ($p=0.0115$; Mann-Witney U-test).

Expression of $\alpha 4\beta 7$ was detected in all monocyte subsets although the proportion of $\alpha 4\beta 7+$ cells was significantly lower in non-classical monocytes in both groups of subjects. There were no significant differences in the proportion of $\alpha 4\beta 7+$ monocyte subsets between IBD patients and healthy controls.

In a subset ($n=6$) of patients, monocyte numbers were determined before and after vedolizumab therapy. Numbers of non-classical monocytes increased significantly ($p=0.031$; Wilcoxon paired test) following vedolizumab.

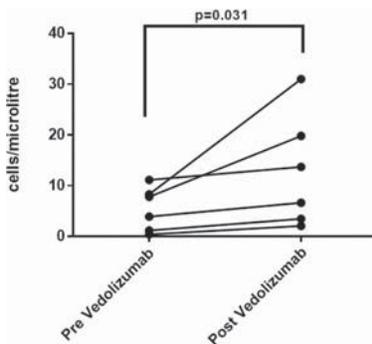


Figure 1. Non classical monocytes (pre and post vedolizumab therapy.)

Vedolizumab therapy did not affect numbers of classical or intermediate monocytes (not shown).

Conclusions: Altered monocyte populations in IBD, expression of $\alpha 4\beta 7$ and an effect of vedolizumab on circulating monocytes suggest a contribution of $\alpha 4\beta 7$ -dependant recruitment of these innate immune cells to the disease process in IBD. Changes in non-classical monocytes, the likely final cells in a monocyte differentiation pathway, may be influenced by effects on their classical and intermediate precursors, a high frequency of which express $\alpha 4\beta 7$.

P054

Metformin protects against intestinal barrier disruption via AMPK α 1-dependent inhibition of JNK signaling pathway

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Background: The intestinal epithelium serves as an important barrier to prevent intestinal penetration of luminal bacteria, toxins and antigens. The disruption of intestinal epithelial barrier contributes to IBD pathogenesis. C-Jun N-terminal kinase (JNK) is involved in the disruption of epithelial barrier. There is increasing evidence that metformin has additional beneficial effects including anti-inflammation and upregulation of blood-brain barrier functions. The aim of the

current study is to investigate whether metformin protects against intestinal barrier disruption and the potential mechanisms in colitis.

Methods: we used confluent Caco-2 cell monolayers and C57BL/6 mice treated with 3% DSS to induce intestinal barrier disruption *in vitro* and *in vivo* with or without metformin treatment. Barrier function was determined by transepithelial electrical resistance (TEER), FITC-dextran (FD4) flux and bacterial translocation. The level of tight junction proteins (TJs) occludin and Zo-1 was assessed by western blot and immunofluorescence staining. The role of AMPK and activation of JNK pathway were detected by western blot.

Results: Metformin treatment significantly alleviates DSS-induced the loss of TEER and the increasing flux of FD4 in Caco-2 cell monolayers. Western blot and immunofluorescence staining showed that the level of TJs occludin and Zo-1 reduced by DSS were reversed by metformin treatment. In DSS-induced acute colitis of mice, metformin can significantly ameliorate the induction of colitis, prevent the reduction of body weight, colon length, reduce DAI score and inhibit the production of inflammatory factors IL-6, TNF- α and IL-1 β . The intestinal barrier function of mice was maintained by metformin in DSS-induced colitis, as metformin protected against the loss of TJs occludin and Zo-1 and reduced the permeability of FD4 in colon. Also, metformin significantly reduced the commensal bacterial translocation in colitis. DSS-induced JNK activation in Caco-2 cell monolayers and in colon of mice, while metformin treatment inhibited the activation of JNK and promoted the phosphorylation of AMPK α . The inhibition effect of JNK activation by metformin was disappeared when AMPK α 1 was silenced by siRNA, but not AMPK α 2. Metformin couldn't maintain the barrier function of AMPK α 1-silenced cell monolayers after DSS administration.

Conclusions: Metformin can protect against DSS-induced intestinal barrier disruption. The potential mechanism is involved in the inhibition of JNK activation via a AMPK α 1-dependent signaling pathway.

P055

Mitochondrial DNA is a damage-associated molecular pattern released during active IBD promoting TLR9-mediated inflammation

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Background: Due to common evolutionary origins, mitochondrial DNA (mtDNA) shares many similarities with immunogenic bacterial DNA, and is recognised as a damage-associated molecular pattern (DAMP) that activates pro-inflammatory TLR9 signalling pathways. We hypothesised that mtDNA-TLR9 mediated inflammation is important in IBD, and mtDNA is released during active disease serving as a key pro-inflammatory trigger.

Methods: Between 2015–2016, we collected plasma separated within 2 hours of sampling from 128 prospectively recruited IBD patients comprising 98 ulcerative colitis (UC) and 30 Crohn's disease (CD), and 39 non-IBD controls, with 210 sample points. We assessed plasma mtDNA levels by qPCR using primers amplifying mitochondrial specific ND2 and COXIII genes. In parallel, we investigated plasma mtDNA *in vivo*, in acute DSS- and chronic spontaneous mdr1a-deficient colitis models; in human IBD: faecal mtDNA levels ($n=12$ UC vs. 12 healthy controls), electron microscopy (EM) of inflamed colonic mucosa (6 UC vs. 6 healthy controls; intestinal TLR9 protein expression (10 UC, 10 CD and 20 age-matched controls); and acute DSS-colitis in tlr9-deficient mice.

Results: Increased cell-free plasma mtDNA was detected in UC ($p < 0.0001$) and CD ($p < 0.003$), as well as acute DSS- and chronic mdr1a-deficient colitis (both $p < 0.05$). MtDNA levels were higher in active disease compared to those in remission in UC ($p < 0.001$) as measured by the Simple Clinical Colitis Activity Index (SCCAI), and mtDNA levels correlated positively with C-reactive protein ($r = 0.33$, $p < 0.0001$) and negatively with albumin ($r = -0.32$, $p < 0.0001$). MtDNA levels also correlated with severity of DSS-colitis. MtDNA is significantly higher in faecal samples during active UC vs. controls (> 20 fold, $p = 0.005$) indicative of local gut release and supported by the presence of intestinal sub- and epithelial deposits of mitochondrial debris by EM. TLR9 expression is higher in intestinal human IBD epithelium suggesting that a downstream pathway is present. Finally, tlr9-gene deletion in mice resulted in significant attenuation of acute-DSS colitis (colitis score, weight loss, and histological severity) confirming the importance of TLR9 pro-inflammatory signalling in colitis.

Conclusions: For the first time, we show that significant levels of mtDNA are found systemically and locally in human IBD and in mouse models of acute and chronic colitis. These levels are associated with disease severity. TLR9, the target of mtDNA, is highly expressed in the gut and tlr9-deletion is protective in colitis. Collectively, our data suggest that mtDNA-TLR9 signalling is important and a targetable pathway, and mtDNA itself represents an attractive functional potential biomarker in IBD.

P056

Gut microbiota characterisation in South Asian IBD patients resident in the UK

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Background: The pathogenesis of inflammatory bowel disease (IBD) is understood to be a result of a complex interplay between genetics, host immune response and gut microbiota. There is however emerging data to highlight the role of the environment as supported by the evidence of extensive geographic variation in IBD and migrant studies in the South Asian population. The distinct genetic background as well as the lack of certain risk loci in South Asian IBD patients in contrast to their Caucasian counterparts, and the emergence of Western diet and lifestyle highlight a crucial role of the environment in disease pathogenesis. As the gut microbiota has been shown to be different in the native South Asian population compared to those in developed countries, we aimed to investigate if there were ethnic differences in dysbiosis in IBD patients.

Methods: We recruited ten Caucasian (8 with ulcerative colitis, 2 with Crohns; 2 had moderately active disease) and six South Asian (5 with ulcerative colitis, 1 with Crohns; 2 had moderately active disease) patients with IBD attending routine out-patient appointments in to the study. Patient characteristics and disease demographic data was collected along with a stool sample. Microbial DNA was extracted using a modified method of the QIAamp Stool mini kit. To analyse community structure, we amplified the V3-V4 hyper-variable

region of the 16S rRNA gene from faecal DNA, using barcoded sequencing primers. These products were sequenced using the Illumina MiSeq and data analysis was performed using the QIIME pipeline and GreenGenes database to compare differences in microbial composition and diversity between.

Results: We found no differences in the microbial diversity nor phylae and genera in luminal gut microbiota between South Asian and Caucasian patients with IBD. This observation did not vary regardless of patient and disease characteristics or medications. Similar to previous observations both groups of patients with IBD demonstrated reduced bacterial diversity and an expansion in *Proteobacteria*, *Bacteroides* and *Clostridiales* along with a decrease in *Firmicutes*. The *Firmicutes* to *Bacteroides* ratio was characteristically low as expected in IBD.

Conclusions: The gut microbiota in South Asian IBD patients is similar to Caucasian IBD patients. A larger cohort of IBD patients are needed to validate these findings and study the role of travel and diet to changes in gut microbiota associated IBD disease activity.

P057

IL-6 induces NLRP3 inflammasome activation through JAK/STAT3-dependent NOX2 induction in colon epithelial cells

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Background: IL-6, in addition to TNF α , plays an important role in the pathogenesis of inflammatory bowel disease (IBD), which is supported by clinical observations of close correlation between IL-6 production and severity of the disease in IBD patients. IL-6 plays a role in the recruitment process of neutrophils and monocytes to lesion sites, resulting in aggravated and chronic inflammation. Recently, TNF α is shown to prime TLR-independent NLRP3 inflammasome activation. IL-6, however, has not been shown such activity. The present study aims to investigate whether IL-6 induces NLRP3 inflammasome formation, and NADPH oxidase is involved in that process.

Methods: The IL-6-induced adhesion of monocytes (U937 cell line) to colon epithelial cells (HT-29 cell line) was examined by co-culture of HT-29 cells with U937 cells that were already labeled with BCECF-AM (10 μ g/mL). After 3 h treatment with IL-6, BCECF fluorescence from adhered cells was measured. To identify signaling pathway, siRNA transfection, RT-PCR and Western blot analyses were performed. Reactive oxygen species (ROS) was measured by lucigenin chemiluminescence assay.

Results: IL-6 significantly increased U937 monocytic cell adhesion to HT-29 colonic epithelial cells, which was accompanied by up-regulation of adhesion molecules (ICAM-1 and VCAM-1), NLRP3, caspase-1, and IL-1 β . Concurrently, IL-6 significantly increased ROS production in a time-dependent manner, which matched significant induction of NOX2 and its regulatory subunits. The IL-6-induced ROS production and increased expression of NLRP3, caspase-1, and IL-1 β were attenuated by pretreatment with NADPH oxidase inhibitors (VAS-2840, DPI and apocyanin), but not by inhibitors against other enzymes, such as cytosolic COX-2 (celecoxib), mitochondria (antimycin A), xanthine oxidase (allopurinol), and iNOS (NAME) in HT-29 cells. Similarly, inhibitors of JAK (tofacitinib) and STAT3 (stattic) suppressed IL-6-induced ROS production, NOX2 induction, and the changes in inflammasome proteins in HT-29 cells.

Conclusions: Taken together, our results suggest that IL-6 induces

NLRP3 inflammasome activation through JAK/STAT-dependent NOX2 induction in HT-29 colonic epithelial cells.

P058

Comparison of Calprotectin levels in stool and rectal mucus in subjects with suspected or confirmed inflammatory bowel disease

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Background: The OriCol™ sampling device retrieves mucocellular material from the rectum, providing a unique sample for the study of gastrointestinal disease. The sample can be quickly taken by a trained health care professional and requires no bowel (or other) preparation. OriCol™ has been used in >2500 patients and is well accepted. Samples collected with the OriCol™ device can be used in a range of downstream analyses including investigation of DNA (mutation detection and methylation analysis), protein and antibodies as well as the microbiome.

Faecal calprotectin is routinely used as a marker of inflammation in the initial diagnosis and subsequent management of patients with inflammatory bowel disease (IBD) and its discrimination from irritable bowel syndrome (IBS) which presents with similar symptoms. Here we present data from an ongoing clinical study investigating the potential and suitability of the OriCol™ sample for analysis of calprotectin. The study aims to assess the relationship between calprotectin levels in stool and rectal mucus and thereby establish a threshold in rectal mucus samples that corresponds to the threshold in faeces for determination of inflammatory versus non-inflammatory bowel disease.

Methods: Patients referred with symptoms indicative of new onset IBD or patients with confirmed IBD attending specialist clinics were recruited. OriCol™ and matched stool samples were collected and processed following standard operating procedures. Calprotectin levels were measured using commercially available assays, with 2 protocols being used for processing of OriCol™ samples.

Results: Calprotectin is readily measurable in the OriCol™ samples. Interim analysis in a cohort of 35 patients looking at data from 2 assays showed good correlation between the OriCol™ results from the different kits (correlation coefficient 0.978 and 0.971 compared with 0.883 for parallel stool samples). There was good linearity and recovery of calprotectin measured in the OriCol™ samples in both cases and a clear relationship was seen between calprotectin levels in OriCol™ and stool samples.

Conclusions: The initial results indicate that samples collected with the OriCol™ device can be used to measure calprotectin. Correlation with patient diagnosis and calculation of appropriate thresholds for rectal mucus will be carried out using the full data set with measurements from 4 commercially available assays.

P059

Mucosal inflammation promotes activation of circulating Vδ2+ T-cells in Crohn's disease

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Background: Phosphoantigen-responsive lymphocytes (Vδ2T-cells) are absent in rodent models but common in human blood, where they mediate host protection against tumour cells and bacteria. In health, activated Vδ2T-cells traffic to mucosal tissues and contribute to epithelial barrier protection, whereas in Crohn's disease (CD) these cells promote intestinal inflammation via enhanced expression of TNFα. Microbial activation increases Vδ2T-cell sensitivity to azathioprine (AZA) *in vitro*, and routine AZA therapy selectively ablates Vδ2T-cells in CD patients *in vivo*, but the factors that influence drug susceptibility of circulating Vδ2T-cells are unknown. We assessed whether the AZA sensitivity of blood Vδ2T-cells in CD patients can be attributed to release of stimulatory factors from the inflamed mucosa into the peripheral circulation.

Methods: Peripheral blood was subjected to density gradient separation of mononuclear cells (PBMC) or directly labelled with monoclonal antibodies for phenotypic analysis of circulating Vδ2T-cells by flow cytometry. PBMC were cultured with/without microbial phosphoantigen in the presence or absence of blood plasma from CD patients or healthy controls to assess Vδ2T-cell stimulatory/suppressive potential of circulating soluble factors. T-cell phenotype, proliferative capacity, and gut-homing potential were assessed by flow cytometry.

Results: Blood Vδ2T-cells were selectively ablated in CD patients receiving routine AZA therapy but only moderately reduced in a control group of patients receiving the same treatment regimen (2mg/kg/day) for Behçet's disease without gut involvement, suggesting that mucosal inflammatory activity influences peripheral stimulation and loss of Vδ2T-cells. Consistent with this concept, blood Vδ2T-cells from CD patients displayed significantly reduced expression of the inhibitory cell surface receptor PD-1 in active disease (CRP >5mg/L). Microbial stimulation of healthy control Vδ2T-cells in the presence of human blood plasma stimulated marked proliferation and upregulation of MHC class II and gut-homing integrin β7. However, while healthy plasma restrained PD-1 upregulation by control Vδ2T-cells, blood plasma from CD patients enhanced PD-1 expression and supported further upregulation of this molecule upon microbial activation *in vitro*. These data suggest that CD plasma contains stimulatory factors that induce differential activation of blood Vδ2T-cells in health and disease.

Conclusions: Activation of gut-tropic Vδ2T-cells in the blood of CD patients is influenced by mucosal disease activity and may be enhanced by translocation of phosphoantigen and/or release of pro-inflammatory mediators into the circulation.

P060

Role of innate lymphoid cells in the chronic colitis under anti-il-17a therapy

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Background: Unlike psoriasis and rheumatoid arthritis, anti-IL-17 therapy did not improve clinical outcomes in patients with Crohn's disease. We aimed to evaluate role of RORγt+ innate lymphoid cells (ILCs) in the chronic colitis under absence of IL-17.

Methods: To induce chronic colitis, CD4+CD45RBhi T cells of either wild-type (WT) C57BL/6 or Il17a-/- mice were transferred to Rag2-/- mice. Flow cytometry analysis was performed for analyzing RORγt+

ILCs in the colonic lamina propria of the chronic colitis model. Transcript expression was analyzed using the polymerase chain reaction. **Results:** Body weight of Rag2^{-/-} mice with T cell transfer from Il17a^{-/-} mice was higher than that of Rag2^{-/-} mice with T cell transfer from WT mice in early phase of colitis. At 9th week from the T cell transfer, however, body weights did not differ between the WT mice T cell transfer and Il17a^{-/-} mice T cell transfer groups (81.9% vs. 82.2%; p=0.922). Intestinal inflammation score did not differ between two groups (p=0.494). Proportion of Lin-RORγt⁺ cells in lymphocytes was higher in the Il17a^{-/-} mice T cell transfer group than in the WT mice T cell transfer group (22.6% vs. 16.8%). Proportion of Lin-CD4-RORγt⁺ cells was also slightly higher in the Il17a^{-/-} mice T cell transfer (4.5% vs. 0.3%). Additionally, Il6, Il22, and Ifng were highly expressed in the Il17a^{-/-} mice T cell transfer group. **Conclusions:** IL-17A blockade could not attenuate chronic colitis. IL-17A blockade may induce increasing of ILC1s as well as RORγt⁺ ILCs, and eventually worsen chronic colitis.

P061

Epigenetic alterations at diagnosis predict susceptibility, prognosis and treatment escalation in inflammatory bowel disease – IBD Character

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Background: Biomarker discovery to predict disease outcomes is a key focus in Inflammatory Bowel Disease (IBD). We have characterized disease-associated methylation changes in newly diagnosed IBD, defined the relationship to genetic variation (meQTL) and assessed the prognostic utility of the methylome in IBD.

Methods: Genome-wide methylation was measured in peripheral blood DNA (N=641: 298 controls, 150 CD, 167 UC, 26 IBDU) using Illumina 450k chips with covariates of age, sex, and deconvoluted cell counts; genotyping was performed using Illumina HumanOmniExpressExome-8 BeadChips. Samples were obtained from new IBD cases in six European centres as part of the IBD-Character project. Outcome data were captured for the Edinburgh and Oslo IBD cohorts. Treatment escalation in IBD was defined as the need for surgery and/or biologic therapies after initial induction of disease remission.

Results: Disease-associated methylation changes were consistent between centres, and with previously published findings [1],[2]. 290 probes exhibited Holm significant IBD-associated methylation changes, including *VMP1/MIR21* (p=7.5 × 10⁻¹⁴) and *RPS6KA2*

(1.1 × 10⁻¹⁹), with novel findings including *PHOSPHO1* (2.5 × 10⁻¹⁰) and *MUC4* (5.5 × 10⁻⁸).

Paired genetic and methylation data showed 1037 Bonferroni significant MeQTLs indicating a genetic influence on several key loci — *RPS6KA2* (8.6 × 10⁻³⁴), *ITGB2* (3.3 × 10⁻³⁸), and *VMP1/MIR21* (rs8078424, p=4.4 × 10⁻²⁵, rs10853015, p=7.4 × 10⁻²¹).

Follow up data were available for 214 patients with IBD. A total of 26 (33%), 21 (17%), and 2 (18%) patients required treatment escalation in the CD, UC, and IBDU groups respectively. 11 DMPs were significantly associated with treatment escalation after Holm correction (top probe p=0.003). In UC and CD individually, 1 and 3 probes respectively survived correction for multiple testing. Supervised and unsupervised clustering identified 2 IBD patient subgroups with distinct disease courses (HR 10.5, 95% CI: 4.3–25.6; logrank p=1.5 × 10⁻²⁴).

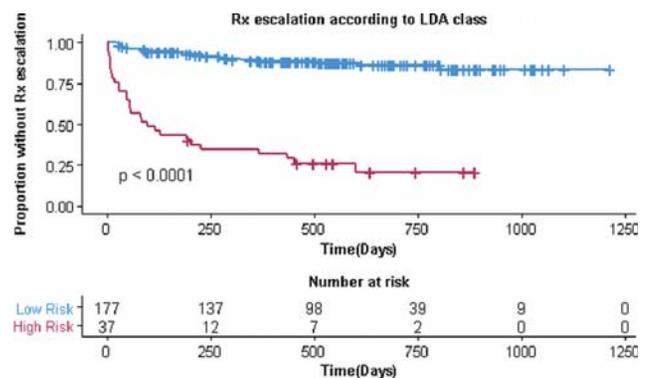


Figure 1. Prediction of requirement for treatment escalation by LDA.

The 6 probe marker outperformed conventional biomarkers in predicting treatment escalation (hsCRP >4 mg/L, HR 3.2 (1.7–5.8), logrank p=0.0004 and Alb <36 g/L, HR 2.9 (1.5–5.6), p=0.0001).

Conclusions: These data allow profiling of the IBD methylome, involving novel associations and important unequivocal replication of recent discoveries and provide insight into germline variation of epigenetic mechanisms in IBD. As biomarkers, the methylome shows promise in predicting disease course in IBD.

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P062

The narrow spectrum kinase inhibitor TOP1288 demonstrates potent anti-inflammatory effects in a T cell adoptive transfer colitis model through a topical mode of action

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Background: Unwanted systemic side effects are often associated with current therapies for inflammatory bowel disease, particularly corticosteroids, immunomodulators and tofacitinib. A series of nar-

row spectrum kinase inhibitors (NSKIs) have been specifically designed to have topical, non-systemic, effects in the colon after oral dosing. TOP1288 has already entered clinical development and is safe and well tolerated in a Phase 1 study. Here we compare the efficacy of an NSKI, TOP1288, to the systemically available immunosuppressant cyclosporine A (CsA) in a preclinical model of colitis.

Methods: *In vitro* anti-inflammatory activity was assessed in lipopolysaccharide stimulated peripheral blood mononuclear cells (PBMCs) and anti-CD3/anti-CD28 stimulated PBMCs. Pharmacokinetic profiling was performed in C57BL/6 mice who received a single 5 mg/kg dose of TOP1288 by oral gavage. Compound levels in plasma and colon tissue were determined over 24hrs post dose. Compounds were also assessed in an adoptive transfer (AT) colitis model where mice received TOP1288 (3 mg/kg BID) or CsA (75mg/kg QD), by oral gavage, for 28 days. Plasma exposure was measured on days 22 and 38. Efficacy was assessed on measures of colon oedema, histopathology and colon tissue cytokine levels.

Results: TOP1288 exhibits a broad and potent *in vitro* anti-inflammatory profile. In a PK study, TOP1288, after a 5mg/ml oral dose, had negligible systemic exposure (below the limit of detection, 1 ng/ml). In contrast, high colon exposure was observed (C_{max} 3083 ng/ml and AUC 19841 hr*ng/ml). In an AT model of colitis, TOP1288 was comparable to CsA with marked anti-inflammatory effects on both histological endpoints and inflammatory cytokine release. Inhibition of IL-8 release correlated with a reduction in neutrophil infiltration. TOP1288 systemic exposure in the model was very low and comparable to that in the PK study. In contrast, CsA achieved very high systemic levels (>1.5 µg/ml).

Conclusions: TOP1288 has broad-acting, potent anti-inflammatory activity *in vitro* and *in vivo*. PK profiling of TOP1288 following oral dosing indicates that efficacy in the AT model *in vivo* is through a topical mode of action and is, at a 13 fold lower dose, comparable in effect to systemically available cyclosporine A. This data highlights the therapeutic potential of topical NSKIs, offering an improved efficacy and safety profile over current therapies.

P063

HDAC as versatile regulators of the intestinal epithelial barrier in inflammatory bowel disease

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Background: Recent studies have highlighted the importance of the intestinal mucosal barrier function in maintaining gut homeostasis as well as contributing to disease pathophysiology of inflammatory bowel disease (IBD). When we could demonstrate that pan-inhibition of histone deacetylases (HDAC) ameliorates experimental colitis and colitis associated tumorigenesis, HDAC moved into our focus as promising targets for diagnosis and therapy. Even though a specific immune regulatory function of various single HDAC have already been shown, the impact of single HDAC on the intestinal epithelial barrier is little understood.

Here, we aim to investigate the role of HDAC on the epithelial barrier and further assess the impact of HDAC7 on barrier function by analyzing the role of HDAC7 in the physiology of colonic epithelial cells (CEC) under pro-inflammatory conditions with special emphasis to IBD and CRC.

Methods: To define the relevance of HDAC for gut homeostasis

primary CEC were isolated from human biopsies and analyzed for HDAC expression using quantitative PCR. Further we examine effects of pan-HDAC inhibitors on the integrity of the gut epithelial barrier by treating human T84 and murine CMT93 cells with Givinostat and Vorinostat. For functional characterization of HDAC7, KO cells were generated from murine CMT93 cells by using the CRISPR/Cas9 system. Cell migration was assessed via wound healing assay. Integrity and functionality of the monolayer were measured by the trans-epithelial electrical resistance (TER), cytokine secretion and the trans-epithelial flux of 4 kDa FITC-Dextran.

Results: Expression analysis revealed an overall reduction of HDAC in IBD (Crohn's disease and Ulcerative colitis). Human T84 and murine CMT93 cells demonstrated enhanced cell migration, increased secretion of regenerating IL-8 as well as a reduced decrease of the TER under inflammatory conditions when treated with HDAC inhibitor. An enhanced integrity and functionality of the monolayer could also be confirmed by an impaired flux of 4 kDa FITC-Dextran in the presence of HDAC inhibitor. On the other hand functional analysis of single HDAC KO cells displayed divergent effects as shown by a reduced TER as well as delayed cell migration in CRISPR/Cas9 generated HDAC7 KO cells. These effects were accompanied by a reduced expression of cell adhesion and migration molecules as shown by RNA sequencing.

Conclusions: Our results indicate an integrated role of HDAC in the maintenance of the intestinal barrier and further point to a regulatory function of HDAC7 in the development of the intestinal epithelial barrier and the inflammatory response of CEC.

P064

EBI2 and oxysterols in the development of intestinal lymphoid structures and colitis

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Background: Immunological mechanisms leading to gut inflammation in inflammatory bowel diseases remain insufficiently understood. The colon comprises two types of lymphoid structures, colonic patches (CLP) and solitary intestinal lymphoid tissues (SILT). The formation of gut lymphoid structures includes the interaction between a variety of chemotactic factors and their ligands. Epstein Barr virus induced gene 2 (EBI2) is a G-protein coupled receptor expressed on immune cells. The EBI2 ligand 7 α ,25-Dihydroxycholesterol is produced by two enzymes, CH25H and CYP7B1. EBI2 and its oxysterol ligand were shown to mediate migration, positioning and differentiation of B cells within secondary lymphoid organs. SILTs and EBI2 have not been implicated in the pathogenesis of colitis.

Methods: Using a whole mount approach the colons of EBI2^{-/-} mice and wildtype littermates were stained to determine the number of B cell follicles. DSS colitis was induced by administration of 2-3% dextran sodium sulfate (DSS) for 7 days or 4 cycles of 7 days interspersed with 10 day recovery periods. To study the effect of EBI2 in the IL10 colitis model, EBI2^{-/-} and IL10^{-/-} mice were crossbred and examined after 200 days. T cell transfer colitis was induced by transfer of naïve T cells from wildtype or EBI2^{-/-} mice to immunodeficient RAG2^{-/-} mice.

Results: EBI2^{-/-} mice showed significantly less B cell follicles within the colon than littermate wildtype controls. The difference was restricted to smaller lymphoid structures, pointing to an anomaly in SILT development. Despite the defective colonic lymphoid tissue, loss

of EBI2 did not affect the severity of acute or chronic DSS colitis. However, EBI2^{-/-} mice did not show an increase in the number of lymphoid structures upon chronic inflammation, which we observed in wildtype controls. In acute and chronic DSS colitis, mRNA levels of CH25H and CYP7B1 were upregulated in the colon. A similar up-regulation was found in rectal biopsies of ulcerative colitis patients, suggesting increased oxysterol production upon inflammation. Lack of EBI2 in IL10^{-/-} mice leads to a later onset and a less severe colitis. Furthermore, transfer of T cells lacking EBI2 leads to a lower grade of inflammation in the transfer colitis model.

Conclusions: We could show that EBI2 is involved in the development of intestinal lymphoid tissue during homeostasis and after immunological challenge. Oxysterol production is likely increased in the inflamed gut and knockout of their receptor EBI2 affected the severity of colitis in experimental mouse models. These findings establish a role for EBI2 and oxysterols in the maturation of the gut immune system and in the pathophysiology of inflammatory bowel diseases.

P065

Effects of gut bacteria on the intestinal immune cell composition and barrier function

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Background: Inflammatory bowel diseases (IBD) go along with a dysbiosis of intestinal microbiota. Little is known about the effect of these changes on the local immune cell subsets and intestinal integrity.

The aim was to determine the consequences of changes in the intestinal microbiota compositions for epithelial integrity and immune cell composition in the gut.

Methods: The immune cell phenotype in the gut of germ free (GF), specific pathogen free (SPF) mice and GF mice colonised with SPF microbiota at the age of 5 weeks was assessed in health and inflammation. The phenotype of lamina propria mononuclear cells (LPMC) was determined by flow cytometry and immunohistochemistry. LPMC were stimulated with lipopolysaccharides (LPS) in the presence of Brefeldin A to assess intracellular tumor necrosis factor (TNF) α -expression by flow cytometry.

Acute colitis was induced by dextran sodium sulphate (DSS). Colonic barrier function was assessed by electrophysiology using the Ussing chamber. Supernatants of cultures of *ex vivo* isolated colon tissue were analysed regarding cytokine production by Cytometric Bead Array. To confirm successful colonisation ceacal content was sequenced for 16 S ribosomal RNA. Mucins were analysed using periodic acid-Schiff reagent/Alcian blue staining on histological sections. **Results:** In the terminal ileum of GF mice the number of T cells was profoundly decreased. The amount of Ly6C⁺ monocytes as well as F4/80⁺ CD11b⁺ macrophages were decreased in the distal part of the ileum. The immune cell composition in the healthy colon was similar in GF and SPF mice. However, colonic macrophages from GF mice showed an increased TNF α -expression after LPS-stimulation compared to macrophages from SPF mice. Furthermore, in GF mice

the total resistance of the colon was decreased accompanied by an increased ³H-Mannitol flux suggesting a barrier dysfunction. Less mucin was expressed by the intestine of GF mice.

GF mice died following the exposure to DSS, whereas SPF mice survived and showed signs of colitis. Colonisation rescued GF mice from death. However, the inflammation score and the expression of monocyte chemoattractant protein-1 and interleukin-6 in the colon were higher in SPF than in colonised mice whereas the immune cell composition as well as intestinal microbiota was similar in these mice.

Conclusions: The microbiota is essential for the development of the colonic integrity and local immune cell composition in the ileum. The dysbiosis might play a role in the pathogenesis of IBD and could provide a potential target for therapeutic intervention.

P066

Fibrostenotic phenotype of fibroblasts in Crohn's disease is dependent on tissue stiffness and reversed by LOX inhibition

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Background: In Crohn's disease, intestinal inflammation often leads to fibrosis, characterized by excess extracellular matrix (ECM) deposition, increased tissue stiffness and stricture formation. Modulation of ECM is mainly mediated through activity of fibroblasts, which both deposit and degrade ECM components. To evaluate the role of fibroblasts in intestinal fibrosis in Crohn's disease, we compared phenotype and function of fibroblasts obtained from normal, inflamed and stenotic regions of the intestine.

Methods: Fibroblasts were isolated from resection specimens of normal, inflamed and stenotic ileum within the same Crohn's disease patients and analyzed for gene expression profile. Fibroblasts were cultured in matrigel/collagen mix to measure ECM contraction *in vitro*. Matrix metalloproteinase (MMP) activity was measured upon culture in both soft and stiff matrices, mimicking normal and stenotic tissue conditions.

Results: Transcriptional analysis showed that fibroblasts from stenotic ileum were distinct from both inflamed and normal fibroblasts with respect to genes involved in ECM organization and collagen production. In accordance with transcriptional data, stenotic fibroblasts showed an unexpected high activity of MMPs compared to normal and inflamed fibroblasts when cultured in the absence of ECM. This was counterintuitive, since MMP activity would be expected to be decreased in stenosis. However, when cultured in ECM with the compliance of their native stiff environment, stenotic fibroblasts displayed *decreased* MMP3 activity. This activity increased when cultured in soft environment. In sharp contrast, fibroblasts isolated from *normal* ileal regions had increased MMP3 activity upon stiffening of the ECM, suggesting a regulatory function to maintain tissue homeostasis. Functionally, stenotic fibroblasts induced significantly more ECM contraction than both normal and inflamed fibroblasts, consistent with tissue contraction *in vivo*. In addition, stenotic fibroblasts expressed increased levels of the collagen crosslinking enzyme lysyl oxidase (LOX), further contribut-

ing to tissue stiffness. Inhibition of LOX restored MMP3 activity of stenotic fibroblasts in a stiff ECM, resembling MMP3 activity level of fibroblasts cultured in soft matrix. Consequently, LOX inhibition prevented ECM contraction induced by stenotic fibroblasts. In normal fibroblasts, LOX inhibition did not affect ECM contraction.

Conclusions: Stenotic fibroblasts display inherent alterations in gene expression and exhibit an aberrant response to tissue stiffness, contributing to ECM deposition and fibrosis. Altering the microenvironment by LOX inhibition corrects this phenotype, suggesting this as a potential anti-fibrotic agent in Crohn's disease.

P067

Molecular profiling of early Crohn's disease reveals a prominent role for WNT5A

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Background: Crohn's disease (CD) is characterized by a chronic inflammation of the gut, progressing to stricturing and/or penetrating complications in most patients. Effective intervention before the onset of bowel damage, and thus in the early phase of the disease, is required to optimize patient outcomes. We aimed to define the molecular landscape of early CD by using the unique post-operative recurrence (POR) model.

Methods: Ileal mucosal biopsies were obtained during colonoscopy from (1) 25 patients with early recurrence CD (Rutgeerts' score i2b, i3 or i4) within 18 months after ileo-colonic resection with ileo-colonic anastomosis (= POR CD); (2) 19 CD patients within 18 months after diagnosis (= new CD); and (3) 14 active CD patients >3 year after diagnosis and/or >3 year after ileo-colonic anastomosis (= late CD). As comparison, 12 controls were included. Total RNA was used to study mRNA and microRNA (miRNA) expression via Affymetrix Human Gene 1.0 ST and Affymetrix miRNA 2.0 arrays, respectively. A false discovery rate (FDR) <5% and >2-fold change (mRNA) or >1.5-fold change (miRNA) were considered biologically significant. Gene and miRNA expression profiles were integrated using the Ingenuity miRNA Target Filter.

Results: When comparing POR, new and late CD with controls, we observed respectively 353, 608 and 614 significantly differentially expressed gene probe sets. Comparative analyses of the miRNA expression profiles in POR, new and late CD versus controls identified respectively 13, 5 and 1 significantly differential signal(s). Integration of dysregulated genes and miRNAs in POR CD found 64 miRNA-mRNA pairs with negative correlation in expression profiles, five of which experimentally supported in literature: hsa-let-7g-5p is known to target PRDM1 and PTGS2, hsa-miR-30d-5p targets SLC7A11 and WNT5A, and hsa-miR-196a-5p targets ANXA1. To be sure that POR i2b/i3/i4 represents a true baseline model for early CD, we looked at gene expression in ileal biopsies from 3 CD patients with uninfamed post-operative ileum (i0), and 6 CD patients with POR i1. Comparison of i0, and i1 versus controls identified respectively 1 and 123 significantly differentially expressed gene probe sets. WNT5A was the only dysregulated gene in i0, and

showed an increased expression with an increasing Rutgeerts' score ($p < 0.0001$).

Conclusions: We showed an important mRNA dysregulation in new/late CD, while dysregulated miRNA expression was more pronounced in POR CD. WNT5A, a non-canonical Wnt ligand, seems to have a key role throughout, being the only dysregulated gene in i0 CD patients, showing an increased expression with increasing Rutgeerts' score, and being targeted by one of the dysregulated miRNAs. WNT5A is known to be involved in reparative inflammation.

P068

Evaluation of the therapeutic potential of metformin-pretreated tonsil-derived mesenchymal stem cells in a chronic colitis model

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Background: Tonsil-derived mesenchymal stem cells (TMSCs), prepared after tonsillectomy in human, have many advantages including a short doubling time, high differentiation capacity, and mixed chimerism property. Metformin has an anti-inflammatory function involving inhibition of signal transducer and activator of transcription (STAT)-3. We aimed to evaluate the anti-inflammatory effect of metformin-pretreated TMSCs in a mouse model of chronic colitis.

Methods: The optimal condition under which maximum decrease in STAT-3 level occurs was evaluated *in vitro* by treating 1×10^5 TMSCs with 0.2, 0.5, 1.0, and 2.0mM metformin and extracting protein at 4, 7, and 14 days. Eight-week-old C57BL/6 mice (n=60) were randomly assigned into 4 groups: normal, colitis, TMSC, and metformin-pretreated TMSC groups. Colitis was induced by oral administration of 1.5% dextran sulfate sodium (DSS) for 5 days followed by 5 days of drinking water continuously for 3 cycles (30 days). TMSCs and metformin-pretreated TMSCs were administered via intraperitoneal injection 4 times, on days 6, 9, 12, and 16. Control mice were injected with phosphate-buffered saline at the same time. The severity of the colitis was assessed by determining the disease activity index (DAI), body weight change, colon length, histologic grading, and cytokine levels.

Results: The STAT-3 level was the lowest in TMSCs treated with 1mM metformin for 7 days, and this concentration was selected for the pretreatment. At 30 days after treatment, DAI (5.8 ± 1.3 vs 2.6 ± 1.0 vs 2.3 ± 0.4 , mean \pm standard error mean values for colitis, TMSC, and metformin-pretreated TMSC groups, respectively, $p=0.025$, ANOVA) and weight loss ($-10.3 \pm 4.9\%$ vs $6.8 \pm 4.3\%$ vs $5.9 \pm 2.7\%$, $p=0.007$, ANOVA) showed significant improvement in TMSC and metformin-pretreated TMSC group than colitis group. However, colon length ($p=0.524$) and histologic improvement ($p=0.054$) were not significantly different between the groups. The survival rate for each group was 62.5%, 86.7%, and 100%, with the lowest rate recorded in the colitis group and the highest in the metformin-pretreated TMSC group ($p=0.028$, Kaplan-Meier analysis). IL-1 β , a pro-inflammatory cytokine, showed higher levels in colitis group than TMSC and metformin-pretreated TMSC groups ($p=0.196$), whereas IL-10, an anti-inflammatory cytokine, showed opposite results ($p=0.337$), without statistical significance.

Conclusions: To our knowledge, this was the first study to evaluate the effect of metformin-pretreated TMSCs in a chronic murine colitis model. Based on the several advantages of TMSCs over other

mesenchymal stem cells in clinical use and the anti-inflammatory effect of metformin, TMSCs pretreated with metformin have clinical feasibility and favourable therapeutic potential for colitis treatment.

P069

Sympathetic but not vagal intestinal innervation regulates murine dextran sodium sulphate-induced colitis

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Background: Targeted vagus nerve stimulation is currently evaluated as an alternative and medicine free treatment for inflammatory bowel disease (IBD). Because the vagus nerve does not directly innervate the spleen or the distal colon, it may not be the optimal peripheral nerve to target. Our first aim was to determine the effect of vagotomy (vx) of the right coeliac branch, or selective sympathectomy of the superior mesenteric nerve (SMNx), on dextran sodium sulphate (DSS)-induced colitis in mice. Secondly, we determined the effect of SMN stimulation (SMNstim) on DSS-induced colitis in rats.

Methods: To induce colitis, we exposed C57BL/6 mice to 2% DSS in the drinking water for 7 days. To determine the effect of vx, SMNx or a combination (cx), we measured the disease activity index (DAI) as a clinical parameter. In addition, we measured colonic cytokine expression by qPCR.

Changes in blood flow towards the intestine due to SMNstim were also determined. To test SMNstim in DSS-induced colitis, we implanted cuff electrodes around the SMN in Sprague Dawley rats with the wires connected to a head mount allowing non-invasive stimulation. 14 days after the surgery, we exposed the rats to 5% DSS in the drinking water for 9 days. At day 3 until day 9, we applied biphasic SMNstim twice a day for 5 minutes, 2 ms, 200 μ A and 10 Hz. We assessed the DSS-induced colitis by measuring the DAI and colonic cytokines and assessing endoscopy and histology of the colon.

Results: Vx had no effect on the severity DSS-induced colitis in mice. However, SMNx as well as cx caused a significantly higher DAI (sham: 2.25 ± 1.375 ; SMNx: 5 ± 1 ; cx: 5 ± 1.25 ; $p < 0.01$) and a trend towards colonic IL-1 β and IL-6 upregulation compared to a sham procedure. Given this worsening effect of SMNx, we performed SMNstim and determined the effect on DSS-induced colitis in rats. Noteworthy, the stimulus was well tolerated by the rats and there were no changes in blood flow towards the intestine. SMNstim led to a significantly improved DAI in rats compared to rats that underwent sham stimulation (sham: 6 ± 4.13 ; SMNx: 2 ± 1.88 ; $p = 0.04$). However, colonic cytokines, endoscopy outcome and histological outcome did not change.

Conclusions: We conclude that the vagus nerve innervating the intestine does not affect DSS-induced colitis. Alternatively, our data imply that the SMN ameliorates colitis in our DSS-induced colitis models. Because we show that SMNstim can be executed safely and non-invasively in rats, our results also open an avenue to explore other nerves in experimental colitis. In the long run, our research contributes to the knowledge about nerve stimulation as an alternative treatment for IBD.

P070

TNF α production by classical monocytes is poorly controlled by IL-10 in patients with IBD

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Background: IL-10 knock-out mice as well as mice with a conditional knock out of the IL-10 receptor (IL-10R α) limited to myeloid populations develop bacterially-driven colitis. This highlights the role of myeloid cell IL-10 signaling in immunoregulatory responses to intestinal bacteria. In humans, loss-of-function IL-10R mutations cause severe early-onset IBD; these individuals may represent the end of a spectrum in which suboptimal control of myeloid cells by IL-10 leads to gut inflammation. Our aim is to investigate whether monocyte populations from adult onset IBD patients exhibit a diminished response to IL-10 compared with controls.

Methods: LPS-induced TNF α production, STAT3 phosphorylation in the presence or absence of IL-10, as well as IL-10R α expression, were measured by flow cytometry in well-characterised circulating monocyte subsets from IBD patients and controls.

Results: Intestinal macrophages are replenished from circulating monocytes. Three subsets of human monocytes are described: classical (CD14+CD16-), which by analogy with murine monocyte populations are likely to replenish intestinal macrophages, intermediate (CD14+CD16+), and non-classical (CD14-CD16+), which remain in the circulation. A mean of 78% (SEM ± 4.46) of classical and 89% (SEM ± 2.39) of intermediate monocytes from healthy donors produced TNF α upon LPS stimulation. This was significantly reduced by 2ng/ml IL-10 in both myeloid populations ($p < 0.001$). The mean reduction of TNF α in classical monocytes (68%; SEM ± 5.59) was significantly greater than in intermediate monocytes (43%; SEM ± 4.53 ($p = 0.009$)), despite similar STAT3 availability and equivalent IL-10-induced STAT3 phosphorylation. Fewer LPS-stimulated non-classical monocytes produced TNF α (mean of 33%; SEM ± 6.24), which was also poorly reduced in response to IL-10 (26%; SEM ± 5.87), an outcome which may be explained by relatively low STAT3-availability and poor IL-10-induced STAT3 phosphorylation. Since classical monocytes were well regulated by IL-10, these cells were compared in health and IBD. Despite increased expression of IL-10R α and IL-10-induced STAT3 phosphorylation, IL-10 was significantly less effective at inhibiting TNF α production by classical monocytes from IBD patients than controls.

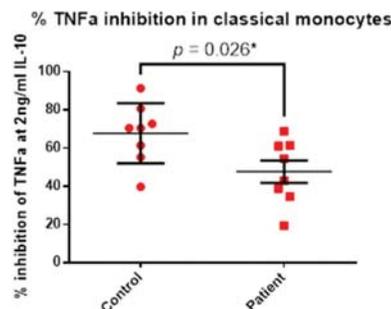


Figure 1. Inhibition of LPS-induced TNF α production in classical monocytes in health & IBD.

Conclusions: TNF α production by intermediate and non-classical monocytes is poorly controlled by IL-10 and may be relevant to inflammation in IL-10-rich environments such as the intestine. However, a sub-optimal response of classical monocytes to IL-10 may also contribute to inflammation in IBD.

P071**The mesentery in Crohn's disease displays mesenchymal abnormalities**

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Background: Recent advances in our understanding of mesenteric anatomy have shown that the mesentery is continuous along the intestinal tract at vascular, lymphatic and connective tissue levels [1]. Thus, the mesentery represents a conduit which may propagate disease [2]. This study aimed to investigate abnormalities of the mesentery in Crohn's disease (CD) at a histological level.

Methods: Samples of mesentery, intestine and intestinal hilum were resected from cadavers (n=5) and CD patients (n=5). Haematoxylin and eosin light microscopy (LM) and scanning electron microscopy (SEM) were utilised to examine tissues. Diseased tissue was graded as in Table 1. Surface mesothelium and connective tissue septal thickness were assessed in addition to adipocyte number in areas of mild, moderate and severe mesenteric disease. Primary mesenteric fibroblast cultures were developed from CD patients (n=3). Adhesion and proliferation of mesenteric-derived fibroblasts and a human dermal fibroblast cell line were characterised using real-time cell analysis (xCELLigence®, ACEA Biosystems).

Table 1. Mesenteric disease activity index in CD

Mesenteric disease score	Severity	Stage	Score
FW minimal, MT minimal	Mild	One	1
FW <25%, MT adipovascular pedicle only	Moderate I	Two A	2
FW <25%, pan-mesenteric MT	Moderate II	Two B	4
FW >25%, pan-mesenteric MT	Severe	Three	6

Results: Mesenteric surface mesothelium thickness ($p<0.001$), connective tissue septal thickness ($p<0.001$) and adipocyte number ($p<0.05$) were all increased with respect to CD severity (Table 2). Upon appraisal of the intestinal hilum, normal mesentery displayed a distinct serosa between the mesentery and muscularis externa. In CD, however, this could not be identified. Additionally, mesenteric mesenchymal abnormalities extended into the muscularis externa and deeper mural layers. Mesenteric-derived fibroblasts (n=3) adhered ($p=0.034$) and proliferated (10–30 h, $p=0.001$) faster than a human dermal fibroblast cell line.

Table 2. Mesenteric abnormalities in CD

	Normal	Mild	Moderate	Severe
Surface mesothelium (μm)	24±13.0	62±16.0	215±70.0	408±73.0
Connective tissue septae (μm)	16±7.0	53±17.0	101±21.0	245±100.0
Adipocytes (cell number per high power field)	23±6	28±4.0	37±7.0	60±7.0

Conclusions: As severity of mesenteric disease increased; surface mesothelium and connective tissue septae thickened while adipocyte number increased. Mesenteric-derived fibroblasts adhered and proliferated faster than a fibroblast cell line.

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P072**The role of the rs8005161 polymorphism on pH-sensing G protein-coupled receptor GPR65 (TDAG8) signalling in intestinal inflammation**

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Background: Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are typically associated with a decrease in local pH. Genome-wide association studies (GWAS) identified over 200 non-overlapping single-nucleotide polymorphism (SNP) genetic risk loci for IBD. The proton-sensing G-protein-coupled receptor T-cell death associated gene 8 (TDAG8 or GPR65) has been found to be a genetic risk factor for IBD in recent GWASs. Thereby, the T genotype of the SNP rs8005161 within the GPR65 gene confers increased IBD risk. In response to extracellular acidification GPR65 activates second messengers: cAMP via the Gs signalling pathway or G12/13/Rho signalling. In this study we analyzed the association of the SNP rs8005161 in the IBD cohort of patients with increased IBD risk, and its functional relevance.

Methods: 1138 individuals (591 non-IBD, 203 UC, 344 CD) were genotyped for risk SNPs, GPR65 (rs8005161, rs3742704) and GALC (rs1805078), with Taqman SNP Genotyping Assays. Additionally, more than 2064 IBD patients from the Swiss IBD Cohort Study (SIBDCS) were genotyped by Illumina sequencing. Ten patients with the genotype rs8005161 TT/CT and CC (Wild Type) from the IBD cohort and ten non-IBD controls (CC) were recruited for the functional study. Human CD14+ cells were isolated from blood samples and subjected to an extracellular acidic pH shift (pH 6.6 vs. pH 7.6) in functional assays: cAMP, RhoA GTPase activation.

Results: rs8005161 was more frequent in UC patients (minor allele frequency (MAF) 14.53% vs 10.05% in the non-IBD group), whereas no statistically significant association with IBD, UC or CD was found for the other variants (GPR65 rs3742704, GALC rs1805078) by Taqman genotyping. Sequenced genotype frequency of rare homozygote rs8005161 in the SIBDCS was 1.17%, MAF - 10.3%. No significant differences were observed in the cAMP production between IBD (TT, CT, WT/CC) and non-IBD (WT/CC) genotype carriers upon pH shift from 7.6 to 6.6. However, a decreased activation of GTPase RhoA was seen for IBD rs8005161 (TT) variant carriers after an acidic pH shift.

Conclusions: GPR65 SNP rs8005161 genotyping showed significant association with UC cases. No differences in cAMP signalling in IBD TT/CT/CC subjects compared to healthy CC subjects were observed. In contrast, TT IBD patients showed impaired activation of RhoA upon an acidic pH shift. Our results support the role of GPR65 in the intestinal inflammation in genetically predisposed individuals, emphasizing the link between acid-base homeostasis and IBD pathogenesis.

P073 Age dependent decrease in gut-homing CD4 lymphocytes

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Background: $\alpha 4\beta 7$ integrin is an important molecule in the regulation of leucocyte migration to intestinal tissue and a therapeutic target for treatment of inflammatory bowel disease (IBD). Although age-related changes in the composition of various lymphocyte subsets have been described, these have not been reported for gut homing (CD4+ $\alpha 4\beta 7$ +) lymphocytes. We postulate that paediatric IBD patients have a higher proportion of gut homing lymphocytes.

Methods: The expression of $\alpha 4\beta 7$ was analysed in peripheral blood from 29 healthy controls (including 2 cord blood samples), 10 paediatric UC and 14 paediatric CD patients. Peripheral blood mononuclear cells were isolated using the Ficoll-density gradient centrifugation method, stained with labelled antibodies against CD3, CD4, $\alpha 4$ -integrin and $\beta 7$ -integrin, and analysed using multi-coloured flow cytometry.

Results: Paediatric controls (healthy, non-IBD) had a significantly higher proportion of gut homing lymphocytes compared to the adult controls ($p=0.008$), Figure 1. There is a non-linear decline in gut homing lymphocytes with increasing age. The rate of decline is greater in the first decade and reaches a plateau in the fourth decade, Figure 2. When compared to healthy children of the same age, a large percentage of paediatric UC (60%) and CD (36%) patients had higher proportions of gut homing lymphocytes than expected, Figure 3.

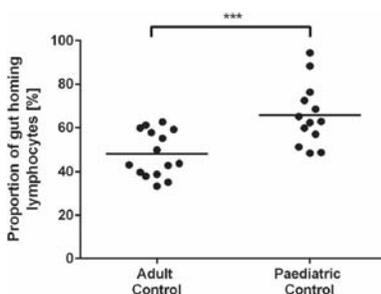


Figure 1. Proportion of gut homing lymphocytes in adult and paediatric controls.

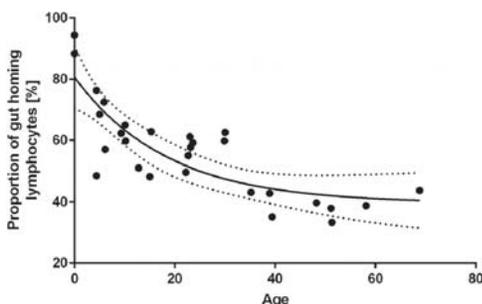


Figure 2. Age-dependent decline in gut homing lymphocytes.

Conclusions: Our study reports a higher proportion of gut homing lymphocytes in the paediatric population. This may have implica-

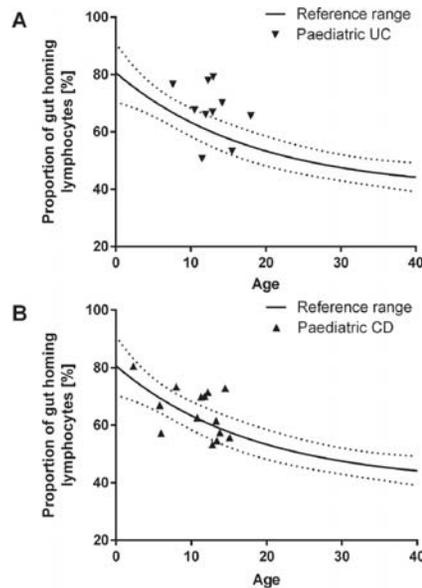


Figure 3. Proportion of gut homing lymphocytes in paediatric UC (A) and CD (B) patients compared to their healthy counterparts.

tions on treatment with Vedolizumab (anti- $\alpha 4\beta 7$ monoclonal antibody). A clinical trial focusing on paediatric patients is needed to assess the efficacy of Vedolizumab in this population, and data from adult studies should not be extrapolated to the paediatric population.

P074 Decreased levels of circulating protein S (PROS1) in patients with active Crohn's disease

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Background: Inflammatory bowel diseases (IBD), ulcerative colitis (UC) and CD are associated with an increased risk of thrombosis. Plasma protein S (PROS1) is an anticoagulant that works as a cofactor for activated protein C. PROS1 deficiency increases the risk of thrombosis. Recent pathophysiological and experimental studies in animals showed that PROS1, expressed in T lymphocytes, is also an anti-inflammatory protein playing an inhibitory role in innate immunity due to its agonist activity on tyrosine kinase TAM receptors (TYRO3, AXL and MERTK), Rothlin et al. 2015, Carrera Silva et al. 2013. A decrease in plasma PROS1 could be related to activity or phenotype of human IBD.

Aims: 1. To investigate whether there are differences between PROS1 levels in patients with CD and UC compared to healthy controls.

2. To study whether there is a relationship between PROS1 levels and IBD activity.

Methods: Free PROS1 (immunoturbidimetry, Liatest, Stago, France) was determined in 86 IBD pts.: M 38, F 48 (UC: n 54, CD: n 32) and 30 healthy controls (M 18, F 12), mean ages 38.9±16.0, 40.4±15.0 and 38.2±12.2 respectively. IBD was classified by activity indexes: CDAI (active CD >150), Mayo score (active UC >2), and Montreal classification.

Results: Mean PROS1 levels in CD (91.3±28.5) were significantly lower vs. controls (109.6±23.9, p=0.0077) and UC (104.0±28.2, p=0.048). In active CD (n 20, CDAI: 265.9±68.2) PROS1 levels (85.8±24.3) were significantly lower than in controls (p=0.0015), but vs. CD in remission (n 12: CDAI: 58.2±43.0) did not show significance (100.2±33.5). In active CD, the difference with controls was provided only from the moderate-severe subgroup (n17, CDAI 275.9±69.6, PROS1 84.2±26.0, p=0.0023) but not from other. PROS1 levels were lower in active CD vs. active UC as a trend p=0.082. In active UC (n 31) PROS1 levels (98.90±27.8) were not different from controls or UC in remission (n=23, PROS1 110.91±27.5). The extent of UC (11 proctitis vs. 43 left or extensive) did not show significant differences (116.2±24.9 vs. 100.9±28.5). PROS1 levels in CD were lower, although not significantly in the Small bowel involvement (80.3±15.8) compared with only colon (94.9±31). In CD disease behaviors and perianal disease did not show different levels.

Conclusions: 1) PROS1 levels were significantly lower in CD vs. controls and UC. 2) In active CD, PROS1 levels were different from controls, based on a decrease in the moderate-severe subgroup. Further studies will evaluate the impact of circulating PROS1 decrease in active CD and the activation of TAM receptors. These findings suggest that the decrease of PROS1 in CD could contribute to the increased risk of thrombosis and potentially to the inflammatory process of this disease.

P075

Calponin 2 protects against colitis associated cancer in mice through mediating inflammatory responses

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Background: Calponin 2 is involved in many types of malignancies, and it has been recognized as a regulator of macrophage motility and phagocytosis. We investigated whether Calponin 2 could represent a functional link between the inflammation and cancer.

Methods: Calponin 2^{-/-} mice and C57BL/6 wild type littermate controls were intraperitoneally injected with azoxymethane (AOM) followed by three cycles of 2.5% dextran sulfate sodium (DSS) in drinking water to induce colitis associated cancer (CAC). Acute colitis and chronic colitis were triggered by DSS. Mesenchymal stem cells (MSCs) were collected from WT and Calponin 2^v mice and bone marrow reconstitution was performed. Macrophages were eliminated and the severity of colitis were evaluated. Intestinal crypts were isolated and incubated within or without macrophages for 24 hours.

Results: Calponin 2^{-/-} mice developed significant tumorigenesis, increased COX-2 and IL-6 production, and showed signs of increased phosphorylation of NF-κB and STAT3 in colitis and CAC. This ef-

fects were associated with increased Calponin free macrophage infiltration, and the reduction in colitis caused by macrophage elimination were observed in Calponin 2^{-/-} mice. Moreover, increased cell proliferation was observed in organoids when co-cultured with Calponin 2^{-/-} macrophages.

Conclusions: Lack of Calponin 2 can promote progression of CAC by mediating macrophages infiltration, leading to increased IL-6 secretion, thus triggers NF-κB and STAT3 phosphorylation and development of CAC. Treatment with Calponin 2 mimic seems to be a highly intriguing therapeutic concept for inflammation-associated tumor development.

P076

IL-26 genetic polymorphisms impair cytokine response to bacterial DNA translocation and increase anti-TNF consumption in patients with Crohn's disease

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Background: Interleukin (IL)-26 is secreted by IL-17-producing helper T cells to support killing of microbes and innate sensing of bacterial derived DNA (bactDNA). BactDNA translocation has been reported in patients with Crohn's disease (CD). We aimed at evaluating the relationship between IL-26 serum levels and bactDNA translocation in CD patients, as distributed by common IL-26 polymorphisms.

Methods: Prospective observational study on CD patients in remission, as established by CDAI<150. IL-26 rs1558744, rs7134599, and rs2870946 polymorphisms were genotyped. IL-26 levels and the concentration of amplified bactDNA in blood were measured. Serum TNF-alpha and free anti-TNF-alpha levels were evaluated according to IL-26 SNPs genotypes and bactDNA presence.

Results: 313 patients were included (Mean CDAI: 83.6±32.8; Mean fecal calprotectin: 55.4±35.3µg/g). 106 patients showed bactDNA fragments in the blood (33.8%), which belonged to the Enterobacteriaceae family in 77% of cases. IL-26 SNP allelic frequencies were 53%, 12.3% and 46.5% for rs1558744 (A>G), rs7134599 (T>C), and rs2870946 (G>A), respectively. The rate of bactDNA translocation among patients distributed by the number of IL-26 SNPs was 34.4% (31/90) in patients without; 45.6% (26/57) in patients with one; 28.8% (36/125) in patients with two; and 31.7% (13/41) in patients with three IL-26 SNPs (p=ns). Serum IL-26 levels were significantly increased in patients with vs. without bactDNA in the blood (98.4±36.6 vs 16.6±10.2 pg/mL, p=0.01), and remained significantly higher irrespective of each studied SNP genotype. The accumulation of IL-26 SNPs was associated with a significant reduction in IL-26 serum levels among patients with bactDNA, although they remained higher than levels in patients without bactDNA in all cases, even in those with all three studied IL-26 SNPs. IL-26 SNPs significantly reduced TLR-9 mRNA expression in patients with bactDNA compared to those without the studied SNPs. The overall correlation found between TLR-9 mRNA expression levels and the amount of amplified bactDNA (r=0.67; p=0.01) was due to patients without or with one IL-26 SNP. Among patients on biologics, a significant reduction in serum TNF-α levels was only achieved in the absence of IL-26 SNPs. The presence of studied SNPs was associated with a reduced amount of free anti-TNF-α serum levels in patients with two or more IL-26

SNPs. An inverse correlation was present between free anti-TNF- α and IL-26 serum levels ($r=-0.36$; $p=0.01$).

Conclusions: IL-26 SNPs may compromise translocated bactDNA clearance in CD patients, facilitating an upheld proinflammatory environment. This may contribute to an increased anti-TNF- α consumption in CD patients with bactDNA.

P077

Histological remission in ulcerative colitis: an analysis of two independent cohorts

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Background: The relationship of histological and clinical or endoscopic measures of ulcerative colitis (UC) is not well-described. Based on prior analysis¹, we proposed a definition of Histological remission (HR) using selected features of the Geboes score (neutrophils in <5% of the crypts, no crypt destruction, ulceration, or erosion). Here we validate the definition in two additional independent UC cohorts.

Methods: Biopsies were collected during endoscopies at screening and post-treatment in two phase 2 clinical trials targeting patients (pts) with moderate to severe UC defined as a Mayo score of 6–12 inclusive, including endoscopy score ≥ 2 (Table 1). All endoscopies were videoed and centrally read using Mayo endoscopy subscore. A Mayo endoscopic score ≤ 1 defined endoscopic healing (EH). A single, blinded histopathologist assessed 453 biopsies from 219 pts in 54781532UCO2001 and 526 biopsies from 103 pts in PROgECT. Association of dichotomous endpoints was assessed by Fisher's exact test. Clinical differences between histological remitters and non-remitters were evaluated by t-test. P-values <0.05 were considered significant.

Results: Performance of the histological endpoint was highly reproducible in 54781532UCO2001 and PROgECT. Histological remission was significantly associated with endoscopic healing in both studies across all the time points. 92% and 90% of pts who achieved endoscopic healing at wk 8 in 54781532UCO2001 and wk 30 in PROgECT, respectively, also achieved histological remission. Furthermore, pts with histological remission had significantly lower disease activity including lower stool frequency and rectal bleeding scores compared to histological non-remitters (e.g. mean Mayo=3.78 vs. 7.52 at wk 8 in 54781532UCO2001). Early (wk 4) HR was also a strong indicator of wk 8 HR, EH, and clinical response/remission in 54781532UCO2001 (all $p<0.005$). In PROgECT, 73% of wk 6 HR achieved long-term (wk 30) HR ($p=0.0013$).

Conclusions: Histological remission defined as minimal residual microscopic disease and absence of epithelial damage is highly reproducible in multiple UC cohorts. Histological remitters are more likely to achieve endoscopic and clinical response/remission.

References:

[1] Strauss R, et al, (2015), OP235 UEGW

P078

Gut microbiome profiling of MMP-9 deficient mice and their wild-type littermates in a model of acute DSS-induced colitis

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Background: Commensal microbiota help to educate the immune system in the periphery and a number of involved immune cells have recently been characterized. However, specific molecular determinants in these processes are not known and, reciprocally, little information exists about single host determinants that alter the microbiome. Matrix metalloproteinase (MMP)-9 deficiency has previously been linked to alterations in gut microbiota composition in a model of infectious colitis [1].

Methods: Acute colitis was induced in MMP-9 knockout (KO) mice ($n=10$) and their wild-type (WT) littermates ($n=10$) via oral administration of 3% dextran sodium sulphate (DSS) for 7 days followed by 2 days of regular drinking water. Control mice (10 WT and 10 MMP-9 KO) received normal drinking water throughout the experiment. Both genotypes were raised under identical environmental conditions for more than 15 years and were co-housed during the experiment according to phenotype (control vs DSS). Faecal samples were collected at time of sacrifice and immediately frozen at -80°C . Illumina MiSeq sequencer was used for 16S rDNA paired-end sequencing targeting the V4 hypervariable region. Sequencing depth was downsized to 10000 reads/sample. Taxonomic annotation was performed with Ribosomal Database Project. PICRUSt was used for metagenome prediction and analysed with STAMP software (version 2.1.3). R software was used for statistical analysis with multiple testing correction (Bonferroni).

Results: No significant differences in clinical or histopathological parameters were found between both genotypes (WT and MMP-9 KO) after induction of acute colitis. Observed microbial richness (genus level, t-test) and microbiota composition (Bray-Curtis dissimilarities, adonis) were not significantly influenced by genotype. In contrast, weight loss, disease activity index, cage and phenotype (control vs DSS) did significantly influence the intestinal microbiota composition (envfit, $r^2>0.7$, $p=0.001$). The genera *Bacteroides* and *Alistipes* explained most of the variability in microbiota composition between genotype in the control group, whereas this was the case for the genera *Bacteroides* and *Allobaculum* in the DSS group (Constrained Principal Coordinate Analyses, capscale). After multivariate analysis (MaAsLin, $p<0.05$), however, cage was identified as the sole driver of microbiota composition variability. Functional profiling indicated

Abstract P077 – Table 1. Trial characteristics of 54781532UCO2001 and PROgECT

	54781532UCO2001	PROgECT
Study	Placebo-controlled	Open-label
Study agent	Peficitinib, a Janus kinase inhibitor	Golimumab, an anti-TNF α therapy
Dosing regimen	Wks 0–8: placebo, JNJ-54781532 25 mg once daily (QD), 75 mg QD, 150 mg QD, or 75 mg twice daily by 1:1:1:1 randomization ratio	Wk 0: 200 mg SC Wk 2: 100 mg SC Wks 6–50: 100 mg per 4 wks or country approved maintenance dose
Endoscopy with biopsies	Wks 0, 4 (optional) & 8	Wks 0, 6 & 30

that both genotype and phenotype influenced the metagenome (PI-CRUST). However, after multiple testing correction, only phenotype remained significantly associated with changes in metagenomic profile.

Conclusions: Changes in gut microbiota composition were mainly driven by DSS and were not significantly altered by MMP-9 gene knockout.

References:

- [1] Rodrigues DM, (2012), Matrix metalloproteinase 9 contributes to gut microbe homeostasis in a model of infectious colitis, *BMC Microbiol*, 105, 12

P079

Association of gut microbiota with mucosal inflammation in ulcerative colitis

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Background: Disturbance in gut microbiota (dysbiosis) is a characteristic feature of ulcerative colitis (UC). However it remains unclear whether this dysbiosis contributes to disease pathogenesis by driving immune dysregulation or is merely secondary to mucosal inflammation and/or a result of host immune response. We aimed to determine whether microbiota dysbiosis varied between areas of inflamed and non-inflamed colon in patients with UC and whether this was associated with a humoral immune response.

Methods: We collected colonic biopsies from histologically confirmed areas of inflamed and non-inflamed colon from 15 patients with active left sided ulcerative colitis or proctosigmoiditis. DNA was extracted using the FASTSpin Kit and gut microbiota was characterized using 16s rRNA based analysis of the V3–V4 region (Illumina MiSeq). Quality control and operational taxonomic unit classification of sequences was executed using QIIME. As a marker of mucosal humoral immune responses, inflamed and non-inflamed colonic biopsy samples were cultured in media (RPMI + 10% FCS) for 1 to 3 days prior to measurement of immunoglobulin production (IgA, IgG and IgM) by ELISA.

Results: Consistent with previous observations patients with UC demonstrated reduced bacterial diversity with an increase in *Proteobacteria*, *Bacteroides* and *Clostridiales* species along with a decrease in *Firmicutes* to *Bacteroides* ratio. No differences were found in the microbial diversity nor phylae and genera in mucosally adherent gut microbiota between inflamed and non-inflamed colonic segments in patients with active UC. This observation was also seen when patients were subdivided based on disease activity as defined by

Mayo scoring. Total immunoglobulin production did not differ between inflamed (n=6, mean 4966 ± sd 3670 ng/ml) and non-inflamed tissue (n=11; mean 5756 ± sd 8989 ng/ml; p>0.05) suggesting that equal numbers of antibody-producing B cells are present regardless of inflammation.

Conclusions: We have demonstrated that the dysbiosis observed in patients with UC is consistent and is not influenced by mucosal inflammation or disease activity. Mucosal immunoglobulin production was not upregulated at sites of inflammation possibly suggestive of a uniform humoral response across the colon; although future work may uncover differences in antibody specificity to UC-associated dysbiosis. The mechanism for the complex interplay between the host immune system and gut microbiota in contributing to mucosal inflammation remains to be understood.

P080

IL-10 induction properties of the TLR-9 agonist cobitolimod – a candidate for treatment of active ulcerative colitis in late stage of clinical development

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Background: Cobitolimod (DIMS0150, Kappaproct[®]) is an oligonucleotide that acts as a Toll-Like Receptor 9 (TLR-9) agonist and is able to induce clinical remission in patients with active ulcerative colitis (UC) after topical administration. To gain further insights into the mechanism of action of cobitolimod we studied the stimulatory properties of cobitolimod in induction of IL-10 *in vitro*.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from buffy coats of healthy blood donors and were cultured with increasing concentrations of cobitolimod (0.1–100 µM). In control experiments a CpG reverted form of cobitolimod (IDX0526) was tested. The IL-10 levels were analyzed by ELISpot and ELISA assays. Furthermore, PBMCs isolated from whole blood of patients with UC were exposed to cobitolimod.

Results: PBMCs from different healthy donors all showed a dose dependent IL-10 induction as analyzed by ELISpot in response to cobitolimod. In agreement with the results obtained by ELISpot data, cobitolimod resulted in a dose dependent increase of IL-10 levels in the supernatant using the ELISA measure. Cobitolimod gave rise to the highest IL-10 response at 100 µM and was not effective at lower concentrations (0.1 µM to 1 µM). In PBMCs derived from patients with UC cobitolimod induced IL-10 expression levels in a dose dependent manner and to a similar extent as observed in healthy individuals.

Conclusions: The data illustrate that cobitolimod induces IL-10 expression in PBMCs derived from healthy individuals and ulcerative colitis patients and that this induction was dose-dependent. The *in vitro* dose response relationship provides further support for the upcoming clinical phase IIb study named CONDUCT in which different doses of cobitolimod will be administered at different frequencies to patients with moderate to severe, treatment refractory, active UC.

P081

10 years of the UK Inflammatory Bowel Disease (IBD) Audit and the journey is just beginning

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Background: The UK IBD Audit aims to improve the quality of care of people with IBD by auditing aspects of patient care and experience. IBD affects more than 300,000 people in the UK. Before 2006 little was known about the quality of care provided to people with IBD. The UK IBD audit was the first truly national audit performed within the field of gastroenterology

Methods: Since 2006 the audit has collected data, analysed and reported at least biannually on one or more aspects of patient care. Publication of results in 2006 showed marked variation in aspects of care delivery and an intervention strategy was developed to improve care. IBD teams contributed keenly, with the benefit of being able to benchmark against their peers. The work was driven by a multidisciplinary steering group and delivered by the Royal College of Physicians of London. Information for each element of the programme can be found: www.rcplondon.ac.uk/ibd.

Table 1. Activity over 10 years

	2006–08*	2008–10	2010–12	2012–14	2014–16
Inpatient care	Y	Y	Y	Y	
Organisation of services	Y	Y	Y	Y	
Inpatient experience			Y	Y	
Primary care survey			Y		
Biological therapies			Y	Y	Y
Transition to IBD Registry					Y

*Adult IBD services only.

Results: Participation increased from 75% in 2006 to 96% in 2015. Advances in technology have allowed for more frequent reporting of progress with real-time graphical displays built into web-based data collection tools.

Table 2. Improvements in key measures

	2008–10	2012–14
At least some IBD nurse provision	62% (127/206)	86% (148/173)
Gastroenterology ward on site	75% (155/207)	95% (146/173)
Mortality during admission	1.54% (46/2981)	0.75% (30/3987)
Patient seen by an IBD nurse during unplanned admissions	27% (614/2269)	48% (1526/3156)
Prophylactic Heparin prescribed	73% (1773/2436)	90% (3282/3644)

National and team level reports were produced with an adaptable slide set and action plan to facilitate local action. Regional workshops supported networking, sharing of best practice and also empowered teams to undertake focussed quality improvement projects. Reporting variation enabled the IBD community to focus on how to eradicate it. Following the 2006 audit a collaborative group was formed and the “IBD Standards” were developed, future audit focused on assessing delivery of care against these standards. Results have shown steady improvement in key areas.

Conclusions: Each round of audit used learning from the previous and the process was one of constant refinement and improvement. As a result of 10 years of the UK IBD audit, there is now a greater understanding of the quality of IBD services and the care provided. There is also a higher expectation of excellence and a desire to continue to improve.

P082

An investigation of azathioprine on autophagy pathway activity

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Background: Autophagy is an intracellular process that degrades damaged or aged proteins and organelles to maintain cellular homeostasis. Defective autophagy has been strongly linked to inflammatory bowel disease (IBD) pathogenesis, with evidence that enhancing autophagy may be therapeutically beneficial by regulating inflammation and clearing intestinal pathogens. Due to the high cost associated with the development of new drugs, a more comprehensive characterisation of commonly used IBD drugs and their mechanism of action are required. Our aim is to investigate the effect of azathioprine on autophagy pathway activity and to determine the molecular mechanisms involved.

Methods: The autophagy response to azathioprine was assessed *in vitro* using several complimentary methods. Live-cell confocal microscopy, flow cytometry and Western immunoblotting were used to assess autophagy in cells engineered to stably express the autophagy marker LC3 fused to GFP (GFP-LC3), or endogenous LC3 was assessed using specific antibodies. In addition cells were transiently transfected with dual GFP-RFP tagged LC3 to measure flux through the autophagy pathway. To determine whether mTORC1, a master regulator of autophagy activity, was affected by azathioprine the phosphorylation of S6 ribosomal protein (rpS6; a surrogate marker of mTORC1 activity), was monitored by Western immunoblotting and in-cell Western.

Results: A significant increase in autophagy was observed in response to 120 μ M of azathioprine, with optimal autophagy activity at 6 hours post-treatment. Confocal microscopy showed an increase in the percentage of cells exhibiting GFP-LC3 foci, and flow cytometry showed an increase in the fluorescent intensity of GFP-LC3 in cells treated with azathioprine compared to control cells. Western immunoblotting also showed that azathioprine treatment leads to an accumulation of LC3-II, the lipidated and active form of LC3. By monitoring cells transiently expressing the GFP-RFP-LC3 fusion protein we show that azathioprine stimulates autophagy pathway activity, and rules out the possibility that accumulation of LC3 positive autophagosomes is due to reduced fusion with lysosomes. Analysis of mTORC1 activity revealed that azathioprine treatment causes a decrease in phospho-rpS6, suggesting that azathioprine may stimulate autophagy via modulation of mTORC1 signalling.

Conclusions: We have used several complimentary methods to demonstrate that the immunomodulatory drug azathioprine strongly induces autophagy *in vitro*. Our results suggest that azathioprine may modulate autophagy via the mTORC1 signalling pathway. Work is now underway to further characterise the mechanism of action of azathioprine in the context of autophagy.

P083

The protective role of vitamin D3 on colitis-associated colorectal cancer in a mouse model

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Background: Epidemiological and cytological studies have found a potential protective function of Vitamin D3 in colitis-associated colorectal cancer (CAC). In this study, we aim to decipher this effect in an azoxymethane (AOM) and dextran sulfate sodium (DSS) induced CAC mouse model and explore the underlying mechanism primarily focusing on the β -catenin signaling pathway.

Methods: In vitro, colon cancer cell line SW480 were treated with 1,25(OH)2D3 at different concentrations (1, 10, 50 and 100nmol/L)

for 24, 48 and 72h and then quantified for proliferation. Transcriptional activity and the protein level of β -catenin were determined in SW480 cells both nontreated (control) and treated with 100nmol/L 1,25(OH)₂D₃ for 48h. Same assay was applied to SW480 cells with FOXM1 and nVDR siRNA knockdowns separately. In animal experiment, C57BL/6 mice were divided into 6 groups. Group 1 was the naïve control given only saline. Group 2 to 6 were given AOM (12.5mg/kg) by intraperitoneal injection and 2.5% DSS by gastric lavage sequentially to establish CAC model. Group 2 was the model control; Group 3 to 5 received Vitamin D₃ at 15, 30, 60IU/g/w before AOM/DSS treatment, while Group 6 (post-dose group) received 60IU/g/w VitD₃ 5 days after DSS intake. Mice were sacrificed after 14 weeks. Macroscopic and pathologic evaluations were carried out to assess the severity of CAC. The mRNA and protein levels of β -catenin were also detected.

Results: The proliferation of SW480 cells was significantly inhibited by 1,25(OH)₂D₃ both dose-dependently and time-dependently ($p < 0.05$). 1,25(OH)₂D₃ significantly decreased the transcriptional activity of β -catenin in SW480 cells by promoting the nuclear export of β -catenin ($p < 0.05$) without affecting the mRNA and protein levels of β -catenin, which could be recovered by knocking down either FOXM1 or nVDR. In mice, Vitamin D intervention groups (G4,5,6) showed a lower tumor number and smaller tumor load than model control (G2) ($p < 0.05$). However, there was no significant difference between the high dose group (G5) and post-dose group (G6). In addition, Vitamin D intervention groups presented lower β -catenin mRNA level than model control ($p < 0.05$). The amount of nuclear β -catenin decreased as the VitD₃ dose increased. Finally, the protein expression level of β -catenin was much less in the high dose group (G5) than model control ($p < 0.05$).

Conclusions: 1,25(OH)₂D₃ downregulates the transcriptional activity of β -catenin by expelling β -catenin out of nucleus and therefore severely dampens the proliferation of SW480 human colon cancer cells. In mice model, VitD₃ treatment successfully inhibits the progression from AOM/DSS-induced colitis to colorectal cancer potentially by downregulating the activity of β -catenin signaling pathway.

P084

Investigation of non-coding RNAs as molecular markers during glucocorticoid treatment in children with inflammatory bowel disease

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Background: Despite the introduction of novel biological therapies, glucocorticoids (GCs) remain widely used for inducing remission in inflammatory bowel diseases (IBD), in particular for ulcerative colitis. Given the high incidence of suboptimal response, associated with a significant number of side effects, that are particularly severe in paediatric patients, the identification of subjects that are most likely to respond poorly to GCs is extremely important.

In this context, recent results obtained in our laboratory suggest a role for the long noncoding RNA growth arrest-specific 5 (GAS5) in modulating GC response, suggesting that it could be considered a marker of GC resistance. To address this issue, we evaluated the

association between the lncRNA GAS5 and the efficacy of steroids in IBD paediatric patients and by *in vitro* models.

Methods: For the clinical studies, seventeen IBD paediatric patients treated with prednisone 1 to 2 mg/kg/day for 30 days, according to standard clinical protocol, were enrolled at the Paediatric Clinic of IRCCS Burlo Garofolo in Trieste. Peripheral blood was obtained from these patients at diagnosis (T0) and after 4 weeks of steroid treatment (T4). RNA was extracted from patients' peripheral blood mononuclear cells at T0 and T4, and used to analyze the levels of the lncRNA. Patients were classified on the basis of their clinical response into 3 groups: steroid resistant (SR), steroid sensitive (SS) and steroid dependent (SD). For the *in vitro* studies, the effect of methylprednisolone on the proliferation of HeLa and LoVo cells was determined by labelling metabolically active cells with [methyl-3H] thymidine, and the expression of GAS5 was determined by TaqMan[®] Assay. The localization of GAS5 during GC treatment was evaluated by subcellular fractionation and the functions of the lncRNA were assessed by silencing this lncRNA *in vitro*.

Results: Among the 17 patients enrolled, 3 were SR, 8 SD and 6 SS; patients with unfavorable steroid response (SD + SR) presented higher GAS5 levels in comparison with SS group, supporting a contribution of GAS5 to steroid ineffectiveness. GAS5 was upregulated in GC resistant cells and accumulated more in the cytoplasm compared to the nucleus in response to the drug; in addition, GAS5 knock-down reduced the proliferation during GC treatment.

Conclusions: We hypothesize that higher levels of GAS5 can result in the suppression of GC activity, and if these results are confirmed in a larger number of subjects, GAS5 should be considered a novel biomarker useful for the personalization of GC therapy in paediatric IBD patients and for elucidating the molecular pathways that underline GC resistance.

P085

The effect of vitamin D on macrophage function and polarization in Crohn's disease

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Background: Defective bacterial clearance by macrophages is believed to play an important role in Crohn's disease (CD). Phenotypes of macrophages include inflammatory M1 and anti-inflammatory M2. Vitamin D has been shown to reduce colitis severity but the mechanisms remain unclear. The effect of Vitamin D on M1 and M2 macrophages in IBD has not been investigated. The aim was to identify possible differences in M1 and M2 macrophages between CD patients and controls and to determine the effect of 1,25 vit D on macrophage function and phenotype markers.

Methods: PBMC were isolated from peripheral blood of 45 CD patients and 33 controls not taking vitamin D supplements. REB approval and patient consent was obtained. Monocytes were isolated using CD14 microbeads. M1 and M2 type macrophages were generated by culturing of monocytes in the presence of GM-CSF and M-CSF, respectively. Cytokines were determined by ELISA following stimulation with 100 ng/ml LPS. Phagocytosis was determined by measuring the uptake of FITC-latex beads using flow cytometry. Chemotaxis assays were performed in transwell plates. Expression of M1 and M2 markers was determined by qPCR.

Results: No difference in chemotaxis or phagocytosis was observed in CD macrophages compared to controls. M2 displayed greater phagocytic activity than M1 (94.6% vs 80.3%). Phagocytosis was

not altered after treatment with 1,25D. M1 migrated in slightly higher numbers toward CCL2 and fMLP compared to M2. Vit D slightly increased migration of both types toward fMLP (+18–26%). LPS-induced production of TNF α , IL-12p40 and IL-10 was comparable between macrophages in CD and controls. M1 produced higher amounts of IL-12p40 and TNF α compared to M2 ($p < 0.0005$ and $p < 0.05$, respectively) whereas IL-10 production was greater in M2 (1566 vs 152 pg/ml, $p < 0.005$). Preincubation with 1,25D greatly decreased IL-12p40 production by M1 (-64.9%, $p < 0.0005$) as well as that by M2 (-100%, $p < 0.05$). 1,25D also decreased TNF α production by M1 (-49.6%, $p < 0.05$) and IL-10 by M2 (-28.2%, $p < 0.05$). M2 macrophages preferentially express F13A1, PTGS2, CD163, CXCL10, CD14 and MMP2, whereas TGF β , CCL1 and CYP27B1 expression was higher in M1. Marker expression was similar between CD and control macrophages. M1 and M2 markers were not differentially modulated by vit D.

Conclusions: Peripheral blood derived macrophage chemotaxis and phagocytosis in CD is similar to those from controls. The main effect of 1,25D was to markedly decrease pro-inflammatory cytokine production from M1 macrophages. However, 1,25D did not modulate macrophage polarization to the anti-inflammatory M2 phenotype. This study was supported by a grant from the Dairy Farmers of Canada.

P086 MMP-12, a novel mediator of nociception in Crohn's disease

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Background: The activation of pain sensing nerves (nociceptors), which innervate the gut, by mediators released from the inflamed bowel is thought to be a principal cause of pain in Crohn's disease. Our current understanding of this process is limited, and further investigation is needed to provide insight into the mechanisms of nociception in Crohn's disease, which can then be targeted to relieve abdominal pain. To address this, we have developed an experimental approach to study visceral nociception in colitis by comparing transcript expression in patient biopsy samples, with the ability of supernatants generated from the biopsy to stimulate nociceptors. Using this system, we have identified matrix metalloproteinase-12 (MMP-12) as a putative mediator of nociception in Crohn's disease (Tranter et al (2016). World Congress on Pain, IASP). Here, we confirm a role for MMP-12 in nociception by describing its direct effects on nociceptor signalling.

Methods: Nociceptor activity (serosal and mesenteric) was recorded from teased splanchnic nerve fibres using an *in vitro* mouse colon flat-sheet preparation as described previously (Hockley et al (2014) Pain; 155 (10), 1962–1975). Changes in firing were determined following direct application of MMP-12 (or vehicle) alone; application of MMP-12 in combination with an experimental soup of inflammatory mediators (bradykinin, histamine, 5-HT, PGE₂, ATP); or in response to mechanical stimulation following MMP-12 ad-

ministration. Responses were expressed as mean \pm sem values, and statistically compared using a Student's t-test, significance set at $p < 0.05$.

Results: Application of MMP-12 (20nM); stimulated visceral nociceptor activity in 3/9 preparations tested, producing a significant increase in nerve discharge compared to vehicle (e.g. 11.4 \pm 1.8 spikes/min vs 1.8 \pm 1.2 spikes/min, MMP-12 vs vehicle $n=3$, $p < 0.01$), and enhanced nociceptor firing in response to inflammatory mediators (e.g. 52% increase in activity vs vehicle $n=5$, $p < 0.05$). Additionally pre-treatment with MMP-12 promoted mechanical hypersensitivity to von Frey hair probing of receptive field by 24% $n=8$, $p < 0.01$.

Conclusions: The data demonstrates a novel role for MMP-12 in nociceptor activation and sensitisation, which in combination with our previous study suggests that MMP-12 may be an important mediator of abdominal pain in Crohn's disease.

P087 Increased wnt ligands expression in M2c macrophages is associated with fibrosis in Stat6 knockout mice

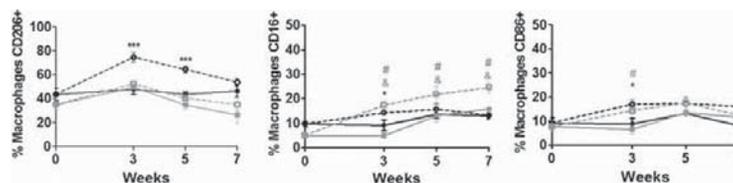
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Background: STAT6 plays a crucial role in M2a macrophage polarization *in vitro* and these cells mediate mucosal healing in an acute model of TNBS-colitis through the expression of Wnt ligands [1]. We have recently reported that STAT6 deficiency favours fibrosis in a murine model of TNBS colitis [2] and we aim to characterize here the functional relevance of the macrophage phenotype in fibrosis development.

Methods: WT or STAT6(-/-) mice were given TNBs (0.5, 0.5, 0.75, 0.75, 1, and 1 mg, intrarectally) or saline weekly and they were sacrificed 3, 5 or 7 weeks after the first TNBs administration. The percentage of CD206, CD16, and CD86 positive cells was analyzed by flow cytometry in F4/80+ macrophages isolated from the intestinal mucosa. The mRNA expression of Wnt ligands was evaluated in F4/80+ CD16+ macrophages isolated from the mucosa, 7 weeks after the first TNBs administration and results are expressed as fold induction vs vehicle-treated mice. Data are expressed as mean \pm SEM with $n \geq 8$ in all groups (* $p < 0.05$).

Results: TNBs increased the percentage of CD206 positive macrophages in the mucosa of TNBS-WT animals while it failed to do that in TNBS-STAT6(-/-) mice. The percentage of CD16 positive macrophages increased in a time-dependent manner only in the mucosa of STAT6(-/-)-TNBS-treated mice. The number of CD86+ cells was similar in TNBS-WT and TNBS-STAT6(-/-) mice. In CD16+ macrophages isolated from TNBS-STAT6(-/-) mice the mRNA expression of canonical and non-canonical Wnt ligands was



Abstract P087 – Figure 1. Macrophages population.

significantly increased compared with cells isolated from TNBS-WT mice.

Table 1. Wnt ligands

	Wnt ligand	2B	5A	6	7B	10A	10B
7-week	WT	1.6±0.2	2.1±0.5	1.2±0.1	2.7±0.6	3.3±0.8	1.9±0.2
7-week	STAT6(-/-)	1.9±0.4	6.4±0.6*	2.7±0.4*	15.3±2.2*	2.9±1.0	15.3±2.5*

Conclusions: An increased percentage of M2c macrophages which exhibited an increased expression of Wnt ligands is detected in the mucosa of TNBS-STAT6 knockout mice and it could mediate the increased fibrosis detected in these animals.

References:

- [1] Cosín-Roger J, Ortiz-Masiá D, Calatayud S, Hernández C, Esplugues JV, Barrachina MD., (2016), The activation of Wnt signaling by a STAT6-dependent macrophage phenotype promotes mucosal repair in murine IBD., *Mucosal Immunol.* 2016 Jul;9(4):986–98. doi: 10.1038/mi.2015.123.
- [2] P. Salvador, (2016), STAT6 deficiency alters macrophage polarization and promotes fibrosis in a murine model of chronic inflammation. ECCO2016

P088

Evaluation of Free Vitamin D levels in IBD pediatric patients: the role of inflammation

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Background: Vitamin D is an important regulator factor of the immune system and induces the development of self-tolerance. An association between vitamin D deficiency and inflammatory bowel diseases (IBD) has been described. Studies examining vitamin D levels in IBD usually do not consider the effect of inflammation on vitamin D and do not calculate the unbound, free vitamin D, which is the active form. The aim of our study was to investigate the levels of total 25-hydroxyvitamin-D (T-25OH-D) and free 25-hydroxyvitamin-D (F-25OH-D) in a cohort of IBD pediatric patients and to correlate these values with the disease activity and the markers of inflammation.

Methods: Between January 2015 and May 2016 we enrolled all consecutive children with a new diagnosis of IBD (group A), a group of IBD patients at follow-up in clinical remission (group B) and a group of age- and sex- matched healthy controls (group C). In each subject T-25OH-D and F-25OH-D levels were measured with an enzyme-linked immunosorbent assay (ELISA). Comparison between groups were made using non-parametric Mann-Whitney test. The disease activity was measured with Pediatric Crohn Disease Activity Index and Pediatric Ulcerative Colitis Activity Index for CD and UC, respectively. Moreover, as markers of inflammation, C reactive protein and fecal calprotectin were measured and they were correlated to T-25OH-D and F-25OH-D levels by a linear regression test.

Results: Sixty-four consecutive children were enrolled (group=n): group A=37, group B=27 and group C=18. Levels of T-25OH-D were higher in group A than in group B (19.9±1.7 ng/ml vs 14.2±1.3ng/ml; p=0.01) but were lower in both groups A and B when compared to group C (19.9±1.7 ng/ml vs 28.2±2.8 ng/ml; p=0.008 and 14.2±1.3ng/ml vs 28.2±2.8 ng/ml; p<0.001, respectively). Lev-

els of F-25OH-D were higher in group A compared to both group C (5.3±0.3 pg/ml vs 3.2±0.3 pg/ml; p=0.001) and B (5.3±0.3 pg/ml vs 3.6±0.3 pg/ml; p=0.001). A significant direct correlation was found between F-25OH-D and activity index of disease (r2: 0.18; p≤0.001). A direct correlation, not reaching statistical significance, was also found between F-25OH-D and both C-reactive protein and fecal calprotectin.

Conclusions: IBD children, both at diagnosis and at follow up, have lower levels of T-25OH-D compared to healthy controls. However, among IBD patients, those at diagnosis showed higher levels of T-25OH-D and F-25OH-D than those with longer disease duration. Higher levels of both forms of Vitamin D are present in acute inflammation, suggesting that chronic inflammation is associated with a more severe deficiency of Vitamin D.

P089

Extracellular matrix fragments as markers of cytokine driven intestinal damage or protection; test in a novel intestinal *ex vivo* model

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Background: Mucosal healing is the ultimate end point of treatment in inflammatory bowel disease (IBD). Tumour necrosis factor alpha (TNF α), interleukin-1-alpha (IL-1 α), and IL-6 are key pro-inflammatory drivers of tissue damage and maintenance. TNF α and IL-1 α have demonstrated to affect epithelial restitution, whereas IL-6 has shown to have a protective role on the intestinal epithelial. Extracellular matrix (ECM) deposition and remodelling are high in IBD, so the ECM balance in cytokine driven diseases, e.g. IBD, is important to study disease mechanism but also as a potential drug-screening tool. To gain further insight, we studied the impact of cytokine stimulation on dynamics of ECM protein turnover, mainly collagen, in intestinal tissue.

Methods: A porcine intestinal *ex vivo* model was developed and applied. Porcine intestinal tissue had the tunica muscularis and tela submucosa layer removed (MSLR) or left intact and cut into pieces with biopsy punches. The tissue was incubated in William E culture media for 72 hours. The explants were stimulated with TNF- α (50ng/ml), IL-6 (50ng/ml) and IL-1 α (20ng/ml) or without (w/o) stimuli, at baseline, 22, 28, and 45 hours. Supernatant was retrieved at baseline, 22, 28, 45, and 72 hours. Matrix metalloproteinase (MMP) degraded type III collagen (C3M) and N-terminal pro-peptide of type I collagen (PINP) were measured by ELISAs in supernatant to assess the tissue modulation by the cytokines. One way-analysis of variance, Kruskal-Wallis tests were carried out.

Results: C3M was elevated and quantifiable earlier in MSLR explants compared to intact explants, for all treatments and time points. Also, MSLR explants demonstrated elevated C3M levels at 22 hours (IL-1 α , p=0.035) and at 28 hours (IL-1 α , p=0.006; IL-6, p=0.047), compared to w/o explants. C3M was significantly lower in IL-6 stimulated MSLR than w/o explants at 45 (p=0.01) and 72 hours (p=0.001). At 22 hours the amount of PINP was significantly lower in TNF- α and IL-1- α stimulated MSLR explants compared to w/o explants. At 45 and 72 hours the amount of PINP was significantly higher in IL-1 α stimulated MSLR explants compared to w/o explants (Figure 1).

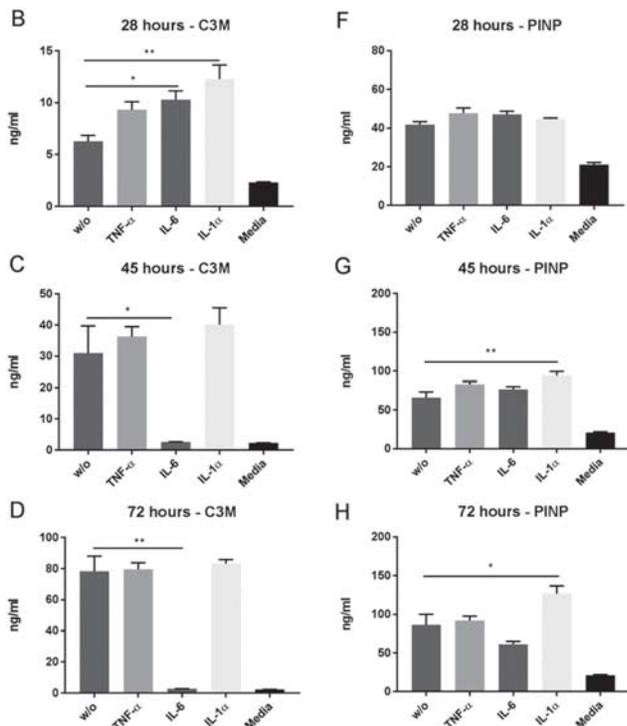


Figure 1. Amount of C3M (A–D) and PINP (F–H) in supernatant from porcine intestinal MSLR explants at 22 hours, 28 hours, 45 hours and 72 hours. w/o explants: n=5; TNF- α , IL-6 and IL-1 α explants: n=11. *p<0.05; **p<0.01. Amounts are presented as mean (ng/ml) \pm standard error of the mean (SEM).

Stimuli did not affect viability.

Conclusions: The model proved to be applicable and informative. Cytokines induced significant time dependent dynamics of intestinal collagen turnover in the intestinal *ex vivo* model, supporting damaging effects of TNF- α and IL-1 α and potential protective effects of IL-6. Also, IL-1 α both decreased and induced collagen formation at different time points in the explants.

P090

Metformin induces late Apoptosis and modulates dysbiosis in western-style diet induced colitic cancer

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Background: Western-style diet (WD) and dysbiosis play an important role in colon inflammation and colorectal cancer (CRC). Metformin (Met) shows anti-inflammatory effects to activate AMP-activated protein kinase (AMPK), resulting in reduced cancer cell proliferation. We investigated the chemopreventive mechanisms of Met in WD induced colitic cancer.

Methods: Male BALB/c mice were randomly divided into three groups: a control diet (CD) group, WD group, and WD+ Met (250 mg/kg/day) group. All mice exposed to azoxymethane (10 mg/kg) followed by 2% dextran sodium sulfate (DSS) for 7 days. Mice were observed daily for water and dietary intake, and they were killed at 13 weeks of age. And we isolated stool extracellular vesicles (EV) of each group during DSS ingestion and analyzed metagenomic sequencing of microbiota in phylum level. Using HCT-116 human colon cancer cell line, expression of AMPK, extracellular signal-

regulated kinase (ERK), cyclin D1, and Bcl-2 was investigated. Cell cycle arrest was assessed by flowcytometry.

Results: WD enhanced the severity of colitis and tumor growth compared with CD. The Met treatment group showed lower severity of colitis and reduced tumor growth. Metagenomic analysis of stool EV in WD showed a higher proportion of gram-negative bacterial EV and Met treatment reduced the proportion. *In vitro* assays showed that the Met treatment promoted late apoptosis by inhibiting cyclin D1 and Bcl-2 and activating AMPK and ERK.

Conclusions: A Met treatment attenuates colon inflammation and tumor growth in WD-induced colitic cancer by promoting late apoptosis and modulating dysbiosis. This strategy could be useful for the chemoprevention of WD induced colitic cancer.

P091

Usefulness of transcriptional whole blood biomarkers as a non-invasive surrogate marker of mucosal healing and endoscopic response in ulcerative colitis

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Background: The importance of objective monitoring of inflammatory activity in IBD is becoming increasingly clear since the amelioration of symptoms alone is not a reliable predictor of mucosal healing. In the context of clinical trials that rely on clinical scores to assess disease activity for patient selection or outcome measurements, this may lead to high placebo response rates, as well as unreliable or un-reproducible results. While endoscopy remains the gold standard, it carries a cost and risk to patients, negatively affecting patient recruitment. The objective of this study was to identify new accurate non-invasive biomarkers based on whole blood transcriptomics that would predict the presence of mucosal lesions in UC patients independently of clinical symptoms.

Methods: A total of 152 UC patients were recruited at the time of endoscopic examination. Endoscopic activity was recorded (Mayo subscore=0–3) and whole blood RNA obtained for transcriptional analysis. Transcriptional changes in the blood of UC individuals (n=25) and non-IBD controls (n=20) was analyzed using microarrays. Genes that correlated with endoscopic disease activity were validated using qPCR in an independent cohort of UC patients recruited at 3 different centers (n=111). Using this cohort, a prediction model for mucosal lesions was evaluated. Responsiveness to treatment of the identified biomarkers was evaluated in a third cohort of UC patients (n=16) that started anti-TNF and were followed-up for 14 weeks.

Results: Microarray analysis identified 120 genes that were significantly altered in the blood of endoscopically active (endoscopic Mayo score \geq 1) UC patients. A significant correlation with the degree of endoscopic activity and inflammatory burden (endoscopic Mayo sum of segments) was observed in 20 and 18 genes, respectively, using qPCR in an independent cohort. Within the identified genes, the ones that showed better correlation and ability to discrimi-

nate between the different degrees of inflammation were HP, CD177, GPR84 and S100A12. Using HP as a predictor of endoscopic disease activity, an accuracy of 67.3% was observed, proving superior to current biomarkers, including CRP, ESR and platelet count (accuracies 52.4, 45.2 and 30.3%, respectively). Finally, at 14 weeks of treatment, anti-TNF induced alterations in the blood transcripts of HP, CD177, GPR84 and S100A12 that correlated with changes in endoscopic activity.

Conclusions: Transcriptional changes of selected genes in whole peripheral blood of UC patients correlate with endoscopic disease activity. Importantly, transcriptional changes in response to treatment in UC patients are sensitive to endoscopic improvement and appear to be an effective and non-invasive way to monitor patients over time.

P092

Exogenous administration of IL-4-treated macrophages prevents intestinal fibrosis in Stat6 knockout mice

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Background: Intestinal fibrosis is a common complication of IBD. Fibrosis is a consequence of local chronic inflammation and is characterized by an excessive extracellular matrix deposition and loss of normal function. Resident macrophages play a key role in maintaining intestinal homeostasis as well as in injury repair, and their phenotype evolves during the phases of inflammation, remission and wound healing. Stat6 is the chief transcription factor involved in macrophage polarization towards the anti-inflammatory phenotype induced by IL-4 treatment, and we have previously reported that Stat6(-/-) mice develop increased mucosal damage and fibrosis in a model of TNBS-colitis. Our present aim is to analyse the rele-

vance of macrophages on the increased susceptibility of Stat6-KO mice.

Methods: Stat6(-/-) mice received increasing doses of TNBS (0.5, 0.5, 0.75, 0.75, 1 and 1 mg, intrarectally) once a week. Two days after each TNBS administration, they received a suspension of IL4-treated peritoneal macrophages (Mf, 2x10⁶ cells) obtained from wild type (WT) or Stat6(-/-) donors. Seven days after the last dose, mice were sacrificed, and the expression of several markers of fibrosis (Tgf-β, E-Cadherin, Vimentin, Col1a1, α-Sma, Mmp2, Fsp-1 and Timp-1) were analysed by qPCR in colonic tissue.

Results: The fibrotic state in TNBS-treated Stat6(-/-) mice was demonstrated by the increased expression of most of the markers analysed (Vimentin, α-Sma, Mmp2, Timp1, Col1a1).

A significant reduction in mortality was observed in mice receiving a weekly injection of IL4-treated Mf obtained from WT mice (p=0.037), but not in mice administered with Mf obtained from Stat6(-/-) donors (p=0.149). Moreover, mice receiving IL4-treated/WT Mf showed a reduced expression of TNBS-induced fibrotic markers when compared to that observed in mice receiving IL-4-treated/Stat6(-/-) Mf (Figure 1).

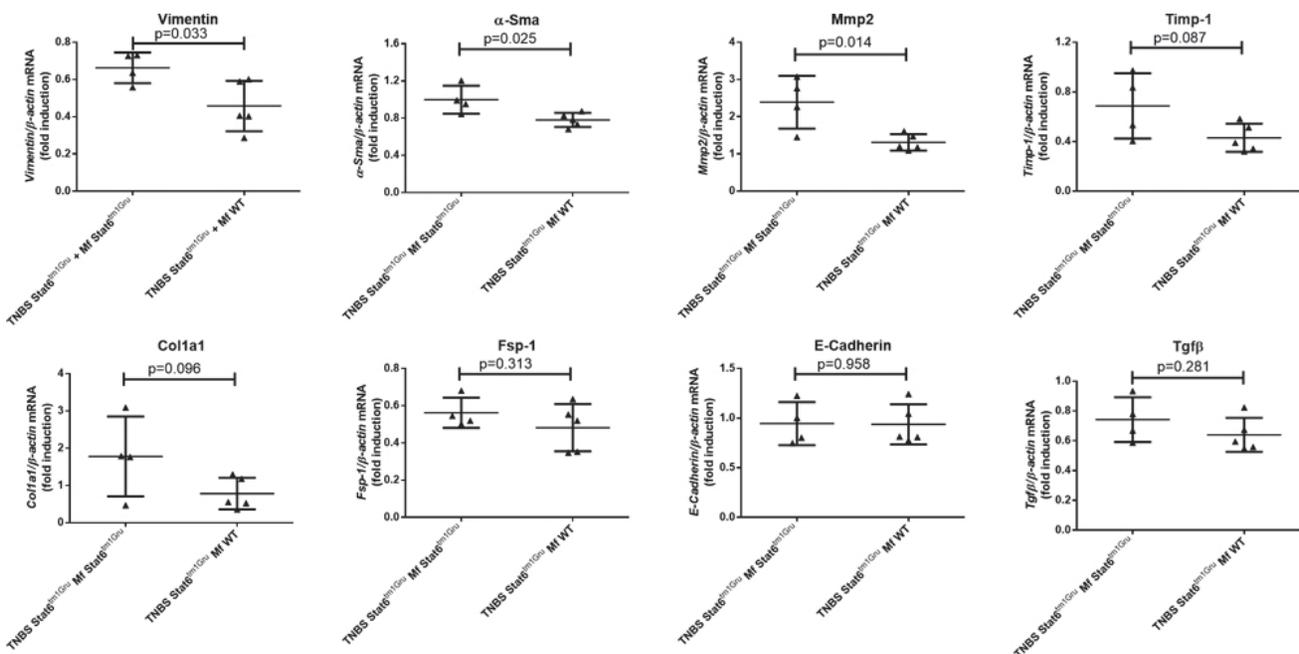
Conclusions: Exogenous administration of macrophages with a Stat6-dependent phenotype exerts a protective effect and reverses the increased susceptibility of Stat6(-/-) mice to TNBS-induced colitis and fibrosis.

P093

Dysregulation of cellular vs humoral immunity to the intestinal microbiota in inflammatory bowel disease

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Abstract P092 – Figure 1. mRNA expression of markers of fibrosis in TNBS-treated Stat6(-/-) mice that had been administered with Stat6(-/-) Mf and WT Mf. Results are expressed as fold induction vs control group.

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Background: The intestinal microbiota is altered in inflammatory bowel disease (IBD), but how interactions between microbes and the host immune system differ in health versus IBD is not understood. Large numbers of lymphocytes reside in gut mucosal tissues and play a key role in barrier function and immune surveillance. We have analysed immune cells and microbes at the mucosal surface and compared acquired memory responses to specific commensal bacteria.

Methods: Colonic biopsies were obtained from healthy donors, or Crohn's disease and ulcerative colitis patients not receiving corticosteroid or biologic therapies. Intraepithelial lymphocytes (IEL) and lamina propria lymphocytes (LPL) were isolated by digestion, phenotyped and counted by flow cytometry. Intraepithelial microbes were labelled with SYBR Green and anti-IgA and analysed by flow cytometry. Commensal bacteria were isolated from the GI tract of healthy donors and identified by 16S rRNA gene sequencing. PBMC were CellTrace Violet™-labelled and cultured with heat-killed bacteria to determine microbe-specific CD4⁺/CD8⁺ T cell and B cell responses after 7 days culture.

Results: Numbers of intraepithelial lymphocytes (IEL), of both resident memory CD8⁺ and $\gamma\delta$ T cell subsets, were dramatically reduced (75–95%, $p < 0.006$) in IBD, and there were 70% fewer resident memory type CD4 T cells in the lamina propria in ulcerative colitis ($p < 0.017$). IgA responses to bacteria on the gut epithelium, and circulating memory B cells responsive to certain intestinal bacteria were increased in IBD, while healthy PBMC demonstrated CD4 memory T cell and occasional CD8 T cell responses but few B cell responses. There were fewer CD8 memory T cell responses to commensals in Crohn's disease, correlating with the low numbers of CD8 T cells in IEL. Circulating B cells from IBD donors showed signs of activation including increased proportions of plasmablasts in Crohn's donors and IgA-switched memory B cells. Our data suggest an imbalance between humoral and cellular immunity towards the microbiota in IBD, with enhanced mucosal antibody secretion concomitant with a loss of mucosal T cell-mediated barrier immunity.

Conclusions: Strong CD4 T cell memory to commensal bacteria develops in health, contradicting the concept of tolerance to intestinal bacteria. Lack of CD8 T cell immunity and deficiency in IEL in IBD may result in compromised barrier function at the mucosal surface, leading to excessive B cell activation and antibody secretion against the microbiota. Therefore, rather than blanket immunosuppression, stimulation of mucosal T cell immunity may improve barrier function and counteract abnormal T cell inflammation and B cell IgA secretion against intestinal microbes in IBD.

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DNA methylation patterns in Crohn's disease mucosal-derived fibroblasts

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Background: More than one-third of Crohn's disease (CD) patients develop a fibrostenotic phenotype that can ultimately result in in-

testinal obstruction. The current available anti-inflammatory therapies are not sufficient to revert or treat intestinal fibrosis. Timely intervention focused on reducing fibrosis is still an unmet need in CD. Continuous activation by microbial-associated molecular signatures and/or cytokines may lead to altered gene expression and modulation of signaling pathways via epigenetic mechanisms. These fibroblasts are then able to independently maintain inflammation and initiate the fibrotic process.

This study aimed to elucidate the DNA methylome of fibroblasts cultured from ileal resections from control patients (HC) and non-inflamed (CDNINF), inflamed (CDINF) or stenotic (CDSTE) ileum from CD patients.

Methods: Fibroblasts were acquired and cultured from patients with CD and colon cancer whereby ileal samples were taken at least 10 cm away from cancerous tissue. Genomic DNA from 8 CD patients and 3 HCs was isolated, bisulfite treated and analyzed using the Illumina Human Methylation EPIC BeadChip array. Similarly, RNA from 11 CD patients and 4 HCs was isolated and mRNA expression profiles were obtained using RNA-seq (Illumina NextSeq 500).

Results: First it was established that there were no major differences in the global DNA methylation between cell culture passages. Then, the DNA methylation of fibroblasts from CD was compared to HC and between the various degrees of CD ileum. Approximately 107 reads were obtained for each sample, alignment and mapping was performed using STAR and differential expression analysis was performed using DESeq2. In summary, we found 8, 65,383 and 109,494 significantly differentially methylated positions (DMPs; Benjamini-Hochberg adjusted p -value < 0.05) when comparing CD versus HC, CDINF versus CDNINF and CDSTE versus CDNINF respectively. The same trend distribution was found in the transcriptome of these cells. Preliminary RNA-Seq data revealed 4, 9 and 101 differentially expressed genes respectively. Our results show that most differences of the methylome and transcriptome are identified when comparing stenotic versus non-inflamed CD tissue. Preliminary enrichment analyses of the DMPs found in the CDSTE versus CDNINF comparison suggested an association to processes such as cellular differentiation and growth, which corroborates the excessive growth phenotype typical of stenosis.

Conclusions: Our study revealed that the DNA methylome and transcriptome of fibroblasts show several differences in CD patients versus control patients and that among the different degrees of CD most differences are observed when comparing stenotic with non-inflamed tissue.

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The genetic risk in ER stress and autophagy translates into quantifiable epithelial ER stress levels in IBD patients

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Background: The crucial role of the intestinal epithelium in IBD is underscored by association of epithelial homeostasis pathways such as bacterial sensing, autophagy and ER stress signaling. Reducing ER stress has therefore gained attention as a novel therapeutic approach. Nevertheless, molecular tools for patient stratification and therapeutic decision making are lacking.

Therefore, we wanted to study whether ER stress profiles could be quantified in patient-derived (*ex vivo*) intestinal epithelial cell (IEC) cultures.

Methods: IBD patients (n=35) undergoing endoscopic evaluation were selected based on the number of IBD-associated ER stress risk alleles in *XBPI* (rs35873774) and *ORMDL3* (rs2872507). In addition, autophagy risk alleles in *ATG16L1* (rs2241880), *IRGM* (rs10065172 and rs4958847), *MTMR3* (rs2412973), *LRRK2* (rs11175593) and *ULK1* (rs12303764) were also investigated since autophagy is a compensatory ER stress resolving mechanism. For this second analysis, patients were grouped into genetic risk quartiles based on the combined ER stress and autophagy risk allele (RA) distribution (Q1: ≤ 4 RA, Q2: 5 RA, Q3: 6 RA, Q4: ≥ 7 RA). As described previously, we were able to culture IECs derived from mucosal biopsies. These cultures were subjected to ER stress using thapsigargin (Tg, 0.4 μ M) and the ER stress response was measured in cell lysates with a binding immunoglobulin protein (BiP)-ELISA. Statistical analyses were performed with Mann-Whitney U tests ($\alpha=0.05$).

Results: Median [IQR] Tg-mediated BiP-induction (vs. untreated) read-outs were 2.67 [1.01–6.07], 1.87 [1.50–3.16], 1.70 [1.32–2.41] and 4.48 [3.76–4.64] in IECs from patients carrying 0 (n=4), 1 (n=17), 2 (n=11) or 3 (n=3) ER stress risk alleles, respectively. Patients with 3 ER-stress-related risk alleles had significantly more epithelial ER stress (BiP) induction rates when compared to patients with 1 or 2 risk alleles ($p=0.026$ and 0.043 , respectively). When risk alleles in autophagy genes were added, median [IQR] Tg-mediated BiP-induction read-outs were 1.34 [1.08–1.91], 2.16 [1.68–4.05], 3.60 [1.39–4.48] and 2.41 [1.61–3.27] in IECs from patients belonging to Q1 to Q4, respectively. Patients in Q2 (n=10), Q3 (n=7) and Q4 (n=10) had significantly higher ER stress induction rates when compared to Q1 (n=8) ($p=0.034$, 0.040 and 0.034 , respectively).

Conclusions: IBD patients with an increased genetic risk for ER stress and autophagy have more ER stress as measured in patient-derived IECs. These patients would benefit most from ER stress reducing therapies such as tauroursodeoxycholic acid (TUDCA), which has already shown to reduce inflammation in murine IBD models. We thus present a novel tool for molecular characterization of IBD patients for which pilot studies should be considered.

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Combined detection variants of NUDT15 could highly predict thiopurine-induced leukopenia in Chinese patients with inflammatory bowel disease: a multi-center analysis

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Background: UDT15c.415C>T was a novel genetic marker discovered in our center for thiopurine-induced leukopenia in Chinese inflammatory bowel disease (IBD). For validation, a large cohort study is needed. Meanwhile, the newly discovered NUDT15 coding variants (c.36_37insGGAGTC, c.52G>A) has not been studied in IBD patients. We aimed to further confirm the influences of NUDT15 three variants (c.415C>T, c.36_37insGGAGTC and c.52G>A) on thiopurine-induced leukopenia in Chinese IBD patients.

Methods: Patients prescribed on thiopurines for at least two weeks were recruited from four tertiary hospitals. Clinical data were collected. NUDT15 genotypes were determined with PCR-RFLP and sequencing. The interactions between variants and leukopenia were analyzed.

Results: A total of 732 patients were included, 177 (24.3%) of which developed leukopenia. There were strong association of NUDT15 c.415C>T, c.36_37insGGAGTC and c.52G>A with thiopurine-induced leukopenia ($p=1.81 \times 10^{-20}$, $p=4.74 \times 10^{-8}$, $p=0.04$ respectively), while there was no relevance for TPMT genotypes ($p=0.25$). The predictive sensitivity of NUDT15 c.415C>T was 49.2%, while it increased to 55.4% when combined analysis with c.36_37insGGAGTC and c.52G>A. Notably, not only the homozygotes with NUDT15 c.415C>T, but also the heterozygotes both carrying c.415C>T and c.52G>A developed early leukopenia. The average dosage for NUDT15 c.415C>T carriers was significant lower than that for wild type ($p<0.001$).

Conclusions: We confirmed NUDT15 c.415C>T, c.36_37insGGAGTC and c.52G>A variants were risk factors for thiopurine-induced leukopenia. Combined detection of the three variants could increase the predictive sensitivity of thiopurine-induced leukopenia and help to distinguish early leukopenia in heterozygotes of c.415C>T. Treatment monitoring by NUDT15 variants may be promising in individualized therapy.

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Th2 cytokines are potent stimulators of pro-fibrotic responses by human intestinal subepithelial myofibroblasts

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Background: In most cases, chronic inflammation precedes and triggers intestinal fibrosis in Crohn's Disease (CD). Excessive collagen deposition by subepithelial myofibroblasts (SEMFs) has a key role in fibrogenesis. Our hypothesis was that pro-inflammatory cytokines affect the expression of interleukin receptors on SEMFs and cytokine milieu reflecting alternative helper T cell (Th) polarization had a differential pro-fibrotic effect on SEMFs.

Methods: SEMFs were isolated from endoscopically-obtained colonic biopsies from healthy controls, set to culture and stimulated with recombinant IL-1 α and/or TNF- α for 6h. Total RNA was extracted and interleukin receptors mRNA expression was assessed with reverse transcription quantitative (RT-q) PCR. Next, cultured

SEMFs were stimulated for 6h with: a) the Th1-related cytokines TNF- α and/or IFN- γ , b) the Th2-related cytokines IL-4 and/or IL-13, c) the Th17-related cytokines IL-17 and/or IL-22 and d) the Treg-related cytokines IL-10 and/or TGF- β 1. Collagen type I and type III expression was also quantitated with RT-qPCR.

Results: Unstimulated SEMFs had a basal expression of most of the studied interleukin receptors. As to Th1-related receptors, IL-1 α and/or TNF- α stimulation downregulated the expression levels of some receptors (e.g. IL1R1: -0.3-fold, \pm 0.04, $p < 0.01$) and up-regulated others (e.g. IFNGR2: 9-fold, \pm 0.5, $p < 0.01$). Moreover, IL-1 α and/or TNF- α stimulation upregulated the Th2-related receptors (e.g. IL-13RA2: 68-fold, \pm 22, $p < 0.01$), the Th17-related receptor IL-22R (13-fold, \pm 3.1, $p < 0.01$) and the Treg-related receptors (e.g. TGFBR1: 2.5-fold, \pm 0.2, $p < 0.01$). Stimulation of SEMFs with either Th1 or Th17 interleukin combinations also downregulated collagen expression (e.g. IL-17+IL-22: -0.56-fold, \pm 0.09, $p < 0.01$), whereas Treg or Th2 interleukin combinations induced collagen expression (e.g. IL-4: 3.5-fold, \pm 0.17, $p < 0.01$), with Th2 cytokines being the most potent.

Conclusions: Data presented suggest that SEMFs may be a dynamic crosslink between the inflammatory and the fibrotic process, as they express most of the Th-related interleukin receptors and their expression is modulated by pro-inflammatory cytokines, abundant in the inflamed mucosa of CD patients. Th2-related cytokines are the most potent stimulators of collagen production by SEMFs and thus the ones with a higher profibrotic potential.

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Oregonin inhibits intestinal epithelial injury by modulating heme oxygenase-1

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Background: Inflammatory bowel disease (IBD) is a chronic, relapsing inflammatory disorders of the intestinal tract and the pathogenesis of IBD remains unclear. Heme oxygenase-1 (HO-1) is the rate-limiting enzyme and response to different inflammatory mediators and have protective effect in many inflammations. Oregonin has been known to exert anti-inflammatory and anti-oxidative effect and used for traditional oriental medicine. In this study, we have investigated whether oregonin have anti-inflammatory properties in intestinal epithelial cells and mouse model of colitis.

Methods: Caco-2 cells were stimulated with tert-butyl hydroperoxide (t-BH). Monolayer permeability was assessed by measuring the transepithelial electrical resistance and inulin flux. Colitis was induced in mice by intrarectal administration of trinitrobenzene sulfonic acid (TNBS). The mRNA levels were analyzed by real-time polymerase chain reaction (PCR). The protein expression of cyclooxygenase-2 (COX-2), intercellular adhesion molecule-1 (ICAM-1), nuclear factor kappa B (NF- κ B), (ZO-1), claudin-1, HO-1, ERK1/2 and JNK were analyzed by Western blot. To silenced HO-1 expression, the cells were transfection with HO-1 siRNA.

Results: Oregonin administration improved the clinical parameters and tissue histological appearance. Oregonin prevented the t-BH-induced increase in permeability by inhibiting the reduction in zonula occludens-1 (ZO-1) and claudin-1 expression. Oregonin inhibit tu-

mor necrosis factor (TNF)- α -induced COX-2 and ICAM-1 expression in the HT-29 cells, as well as NF- κ B translocation. It is also induced HO-1 protein expression, whereas, the reduction of COX-2 expression by oregonin were reversed in HO-1 deficient cells. Additionally, pretreatment with ERK and JNK inhibitors also attenuate anti-inflammatory effect of HO-1 which was induced by oregonin. It indicates that HO-1 induction may be regulated by MAPK pathway. In addition, oregonin-induced HO-1 expression also exhibit protective activities in Caco2 cells. t-BH-induced ZO-1 and claudin-1 loss were reversed by oregonin pretreatment and due to oregonin-mediated HO-1 in ERK/JNK pathway.

Conclusions: In this study, we suggest that oregonin inhibits TNF- α induced inflammation and epithelial barrier disruption mediated by HO-1 induction. Thus, our results elucidated the oregonin-mediated HO-1 expression might contribute to the suppression of intestinal inflammation in intestinal epithelial cells, may be potential therapeutic agent for IBD.

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Altered intrinsic brain function in Crohn's disease

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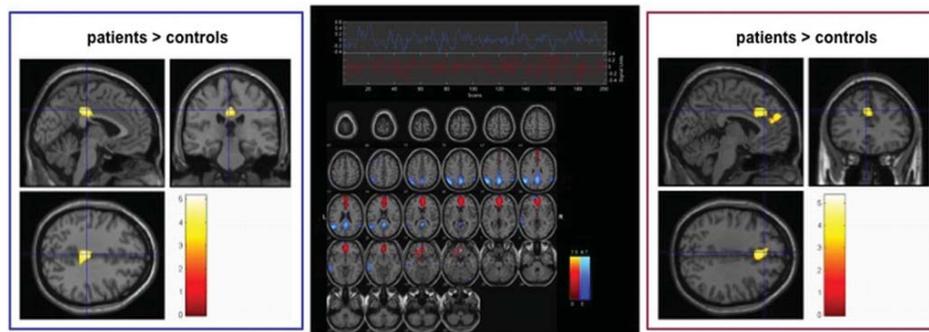
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Background: Psychological factors play an important role in inflammatory bowel diseases (IBD), where comorbidity of mental disorders shows a higher prevalence than in the general population. As suggested by previous neuroimaging studies, such comorbidity could be associated with a specific neural phenotype. Brain regions associated with emotion regulation and self-referential processing, including areas assigned to the so-called "default mode network" (DMN), could be promising candidates in this regard. Here, we investigated the functional integrity of multiple intrinsic neural networks in remitted patients with Crohn's disease (CD). We also sought to establish relationships between neural network connectivity and psychiatric symptoms, such as anxiety and depression.

Methods: Resting-state functional magnetic resonance imaging at 3 Tesla was conducted in 15 CD patients in stable remission and 14 healthy controls (HC). All participants underwent testing for cognition, depression and anxiety. An Independent Component Analysis was computed to identify spatiotemporally distinct intrinsic neural networks. From a total of 27 estimated independent components, 4 networks of interest (anterior and posterior DMN [aDMN, pDMN] as well as left and right lateralized frontoparietal networks) were chosen for further analyses. Between-network functional connectivity was investigated using a constrained maximal lag correlation approach.

Results: The groups did not differ in cognition, depression or anxiety scores. Abnormal connectivity in CD patients was observed in the aDMN and pDMN. Increased connectivity in CD was found in the anterior cingulate and left superior medial frontal gyrus (aDMN) and the middle cingulate cortex (pDMN). Middle cingulate activity significantly correlated with anxiety scores in patients ($r = 0.562$, $p = 0.029$). Between-network coupling did not significantly differ between the groups.

Conclusions: This study provides first evidence of selectively disrupted intrinsic neural network connectivity in remitted CD patients.



Abstract P099 – Figure 1. Increased connectivity in the posterior and anterior default mode network in Crohn's disease.

The data suggest abnormalities of self-referential neural networks, in contrast to systems predominantly related to extrinsic processing. An increased sensitivity to self-related affective and somatic states in CD patients could account for these findings and explain a higher risk for anxiety symptoms.

P100
Intestinal epithelial cells under endoplasmic reticulum stress boosts serine proteolytic activity and modulates barrier function

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Background: Studies on ulcerative colitis (UC) patients show an excessive induction of endoplasmic reticulum stress (ERS) in intestinal epithelial cells (IEC) of the colonic mucosa, leading to intestinal barrier disruption and inflammation. Moreover, the secretion of serine proteases from IEC is enhanced in UC patients. Herein, we hypothesized that intestinal barrier (IB) disruption and mucosal inflammation associated to ERS in UC are mediated by an increased release of serine proteases. Therefore, we aimed to study the link between ERS and proteolytic activity and its impact on IB functions

Methods: Monolayers of differentiated Caco-2 cells grown in a transwell system were stimulated with thapsigargin or tunicamycin to induce ERS. After 6 and 24 hours, supernatants were collected to quantify trypsin-like activity. Paracellular permeability to dextran-FITC, ELISA to IL-8 and gene expression of antimicrobial peptides (AMC) were assessed to evaluate the impact of proteases on IB, by treating cells with the irreversible serine protease inhibitor (AEBSF). Moreover, antagonists of protease-activated receptors (PAR-1, -2 and -4) were used to characterize the mechanism of action.

Results: ERS activation increased trypsin-like activity in supernatants from the apical side of Caco-2 monolayers, at 6 hours, while this effect is lost at 24 hours, probably due to store depletion. After ERS induction, we observed increased paracellular permeability, enhanced IL-8 release and upregulated AMP (DEFB1 (HBD1), DEFB4 (HBD2), MUC2, MUC5 and TTF3). In contrast, AEBSF recovered paracellular permeability, diminished IL-8 release, and at 24h, AMP mRNA levels were stabilized in ERS-induced cells. F2LR1 (PAR-2) and F2LR3 (PAR4s) mRNA levels increased after ERS induction. Furthermore, the increase of paracellular permeability associated to ERS activation was reduced 24h after treatment with PARs antagonists.

Conclusions: IEC under ERS increases TLA, which in turn disturbs IB by promoting paracellular permeability, chemokine induction and

deregulation of AMP expression. Besides, the disturbance of IB and inflammation seems to be mediated by PAR activation. In conclusion, our data suggest a crosstalk between ERS and proteolytic activity, two fundamental features of UC.

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Interleukin-13 induces polarity defects in the intestinal epithelia

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Background: Epithelia reveal an asymmetric distribution of proteins along the apico-basal axis. It is well established that transiently epithelial cells abolish their polar orientation, e.g. in growth or wound healing processes or - pathologically - in malignant transformation and invasiveness.

Polarity changes in inflammatory processes are less well established. Interleukin-13 (IL-13) is involved in the barrier defect found in ulcerative colitis (UC). Herein, we have characterized the polarity defects in intestinal epithelial cells and in intestinal biopsies of UC patients.

Methods: Mucosal explants (human sigmoid colon) were mounted to Ussing chamber to determine epithelial resistance (Re). Consecutively expression of polarity complexes were done (confocal microscopy after immunostaining: ZO-1, occludin, JAM-A, Pard3, Dlg1, F-actin, beta-catenin, E-cadherin). *In vitro* experiments included exposure of various IECs (Caco-2, T84, HT-29/B6) with IL-13. Measurement of transepithelial resistance (TER) was followed by sandwich assay to reveal macromolecular passage and LSM-assisted polarity complex analysis. Finally, effects of IL-13 on cell polarity were determined in 3D Caco2-cysts (Matrigel). In cyst measurement of the paracellular barrier was done with TMR-dextran3000.

Results: As expected we found a reduced Re in colonic mucosal explants of UC patients. Moreover, IL-13 induced a barrier defect in intestinal epithelial culture cells (significant reduction in TER in all intestinal epithelial cells; sandwich assay resolved macromolecular leaks; increased TMR-Dextran3000 permeability in the 3D cyst model).

In correspondence to the defective barrier we found an altered expression and localization of polarity complex proteins in intestinal biopsies, which was in some, but not all proteins associated with the extent of the inflammatory infiltration of the mucosa. As a surrogate of epithelial dyspolarity we also identified an increased number of aberrant cysts (i.e. disturbed lumenogenesis), which was associated with IL-13-caused alterations in the expression of polarity protein complexes in the 3D cyst model.

Conclusions: Presenting evidence for an L-13-induced defect in polarity proteins underscores the relevance of IL-13 for pathophysiology of inflammation in UC. Alterations in polarity might add to other mechanisms in generation of colitis-associated carcinomas.

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Hypoxia reduces inflammation through the downregulation of NLRP3/mTOR signaling and the activation of autophagy

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Background: The impact of hypoxia on inflammatory bowel disease (IBD) is controversial with studies showing detrimental and protective effects. Hypoxia regulates autophagy and nucleotide-binding oligomerization domain receptor, pyrin domain containing (NLRP3), two innate immune mechanisms linked by mutual regulation that have been associated to the development of IBD. We investigated the functional impact of hypoxia on the development of colitis with special emphasis on autophagy and NLRP3 regulation.

Methods: Healthy volunteers and patients with IBD, as well as wild-type, interleukin (IL)-10^{-/-}, NLRP3^{-/-} and IL-10^{-/-} NLRP3^{-/-} double knockout mice were subjected to hypoxia and changes in inflammatory signaling and gene expression were analyzed in colon biopsies using RT-qPCR and Western blotting. The effects of hypoxia on autophagy, NLRP3 regulation and inflammation were further assessed *in vitro* using the intestinal epithelial cell line HT-29.

Results: Hypoxia significantly reduced tumor necrosis factor α , IL-6 and NLRP3 expression and increased autophagy gene expression in colon biopsies of patients with Crohn's disease. In normoxia, IL-10^{-/-}, but not IL-10^{-/-} Nlrp3^{-/-} mice presented an accumulation of autophagy proteins and an increase in NF- κ B activation and inflammatory cytokine expression, which was significantly reduced under hypoxia. *In vitro*, hypoxia-induced autophagy downregulated NF- κ B signaling. Hypoxia also reduced NLRP3 expression, and silencing of NLRP3 activated autophagy following the dephosphorylation of mammalian target of rapamycin (mTOR). Co-immunoprecipitation experiments identified NLRP3 as a novel binding partner of mTOR. **Conclusions:** Our results show that hypoxia counteracts inflammation through a novel mechanism involving the downregulation of the binding partner of mTOR NLRP3 and subsequent activation of autophagy.

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Evaluation of efficacy of new vectors for siRNA CYCLIN D1 and E2F1 delivery in control of cancer progression in inflammatory bowel disease

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Background: Many evidences from literature support a connection between inflammation, cancer development due to the deregulation of the cell cycle with alteration in control of the G1/S checkpoint, where Cyclin D1 (CyD1) plays a crucial role. Cyclin-dependent kinases represent critical components of the cell cycle machinery. Moreover, other studies showed that CyD1 is overexpressed in patients with IBD (inflammatory bowel disease) and some evidence indicate also that another factor, the E2F1 (E2 Promoter Binding Factor-1) modulates the beginning of the inflammatory disease. The aim of this study was the analysis of the CyD1 and E2F1 expression, regulation, and potential control of cell cycle progression and inflammation using an *ex vivo* culture model of colon explants from 4 IBD patients and 3 controls.

Methods: We investigated the ability of commercial siRNAs for CyD1 and E2F1 inhibition encapsulating them in invivofectamine and in some new nanoliposomal vectors, to enter in the colon explants with immunofluorescence assay. Colon explants were treated with or without EC-LPS (Lipopolysaccharide from *Escherichia coli*, 1mg/ml; 4 and/or 24hs) which stimulated the mucosal inflammation and cyclin expression. Then, we evaluated the silencing ability of siRNA toward CyD1 and E2F1 through western blot analysis.

Results: Our data demonstrated that commercial siRNAs for CyD1 and E2F1 nanoliposomal vectors were able to enter in the colon explant, without any tissue morphology and integrity alteration. Moreover, CyD1 and E2F1 expression increased in colon explants treated *in vitro* with EC-LPS. We demonstrated also an efficient reduction of the CyD1 expression after treatment of IBD colon explants with CyD1 siRNA and E2F1 siRNA with a "patient-dependent response". **Conclusions:** Our results suggest that the silencing of CyD1 and E2F1 helped to attenuate the expression of these crucial factors and could potentially target inflammatory signals in the gut preventing the deregulation of cell cycle and consequently colon cancer progression.

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Rebamipide, sucralfate, and rifaximin have the suppressive effects on radiation-induced inflammation in the intestine of mouse

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Background: Radiotherapy for malignant abdominopelvic disease results in radiation-induced enterocolitis. However, there is no well-established preventive strategy. The aim is to evaluate the suppressive effect of rebamipide, sucralfate and rifaximin on ionizing radiation (IR)-induced acute inflammation and apoptosis in the intestine of mouse.

Methods: Thirty ICR mice were divided into (1) a vehicle-treated control group before sham IR, (2) a vehicle-treated group before IR, and (3-5) rebamipide, sucralfate or rifaximin-treated groups before IR. The intestine was resected at 4 hours after 4 Gy IR to the abdominopelvis. Pro-/anti-inflammatory and pro-/anti-apoptotic factors were investigated.

Results: NAMPT was down-regulated after IR, which was attenuated by rebamipide, sucralfate and rifaximin ($p < 0.05$). Activation of

NF- κ B and phosphorylation of MAPKs were induced by IR, which were suppressed by rebamipide, sucralfate, and rifaximin ($p < 0.05$). TNF- α , IL-1 β , and IL-6 were increased by IR, while attenuated by rebamipide, sucralfate, and rifaximin down to similar level of control group ($p < 0.05$). The iNOS, COX-2 and PGE2 were significantly induced by IR, which were attenuated by rebamipide, sucralfate, and rifaximin ($p < 0.05$). ICAM-1 was corresponded to above mentioned results. [Ca²⁺] oscillation was increased by IR, which was attenuated by rebamipide, sucralfate, and rifaximin. Proapoptotic gene (Bax, c-Myc) and antiapoptotic gene (Bcl-2, Bcl-xL) expressions were potently suppressed and induced, respectively, by rebamipide, sucralfate, and rifaximin. The release of cytochrome C was increased by IR, while it was attenuated by rebamipide, sucralfate, and rifaximin ($p < 0.05$). Caspase 3 and caspase 7 were also elevated by IR compared to control group, however, they showed decline by rebamipide, sucralfate, and rifaximin ($p < 0.05$).

Conclusions: This study demonstrated that rebamipide, sucralfate, and rifaximin have the suppressive effects on IR-induced acute inflammation and apoptosis in the intestine of mouse. Rebamipide, sucralfate, and rifaximin may have beneficial effects in preventing acute radiation-induced enterocolitis.

P105

An experimental examination of appetite and disordered eating in Crohn's disease patients

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Background: Crohn's disease (CD) patients suffer from nutritional deficiencies when in active disease and it is hypothesised that a disordered eating behaviour might be contributory to this. This study aimed to examine calorific intake, macronutrient choice and the prevalence of disordered eating behaviour in males and females with CD compared to healthy controls (HC).

Methods: 21 CD subjects (14M:7F, Age: 33.7 \pm 2.3, BMI: 25.1 \pm 0.9) and 21 HC (14M:7F, Age: 33.8 \pm 2.4, BMI: 25.1 \pm 0.6) were recruited to this matched pairs cross-sectional study. Main inclusion criteria were active CD defined by a Harvey-Bradshaw index (HBI) of ≥ 5 or faecal calprotectin > 250 ug/g or C-reactive protein > 5 mg/dl, or active disease seen at ileocolonoscopy or MRI. Calorific intake was assessed using a 24-h dietary recall procedure. Disordered eating was assessed using validated psychometric questionnaires [Binge Eating Scale (BES); Power of Food Scale (PFS); Control of Eating Questionnaire (CoEQ); Dutch Eating Behaviour Questionnaire (DEBQ); Three Factor Eating Questionnaire (TFEQ)]. Independent t-tests were conducted to examine the presence of disordered eating across groups. Trial registration number was NCT02379117.

Results: Patients had active disease with mean HBI of 5.5 \pm 0.5, faecal calprotectin of 595 \pm 157 ug/g and CRP of 10.3 \pm 3.8mg/dl. CD patients were characterised by higher scores on BES [$p < 0.001$], TFEQ-Disinhibition [$p < 0.01$] and Hunger [$p < 0.01$], DEBQ-Emotional [$p < 0.001$] and External eating [$p < 0.05$], PFS [$p < 0.001$] and by lower levels of CoEQ-Craving control [$p < 0.01$] and CoEQ-Mood [$p < 0.001$] compared to HC. There were no differences in dietary restraint measures. A greater proportion of CD patients (37%) scored above the clinical cut-off criteria for binge eating (> 17 BES) compared to HC (0%) [$\chi^2(1)=8.9$, $p < 0.01$] and BES score was nega-

tively associated with CoEQ-Mood [$r(39)=-0.512$, $p < 0.001$]. Scores on the Hospital Anxiety and Depression scale were higher in CD patients compared to HC [$p < 0.01$]. There were no differences in calorific or macronutrient intake between groups.

Conclusions: Disordered eating behaviour traits were more prevalent in CD with active disease compared to HC. The greater prevalence of binge eating in CD may be attributed to the lower levels of mood and higher levels of anxiety observed in this group. The higher scores on measures of hedonic responsiveness (i.e. PFS, TFEQ-Disinhibition, DEBQ-External) in CD may be associated with increased food monitoring behaviour that occurs in patients with dietary-controlled conditions. Stronger psychological support with firm dietetic advice for healthy eating should be advocated in CD.

P106

Binding properties of human TLR-9 receptor to cobitolimod – a candidate for treatment of active ulcerative colitis in late stage of clinical development

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Background: Cobitolimod (DIMS0150, Kappaproct) is an oligonucleotide that acts as a Toll Like Receptor-9 (TLR-9) agonist and is able to induce clinical remission in patients with active ulcerative colitis after topical administration. To gain further insights into the TLR-9 binding properties we studied the kinetics of the interaction between cobitolimod (GMP/non-GMP grade) and the human TLR-9 receptor using the Attana A200 system.

Methods: The Attana A200[®] is a dual channel, continuous-flow system for automated analysis based on the Quartz Crystal Microbalance (QCM) technology. To monitor binding, one of the interacting molecules is immobilized on the sensor surface and the sample containing the other molecule is injected over the sensor surface. The signal output is given in frequency (Hz) and is directly related to changes in mass on the sensor surface. TLR-9 was produced using a wheat-germ cell free expression system in the presence of liposomes. Proteoliposomes with TLR-9 or protein mock control were immobilized by adsorption on polystyrene surfaces and cobitolimod was injected in duplicates at different concentrations.

Results: Both GMP and non-GMP grades of cobitolimod bound specifically to the TLR-9 receptor and not to liposomes with control mock protein. Upon subtraction of the reference sensogram, cobitolimod GMP/non-GMP grade presented a 1:1 binding to TLR-9/liposomes. However, stronger binding (lower KD) was detected for cobitolimod GMP grade (KD: 11.8 \pm 3.9 μ M), compared to cobitolimod non-GMP grade (KD: 24.3 \pm 9.9 μ M). The calculated kinetics parameters for cobitolimod with GMP grade show medium-fast association rates (9.14 \pm 2.78 $\times 10^3$ (1/M.s)) and fast dissociation rates (1.08 \pm 0.01 $\times 10^{-1}$ (1/s)).

Conclusions: Using the Attana A200 system the *in vitro* binding of cobitolimod to the human TLR-9 receptor and its affinity has been demonstrated for the first time. These data provide further support and insights in the TLR-9 mediated activity of cobitolimod, a promising compound in late stage of clinical development for the treatment of active ulcerative colitis.

P107 Lactobacillus plantarum 06CC2 induces intestinal IL-10-producing dendritic cells to ameliorate acute experimental colitis in mice

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Background: Lactobacillus plantarum (LP) 06CC2, isolated from Mongolian traditional food, affects the systemic immune activity of NK cells. Here, we investigated the beneficial anti-colitis effect of LP 06CC2 in dextran sulphate sodium (DSS)-induced colitis in C57BL/6 mice.

Methods: Mice treated with 1% DSS were administered PBS only (control group) or heat-killed lyophilised LP 06CC2 (LP group) by oral gavage for 19 consecutive days. We assessed the severity of colitis using a disease activity index, measured colon length and weight, and examined colon tissue macroscopically and histopathologically. We also collected colonic lamina propria mononuclear cells (LPMCs), in which we monitored expression of genes encoding inflammatory cytokines (IFN- γ , IL-6, IL-12, TNF- α , and IL-10). To further characterise the involvement of IL-10 in the effects of LP06CC2, we continuously administered neutralising anti-IL-10 monoclonal antibody to mice with DSS-induced colitis, with or without LP 06CC2 feeding.

Results: Reduction in body weight, disease activity index, and pathology score were all significantly lower in the LP group than in the control group ($p < 0.05$). The LP strain prevented shortening of the large intestine: average colon length was significantly shorter in the LP group than in the control group ($p < 0.01$). IL-10 expression in CD11c-positive cells in colonic LPMCs was significantly higher in the LP group than in the control group, although there was no significant difference in expression of IFN- γ or IL-12 between the groups. After administration of anti-IL-10 neutralising antibody, the reduction in body weight in the LP group was the same as that in the control group. Thus, the positive effects of LP, i.e., prevention of body weight loss following administration of DSS, were abolished by neutralisation of IL-10.

Conclusions: LP 06CC2 attenuated colon inflammation by inducing IL-10 production in colonic dendritic cells.

P108 Oleuropein decreases interleukin-17 and attenuates inflammatory damage in colonic mucosa from ulcerative colitis patients

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Background: Interleukin (IL)-17 is a pleiotropic cytokine which acts on both immune and non-immune cells and is over-expressed in a number of inflammatory disorders, including ulcerative colitis (UC). Treatment with Oleuropein (OLE), the major phenolic secoiridoid of olive tree leaves, has been found to inhibit Th17 response in a DSS-induced mouse model of colitis, but no data exist in UC patients. The aim of this study was to investigate the activity of OLE in the colonic mucosa from patients with UC.

Methods: Biopsies obtained during colonoscopy from 14 patients with active UC (8 M, 39–80 years, median 59; Mayo score 4–9, median 6) were immediately placed in an organ culture chamber and challenged with lipopolysaccharide from *Escherichia coli* (EC-LPS) at 1 $\mu\text{g}/\text{mL}$ in the presence or absence of 3mM OLE for 20 h. Levels of IL-17 were assessed in total protein extracts and culture supernatant from treated colonic biopsies, by Western blotting and ELISA, respectively. A microscopic evaluation of the cultured biopsies was performed by staining with hematoxylin and eosin and immunohistochemistry for CD3, CD4, CD20, CD68 (Novus Biological, Milan, Italy). Data were analysed using the Mann–Whitney U test. A level of $p < 0.05$ was considered statistically significant.

Results: Levels of IL-17 were significantly lower in samples treated with OLE+EC-LPS when compared with those treated with EC-LPS alone, both in colonic mucosal biopsies (0.71 ± 0.08 a.u. vs 1.26 ± 0.42 a.u., $p = 0.03$) and culture supernatant (21.16 ± 8.64 pg/ml vs 40.67 ± 9.24 pg/ml, $p = 0.01$). On histologic evaluation, the presence of OLE reduced lymphocytes T CD3 and T helper CD4 in the submucosa and in the lamina propria; decreased the magnitude of the lymphoid aggregates B type CD20 limiting them in the submucosa as inflammatory residues, attenuates in the inflammatory process with lesser infiltration of leukocytes, mainly mononuclear cells, and increased CD68 histiocytes preserving mucin secretion and restoring goblet cells in the superficial portion of the glands.

Conclusions: In this study we found that OLE downregulates IL-17 production in organ culture of colonic biopsies from UC patients and attenuates the inflammatory damage. This provides new data supporting a potential role for this nutraceutical compound in the treatment of UC.

P109 Profiling of receptor for advanced glycation end products expression in cases of primary sclerosing cholangitis with ulcerative colitis

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Background: The receptor for advanced glycation end products (RAGE) is a multiligand member of the immunoglobulin super family of cell surface molecules. Except in lung, RAGE is expressed at low levels under normal physiological conditions in most tissues. RAGE has been implicated in the pathogenesis of inflammation and cancer.

Aims: i) To analyze the expression of RAGE in biliary and colonic mucosae obtained from cases of primary sclerosing cholangitis (PSC) with ulcerative colitis (UC). ii) To examine functional consequences of tissues exposed *ex vivo* to advanced glycation end products (AGE).

Methods: RAGE expression was determined by immunohistochemistry (IHC) on biliary tissues from cases of PSC ($n = 9$) and compared with that of normal gallbladder mucosa ($n = 16$). For colon, specimens from UC patients with PSC ($n = 8$) was compared with normal colonic mucosa ($n = 8$).

In separate experiments, functional responses of isolated tissues exposed to exogenous AGE ($1 \mu\text{M}$) were examined with regard to ion transport, using electrophysiological techniques as well as cytokine elaboration using ELISA. Preparation of AGE was done by incubation of bovine serum albumin with glycoldehyde and confirmed by HPLC.

Results: IHC showed RAGE expression in epithelial cells of normal gallbladder. Epithelial RAGE expression was significantly down regulated in tissues obtained from patients with PSC. The above results were confirmed using Western blotting of snap frozen tissue samples. In contrast, colonic epithelial RAGE expression did not vary between the 2 groups (PSC/UC patients vs. control group).

In electrophysiological experiments using voltage clamped human colonic or gallbladder mucosa sheets, challenge with exogenous AGE (0.1–1.0 μ M) did not influence short circuit current. AGE exposure had no effect upon ion transport responses to subsequent challenge with the cholinomimetic carbachol (0.01–10 μ M) which was used to confirm tissue viability.

In separate experiments, exposure to AGE (1 μ M) stimulated IL-8 production from sheets of isolated gall bladder (261 \pm 45 ng/mg, treated tissues vs. 139 \pm 21 ng/mg, control; n=9, p=0.03) but not from colonic mucosa. Both the tissues released IL-8 in response to exogenous TNF.

Conclusions: RAGE is expressed in human gallbladder epithelium under normal physiological conditions & significantly down regulated in biliary epithelia of PSC. Patterns of RAGE in human colon are distinct, with no alteration in RAGE expression between normal and UC colon. In terms of function, AGE had no acute influence on electrogenic ion transport in either gallbladder or colonic epithelia. There are contrasting actions of AGE on chemokine release that may give insights into the disease.

P110

Characterization of human intestinal macrophage subsets in health and inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is thought to be driven by an exacerbated immune response to the commensal microbiota. Macrophages (M Φ) are the most abundant mononuclear phagocytes in the gastrointestinal tract, where they are critical at shaping the type of immune elicited towards the microbiota. Hence, we decided to characterize human intestinal M Φ phenotype and function both in healthy controls and IBD patients.

Methods: Colonic biopsies were obtained from the inflamed and non-inflamed tissue from IBD patients (CD and UC), as well as from the non-inflamed tissue from quiescent patients and healthy controls. Biopsies were immediately processed and lamina propria mononuclear cells characterized by flow cytometry both in resting conditions and after overnight culture in the presence/absence of a pattern recognition receptor agonist (LPS).

Results: Human intestinal M Φ were identified within singlet viable cells as CD45+HLA-DR+CD14+CD64+ and further divided into CD11chigh, CD11cdim and CD11c- subsets. CD206 expression was higher compared with CD86 on total M Φ revealing a M2-biased M Φ profile in the healthy gut which however was not associated with any particular subset. However, the CD11c- subset had higher expression of HLA-DR, CD64 and PDL1 coupled with lower expression of SIRP α , CCR2 and CD40 compared with the CD11chigh/dim subsets. CD11c- M Φ had higher production of IL-10 and lower production of IL-6 and TNF α both in resting conditions and after LPS challenge compared with the CD11chigh/dim subsets. Finally, total M Φ numbers were increased in the inflamed tissue from IBD patients (both CD and UC), although not on the non-inflamed tissue or on quiescent patients, due to specifically higher numbers of the pro-inflammatory CD11chigh M Φ subset.

Conclusions: M Φ subsets are likely to represent transition stages from newly arrived monocytes (CD11chigh) into transient (CD11cdim) and resident (CD11c-) tolerogenic M Φ . The higher numbers of pro-inflammatory CD11chigh M Φ shown in the inflamed mucosa from IBD patients is probably reflecting the increased recruitment capacity of circulating monocytes elicited by the mucosa, hence exacerbating the immune response.

P111

The anti-inflammatory effect of a serine protease inhibitor in a chronic colitis transfer model is mediated by the suppression of Th1 cell differentiation

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Background: The GI tract is exposed to high levels of proteases. Increasing evidence suggests that a protease/antiprotease dysbalance might play a role in GI diseases such as IBD. In this study, we aimed to investigate the effect of a serine protease inhibitor, nafamostat mesilate (NFM), on chronic colitis in a murine transfer model.

Methods: Colitis was induced in immunodeficient SCID mice by the adoptive transfer of naive T-cells. Animals were treated twice a day with vehicle or NFM (5 mg/kg, i.p.) starting from week 2. Four groups were included: control mice treated with vehicle or NFM and colitis mice treated with vehicle or NFM. Every 2 weeks, colonic inflammation was assessed by clinical outcomes and colonoscopy. After sacrifice at week 4, colonic inflammation was assessed by macroscopy and cytometric bead array (CBA) for IFN-gamma and IL-6. mRNA of T helper (Th) transcription factors such as T-bet (Th1) and protease-activated receptors (PAR) was quantified with RT-qPCR.

Results: Colitis mice significantly lost weight over time whereas CONTROL mice gained weight. Also the clinical disease, colono-

Abstract P111 – Table 1. Effect of vehicle or NFM on clinical outcomes

	Body weight (%) Week 4	Clin (0–8) Week 4	Colo (0–12) Week 4	Macro (0–12) Week 4	IFN-gamma (pg/ml) Week 4	IL-6 (pg/ml) Week 4
CONTROL	103.2 \pm 1.0	0.6 \pm 0.3	0.0 \pm 0.0	0.0 \pm 0.0	0.7 \pm 0.3	1.9 \pm 0.9
CONTROL+NFM	103.9 \pm 0.9	0.7 \pm 0.3	0.1 \pm 0.1	0.0 \pm 0.0	2.3 \pm 0.5	2.3 \pm 0.2
COLITIS	88.1 \pm 1.9 [#]	7.1 \pm 0.3 [#]	8.3 \pm 0.5 [#]	8.8 \pm 0.4 [#]	202.1 \pm 43.2 [#]	133.6 \pm 48.5 [#]
COLITIS+NFM	95.0 \pm 2.8 ^{#,*}	5.1 \pm 0.6 ^{#,*}	6.7 \pm 0.6 ^{#,*}	7.0 \pm 0.8 ^{#,*}	104.0 \pm 20.4 ^{#,*}	35.3 \pm 6.5 ^{#,*}

Data are presented as mean \pm SEM and analyzed by two-way ANOVA or one-way ANOVA as appropriate with LSD posthoc testing. [#]<0.05 versus CONTROL and CONTROL+NFM, * <0.05 versus COLITIS, n=8 in every group.

Abstract P111 – Table 2. Relative mRNA of Th transcription factors and PARs in colon measured by RTqPCR (vs CONTROL)

	T-bet (Th1) Week 4	GATA-3 (Th2) Week 4	ROR-gammat (Th17) Week 4	PAR-2 Week 4	PAR-4 Week 4
CONTROL	1.0±0.1	1.0±0.1	1.1±0.2	1.1±0.1	1.0±0.1
CONTROL+NFM	1.3±0.1	1.2±0.2	1.0±0.2	1.3±0.1	1.8±0.6
COLITIS	3.5±0.4 [#]	2.5±0.3 [#]	0.2±0.1 [#]	1.1±0.1	2.3±1.1
COLITIS+NFM	2.3±0.3 ^{#,*}	2.5±0.7 [#]	0.4±0.1 [#]	1.1±0.1	0.5±0.1 ^{£,*}

Data are analyzed by two-way ANOVA with LSD posthoc testing. [#]<0.05 vs CONTROL and CONTROL+NFM, ^{*}<0.05 vs COLITIS, [£]<0.05 vs CONTROL+NFM, n=8 in every group.

scopic and macroscopic score significantly increased at week 4 in the COLITIS group versus the CONTROL group. NFM was able to significantly reduce these signs, resulting in an ameliorated body weight and an improved clinical, endoscopic and macroscopic score. Quantification of colonic cytokines by CBA confirmed these findings: IFN-gamma and IL-6 were significantly upregulated in the COLITIS group versus CONTROL and NFM treatment significantly decreased these levels. RT-qPCR experiments showed an upregulation of the mRNA expression of T-bet and PAR-4 in the COLITIS group (vs CONTROL). Treatment with NFM significantly lowered the mRNA expression. Other transcription factors and PAR receptors showed no statistical differences after NFM treatment.

Conclusions: Our results show that treatment with NFM ameliorates the course of experimental colitis. The beneficial effect of NFM on the Th1 transcription factor T-bet and major effector cytokine IFN-gamma make us hypothesize that the Th1 T-cell subset plays a pivotal role in the observed anti-inflammatory effect of NFM. We additionally hypothesize that NFM acts through PAR-4 signaling on the crosstalk between innate and adaptive immunity to induce the switch in CD4+ T-cell differentiation.

P112

Short-chain fatty acids administration is protective in colitis-associated colorectal cancer development

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Background: Reduced short-chain fatty acids (SCFAs) has been reported in patients with ulcerative colitis, and increased intake of SCFAs has shown to be clinically beneficial for colitis. Whether SCFAs suppresses tumorigenesis in colitis-associated colorectal cancer remains unknown. The chemopreventive effect of SCFAs in colitis-associated colorectal cancer was evaluated in this study.

Methods: Model of colitis-associated colorectal cancer in male BALB/c mice was induced by azoxymethane (AOM) and dextran sodium sulphate (DSS). SCFAs mix (67.5mM acetate, 40mM Butyrate, 25.9mM Propionate) was administered in drink water during the study period. Macroscopic and histological studies were performed to examine the colorectal inflammation and tumorigenesis in AOM/DSS-induced mice treated with or without SCFA mix. The effects of SCFAs mix on colonic epithelial differentiation were also assessed using Ki67 immunohistochemistry and TUNEL staining.

Results: The administration of SCFAs mix significantly reduced the tumor incidence (4.0±1.6/mouse versus 8.3±2.4/mouse; p<0.001) and size (1.3±0.5mm versus 2.5±0.4mm; p<0.001) in mice with AOM/DSS-induced colitis associated colorectal cancer (Figure 1). SCFAs mix protected from AOM/DSS-induced colorectal cancer by improving colon inflammation (Severity score: 0.9±0.7 ver-

sus 2.0±0.8; p=0.005), disease activity index score (3.1±0.6 versus 5.6±1.9; p=0.002) as well as suppressed the expression of pro-inflammatory cytokines including IL-6 (mRNA relative expression: 1.9±0.7 versus 3.2±1.2; p=0.015), TNF- α (22.7±6.9pg/mg versus 33.9±6.1pg/mg; p=0.001), and IL-17 (mRNA relative expression: 1.8±0.8 versus 3.6±1.5; p=0.003). A decrease in cell proliferation markers (Ki67-positive: 3.5±1.0 versus 6.8±1.7; p<0.001) and an increase in TUNEL-positive tumor epithelial cells (0.9±0.2 versus 0.6±0.2; p<0.001) were also demonstrated in AOM/DSS mice treated with SCFAs mix.

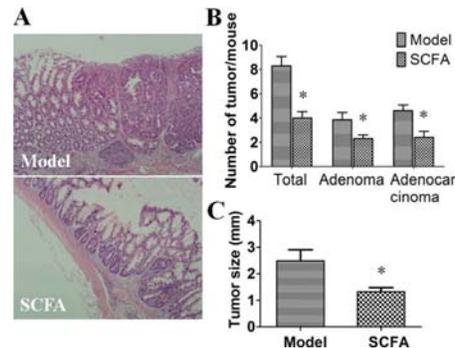


Figure 1. SCFA mix inhibited the formation of AOM/DSS-induced carcinogenesis. (A) Microscopic damage in colitis-associated dysplasia. (B) Number of tumors and tumor size (C) in the colon from AOM/DSS-induced mice treated with and without SCFA mix (*p<0.05).

Conclusions: SCFAs mix administration prevented development of tumor and attenuated the colonic inflammation in a mouse model of colitis-associated colorectal cancer. SCFAs mix may be a potential agent in the prevention and treatment of colitis-associated colorectal cancer.

P113

Model based predictions of the PTG-100 pharmacodynamic responses in ulcerative colitis patients

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Background: PTG-100 is a gut restricted oral peptide antagonist of the T cell homing integrin $\alpha 4\beta 7$, and it alters trafficking of gut homing T cells in preclinical animal models. Its potency and selectivity are similar to that of the anti- $\alpha 4\beta 7$ antibody vedolizumab (Entyvio[®]), which is approved for moderate to severe ulcerative colitis (UC) and Crohn's disease. In preclinical models using healthy or dextran sulfate sodium (DSS) induced colitis mice, we previously showed that PTG-100 causes a dose dependent increase in integrin receptor occupancy (RO) and downregulation of integrin receptor expression (RE) on peripheral blood memory T cells. Similar pharmacodynamic (PD)

responses were observed in the peripheral blood of normal healthy volunteers (HV) after PTG-100 dosing in a randomized, double-blind, Phase 1 trial. The aim of this study was to evaluate modeling approaches for predicting the PD responses in UC patients.

Methods: Semi-mechanistic, nonlinear, mixed effects models were based on the PD responses observed in healthy and colitis mouse studies, and in the Phase 1 HV study. Standard model validation techniques were used including posterior predictive checks that compare model based predictions with observed data. In vitro integrin activation studies were done using memory T cells from human PBMC donors.

Results: There is a significant increase in PTG-100 RO in colitis mice compared to healthy mice at 4 h post dose at all tested doses. The colitis mouse model was structurally connected with the healthy mouse model by estimating colitis mouse multipliers. These multipliers were then used to extrapolate from the human healthy volunteer dose response (DR) relationship to make predictions of the UC patient response. As observed in mice, the model predicts a lower dose of PTG-100 will be needed in UC patients to achieve PD responses equivalent to those observed in healthy volunteers. We also tested the binding properties of PTG-100 to the different activation states of $\alpha 4\beta 7$ integrin. We found that PTG-100 prefers binding to $\alpha 4\beta 7$ that has been activated by incubation of T cells with MnCl₂ or with retinoic acid.

Conclusions: Modeling approaches successfully characterized the observed PD responses in healthy and colitis mice and in healthy human volunteers. Extrapolation of the model to UC patients shows a pronounced lower dose shift in UC patients compared to healthy volunteers. Based on *in vitro* binding data, this shift can be explained by PTG-100's preference to bind the activated state of $\alpha 4\beta 7$. These results suggest that the increased activity of PTG-100 under colitis conditions is caused by the corresponding increased proportion of memory T cells expressing the activated state of $\alpha 4\beta 7$ integrin.

P114

Fecal loss of infliximab is underestimated due to proteolysis

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Background: Patients with acute severe ulcerative colitis (ASUC) often do not respond to infliximab (IFX) induction therapy. In an earlier study we showed that IFX could be measured in feces of these patients, with the highest fecal IFX concentrations in the first days after the first infusion. This "fecal loss" of IFX is believed to contribute to primary non-response. The mucosa of patients with inflammatory bowel disease is characterized by overexpression of proteases (metalloproteinases (MMPs) and high levels of proteases are found in feces. Therefore fecal IFX concentrations from patients with ASUC may be underestimated due to proteolysis.

Methods: Fecal samples of 5 patients with ASUC not receiving biological therapy, were homogenized (0.2 gram/ml) in buffers containing general protease inhibitors (EDTA free, Sigma-Aldrich®), Marimastat, broad spectrum MMP inhibitor ((Sigma-Aldrich®), a combination of the two, or no protease inhibitors at all. Ten µg/ml IFX was added to the fecal supernatants, after which samples were stored

at different temperatures (4°C, 22°C and 37°C) for 24 hours. IFX concentrations were measured using validated ELISA technology by Sanquin Laboratories (Amsterdam, The Netherlands).

Results: In samples without protease inhibitors stored at 37°C IFX concentrations were (median, IQR) 0.2 µg/ml (0.1–5.2). After addition of protease inhibitors, higher IFX concentrations were observed: 0.7 µg/ml (0.5–5.9) for the general protease inhibitor, 0.2 µg/ml (IQR 0.1–4.1) for Marimastat and 0.6 µg/ml (IQR 0.5–3.4) for the combination (Figure 1). In samples without protease inhibitor, the highest concentrations were measured after incubation at a temperature of 4°C (0.8 µg/ml; 0.3–7.5) compared to the lowest concentrations measured after incubation at 37°C (0.2 µg/ml; 0.1–5.2). Overall, the IFX concentrations that were measured were >10 times lower than what was "spiked" to the samples.

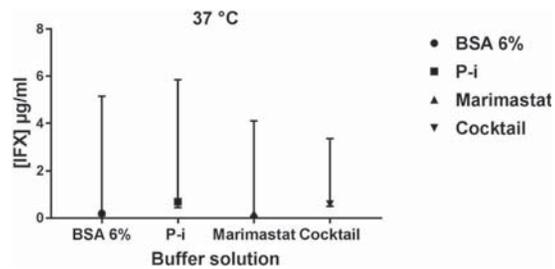


Figure 1. Fecal IFX concentrations of 5 patients with ASUC in different buffer solutions after incubation at 37°C for 24 hours.

Conclusions: Degradation of IFX by fecal proteases is highly relevant, since <10% of IFX added to feces could be measured with an ELISA test. This indicates that fecal loss of IFX in these patients is strongly underestimated. In order to maximize measurements of fecal IFX in patients with IBD samples should be processed in the presence of regular protease inhibitors and at a low temperature (4°C), to minimize proteolytic degradation. In real life, most of the degradation however may already take place in the gut before defecation.

P115

Escherichia coli Nissle 1917 modulate gut microbiota composition in ulcerative colitis patients

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Background: *Escherichia coli* Nissle 1917 (ECN) is a Gram-negative bacteria that belongs to the family of Enterobacteriaceae, and it is currently used as probiotic drug in the management of infectious gastroenteritis and in maintenance of remission in ulcerative colitis (UC) patients. ECN has been described to act also on intestinal epithelial barrier but few information exists on the influence of this probiotic on the gut microbiota composition.

Methods: The aim of our study was to evaluate the effect of administration of ECN in the qualitative and quantitative composition of the intestinal bacterial flora. Five patients affected by UC were treated with ECN (1 pill daily) for 10 days followed by 2 pills per day for further 20 days. Fecal samples were collected before starting the treatment (T0), after 10 days from the beginning of the therapy (T1) and one month following the start of treatment (T2). Genomic DNA

was isolated from fecal samples. The V1-V3 region of 16S rRNA locus was amplified on a 454-Junior Genome Sequencer. Reads were analyzed and grouped into operational taxonomic units (OTUs) by sequence matching against Greengenes database. The α and β diversity and the Kruskal Wallis test were performed by QIIME software. **Results:** The T test on good's coverage index revealed that the qualitative composition of the gut microbiota between the T0 and T2 conditions resulted significantly different. Box plot of Shannon and Chao I indices revealed an increase in the median index values at the time point T1, which means an increase in the OTU total number at T1. This indicates an increase of the microbiota wellness at this time point. Post hoc analysis at phylum taxonomic level, revealed that Firmicutes relative abundance in the condition T0 versus T1 resulted significantly different, with a decrease of Firmicutes at T1. Indeed, at family taxonomic level the post hoc analysis revealed that Clostridiaceae relative abundance in the condition T0 versus T1, and also in T1 versus T2, differed significantly, with a T1 median value higher than the T0 and T2 values. At genus level, the T test confirms the variability in the two conditions (T0 and T2), with significant differences for Actinomyces, Anaerostipes, Bacteroides, Bulleidia, Corynebacterium, Dialister, Enterobacteriaceae, Erysipelotrichaceae, Finegoldia, Granulicatella, Lactobacillaceae, Peptoniphilus, Phascolarctobacterium, Roseburia, Serratia, Veillonellaceae, Veillonella_dispar, belonging to Firmicutes, Bacteroidetes and Proteobacteria phyla. **Conclusions:** Treatment with ECN leads to an improvement of the qualitative gut microbiota composition in UC patients. These effects are stronger at the end of treatment, with a stable variability between the genera after 1 month of treatment.

P116

***Escherichia coli* Nissle 1917 distinctively regulates apoptosis and cell cycling of Caco-2 cells**

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Background: Probiotics are widely used in IBD but the mechanisms of action of the probiotic *E. coli* Nissle 1917 (EcN) is still controversially discussed. The epithelial layer as first barrier line plays an important role and regulates further contact of bacteria with immune and non-immune cells leading to inflammatory responses. Therefore, the aim was to investigate the role of *E. coli* Nissle 1917 on apoptosis and cell proliferation of Caco-2 cells.

Methods: Caco-2 cells were incubated with different concentrations of EcN conditioned medium (CM) for 24, 48 or 72h. Apoptosis was detected by FACS analysis using Annexin V/PI staining. Possibly important factors such as Fas, FasL or p27 and p53, retinoblastom (Rb) were detected by flow cytometry or immunoblotting. Mitochondrial membrane potential was measured using rhodamin123 fluorescence. We evaluated whether apoptosis occurred caspase dependent using caspase inhibitors for caspase 3, 8 or 9.

Cell cycling was measured with flow cytometric analysis by DNA and cyclin B1 staining. CFSE staining revealed cell division after incubation with EcN.

Secretion of important pro- and anti-inflammatory cytokines after EcN-treatment were detected by cytometric bead array.

Results: Apoptosis of Caco-2 was slightly induced compared to baseline level upon stimulation with EcN. Interestingly, mitochondrial membrane potential measured by rhodamine 123 uptake was increased upon stimulation with EcN.

While Fas expression was not affected by EcN, FasL was increased. Bid was induced dose dependently by EcN.

Whereas expression of TNF-R1 was not changed upon EcN stimulation, TNF-R2 expression was induced by stimulation with EcN ($p > 0.05$).

The expression of the tumour suppressor proteins p27 and p53 were marginally decreased whereas the expression of Rb protein, another tumour suppressor protein, was increased upon stimulation with EcN.

Inhibition of the central executor caspase 3 and the initiator caspase 9 decreased apoptosis rate induced by EcN indicating activation of the intrinsic pathway.

CFSE labeling revealed an increased proliferation rate in EcN treated Caco-2 cells.

Cell cycling was significantly induced in a dose dependent manner measured by the regulator protein in cell cycle from S to G2/M phase Cyclin B1 and DNA staining.

Finally, CBA analysis demonstrated a distinct regulation of cytokines by EcN with upregulation of IL1 β , IL8, IL6, IL17, down regulation of TNF α , IL12p70.

Conclusions: *E. coli* Nissle distinctively regulates apoptosis in Caco-2 cells caspase dependently and cell cycling dose dependently. These results demonstrate the fine tuning of epithelial cells regeneration by EcN which could lead to an increased barrier function, less bacterial influx and finally amelioration of inflammatory bowel diseases.

P117

Functional implications of microRNAs in Crohn's disease revealed by integrating microRNA and messenger RNA expression profiling

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Background: Crohn's disease (CD) is a debilitating inflammatory bowel disease that emerges due to the influence of genetic and environmental factors. miRNAs have been identified in the tissue and sera of IBD patients and may play an important role in the induction of IBD.

Our study aimed to identify differentially expressed miRNAs and miRNAs with the ability to alter transcriptome activity by comparing inflamed tissue samples with their non-inflamed counterparts.

Methods: We studied changes in miRNA-mRNA interactions associated with CD by examining their differential co-expression relative to normal mucosa from the same patients. After written informed consent was obtained, specimens were collected from inflamed and adjacent (at least 30 cm away from the inflamed area) non-inflamed areas of the colon. Correlation changes between the two conditions were incorporated into scores of predefined gene sets to identify biological processes with altered miRNA-mediated control.

Results: Our study identified 28 miRNAs differentially expressed (p -values < 0.01), of which 14 are up-regulated. Notably, our differential co-expression analysis highlights microRNAs (i.e., miR-4284, miR-3194 and miR-21) that have known functional interactions with key mechanisms implicated in IBD. Most of these miRNAs cannot be detected by differential expression analysis that do not take into account miRNA-mRNA interactions.

Conclusions: The identification of differential miRNA-mRNA co-expression patterns will facilitate the investigation of the miRNA-mediated molecular mechanisms underlying CD pathogenesis and could suggest novel drug targets for validation.

P118 Balancing JAK/STAT-signaling with Tofacitinib in monocytes of healthy controls and IBD patients

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Background: Monocytes are bridging natural and acquired immunity. Information about JAK signaling in monocytes is scarce. JAK-inhibition is a promising new anti-inflammatory treatment option. However, JAK/STAT activation may be involved both in pro- and anti-inflammatory monocyte programs. We have shown that GM-CSF-activated regulatory monocytes (GMaM) induce Treg-differentiation in co-cultures with naive T-cells *in vitro*. Inflammatory T-cells produce high amounts of GM-CSF, not leading to anti-inflammatory monocytes, likely because of pro-inflammatory cytokines in the environment. We used JAK-inhibitor Tofacitinib to explore mechanisms that block pro-inflammatory pathways and allow anti-inflammatory functions in monocytes.

Methods: Primary monocytes from healthy human donors were isolated and phenotyped by FACS after treatment with GM-CSF and JAK-inhibitor Tofacitinib. Monocytes were co-cultured with autologous naive T-cells and Foxp3+ regulatory T-cell induction was evaluated. Primary monocytes from IBD patients with active disease were used to investigate JAK/STAT signaling and inhibition. JAK1 activation (represented by IFN γ -induced phospho-STAT-1), JAK2 activation (represented by GM-CSF-induced phospho-STAT5) and JAK3 activation (represented by IL-4-induced phospho-STAT6) was analyzed by FACS. Non-toxic dosages of 1–1000 nM Tofacitinib were used.

Results: We aimed to define the dose of JAK inhibition that keeps JAK2 activity (GM-CSF-induced pSTAT5) intact. At 10–100 nM Tofacitinib we found GM-CSF-induced phospho-STAT5 while phospho-STAT1 and phospho-STAT6 were still blocked. Concentrations above 100 nM Tofacitinib led to inhibition of GM-CSF-induced CD39-, CD206-, CD209-expression. 10–100 nM allowed CD39-, CD206-, CD209 expression and IL-10 release while TNF α was still blocked. Co-culture of GMaM and T-cells resulted in increased differentiation of Foxp3+ Treg that was even enhanced when 10nM Tofacitinib was used. Investigation of JAK/STAT activation in monocytes from IBD patients revealed a higher base line phosphorylation of STATs with lower increase after stimulation compared to healthy controls. Furthermore, TNF α expression was not inhibited in monocytes of IBD patients using a similar Tofacitinib dosage which led to TNF α inhibition in healthy controls (10–100 nM).

Conclusions: In summary, Tofacitinib (10–100 nM) facilitates GM-CSF-induced reprogramming of monocytes to anti-inflammatory cells. This could not be confirmed in monocytes from active IBD patients as blockage with similar doses did not inhibit pro-inflammatory cytokine expression. Thus, pro-inflammatory activation in IBD does depend on more complex interplays of multiple factors and solely blocking JAK/STAT activation by Tofacitinib cannot fully restore the GMaM phenotype.

P119 Higher levels of infliximab may alleviate the need of azathioprine comedication in the treatment of patients with Crohn's disease: a SONIC post hoc analysis

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Background: In SONIC (NCT00094458), pts with moderate-severe CD treated with infliximab (IFX) in combination with azathioprine (AZA) achieved higher corticosteroid-free remission at wk26 (CSFR26) vs IFX monotherapy (Colombel et al, 2010). It has been hypothesized that the enhanced benefit of combination therapy occurs via influence of AZA on the pharmacokinetics (PK) of IFX, & a shared mechanism of apoptosis for the 2 drugs. To better understand the value of combination therapy in the presence of different levels of IFX in pts with CD, the exposure-response (ER) relationships within serum IFX concentration (SIC) ranges were evaluated, with & without concomitant AZA.

Methods: Data from 206 pts with trough SIC at wk30 were analyzed; 97 received IFX monotherapy & 109 received combination therapy with AZA. SIC were categorized into quartiles & proportion of pts achieving efficacy outcomes (CSFR26; mucosal healing at wk26 [MH26]) in each quartile were compared between the 2 treatment grps. Pt characteristics & presence of ATI in these quartiles were assessed. Receiver operating characteristics (ROC) of ER relationships were also compared.

Results: While pts on combination therapy were enriched in higher SIC quartiles, proportions of pts achieving CSFR26 were not significantly greater among those receiving combination therapy vs monotherapy within the same quartile (Fig. 1). Contrary to what may be expected of an independent interaction, proportions of pts with CSFR26 while on monotherapy were almost twice those who achieved this endpoint on combination therapy in the lowest SIC

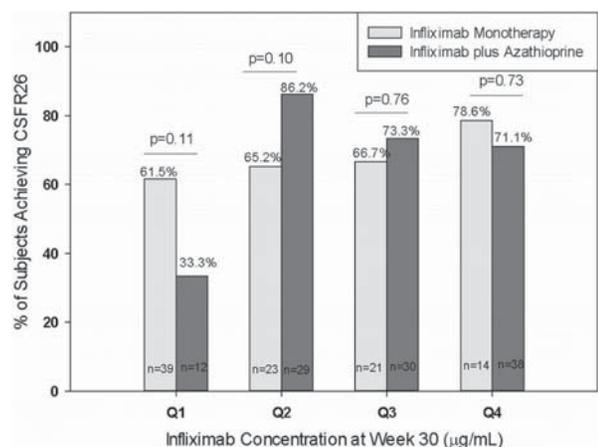


Figure 1. Q1: <0.84 µg/mL; Q2: 0.84 µg/mL to <2.36 µg/mL; Q3: 2.36 µg/mL to <5.02 µg/mL; Q4: ≥5.02 µg/mL.

quartile. Consistent with a drug-sensitive assay, ATI were found only in the lowest SIC quartile across both IFX treatment groups and within this quartile the incidence of ATI was higher among those on monotherapy (35.9%) vs. combination therapy (8.3%). No other notable differences in patient characteristics were seen among SIC quartile groups. In subgroup of patients evaluable for MH26 (n=123), numerically higher proportions of patients achieved MH26 in the combination group relative to monotherapy particularly in lower two SIC quartiles; however, these differences were not statistically significant. Differences in ROC characteristics between both treatment groups could not be established.

Conclusions: Within similar trough SIC ranges, clinical efficacy was not consistently greater with the addition of AZA to IFX. While there was some benefit seen with addition of AZA in MH, this was only notable in the 2 lower SIC quartiles. Overall, data suggests that the benefit of combination therapy is primarily due to AZA's influence on the PK of IFX.

P120

A single-nucleotide polymorphism in the vitamin D receptor gene is associated with a B3-penetrating phenotype in Crohn's disease

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Background: Vitamin D signaling modulates inflammation through the vitamin D receptor (VDR) which is a member of the nuclear receptor family of transcription factors. The presence of C instead of T in the single-nucleotide polymorphism (SNP) rs731236 in the VDR gene has been associated with a higher risk for Crohn's disease (CD). We analysed the relevance of the presence of risk allele C in the evolution of the disease.

Methods: DNA was extracted from blood samples from 99 patients diagnosed with CD and 72 healthy donors from the Hospital of Manises (Valencia) and the SNP was genotyped using PCR-RFLP. We collected clinical data for each patient, including the Montreal classification in several phenotypes. Also, peripheral blood mononuclear cells (PBMCs) from 16 CD patients with the TT or CC genotype were obtained and gene expression of some cytokines was quantified in these cells by real-time RT-PCR.

Results: The allelic frequency of the risk allele was higher in CD patients related to healthy controls (p=0.2881, Fisher's test) and it was significantly different when compared with patients showing a B3 phenotype (p=0.026, Fisher's test). In addition, CD patients homozygous for the risk allele C initiated with the disease at a lower age (Fig. 1; p=0.05, t-test CC vs TT), and exhibited a significant higher risk to have a B3-penetrating phenotype (Fig. 2; p=0.0018,

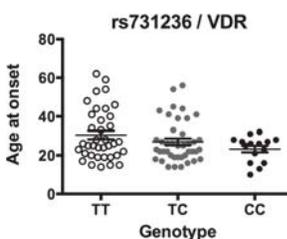


Figure 1

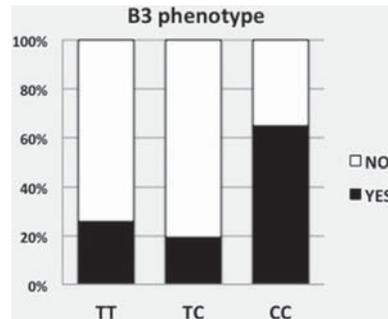


Figure 2

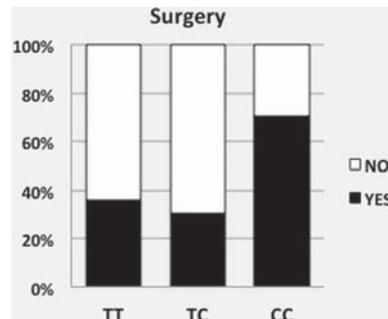


Figure 3

Chi-square; p=0.0078, Fisher's test CC vs TT, OR=5.3) and to need surgery (Fig. 3; p=0.013, Chi-square; p=0.021, Fisher's test CC vs TT, OR=4.3). Finally, PBMCs from patients with the CC genotype showed a higher level of IL1 β (p=0.13, t-test), IL18 (p=0.05, t-test) and IFN γ (p=0.36, t-test) mRNA than patients with the TT genotype.

Conclusions: Our study indicates that homozygosity for the allele C in the SNP rs731236 in the VDR gene confers a higher risk to develop a B3-penetrating phenotype in CD patients, associated with an elevated expression of pro-inflammatory cytokines in PBMCs.

Clinical: Diagnosis and outcome

P121

Antimicrobial antibodies and inflammatory markers are present in the serum of patients with IBD years before diagnosis and can predict disease

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Background: IBD is preceded by a preclinical period where immunological changes can already be detected. Prior studies have shown that antimicrobial antibodies (Abs) and inflammatory markers can be detected years (Y) before diagnosis (dx), but no study has yet looked into the longitudinal evolution of these markers and their power to predict disease at given time-points (TP) before diagnosis.

Methods: Stored pre-dx serum samples from military personnel were obtained from 100 CD, 100 UC, and 100 healthy controls (HC). Cases were identified based on ICD9 codes. Samples were tested for ASCA (IgA, IgG), AntiOmpC, AntiFlaX, antiFla2, antiCbir1, pANCA, and CRP. The distribution of each marker in each subject was treated as a stochastic process, and functional principal component analysis was performed to derive its trajectory along time in CD, UC and HC. A linear mixed effects model was used to compare each marker's differential trajectory. A logistic regression model was used to evaluate the power to predict disease 3Y, 2Y and 1Y before dx. Survival curves were developed for each marker from first seropositivity until dx.

Results: 1000 serum samples (400 from CD, 300 from UC and 300 from HC) at different TP before diagnosis were tested. Median time before diagnosis was -797 days (range: -7118, 2355) for CD, and -849 days (-6536, 31) for UC. In UC, pANCA and CRP presented different trajectories as compared to HC ($p=10^{-6}$, $p=0.001$, respectively), increasing towards dx. In CD all markers trajectories (except pANCA) were significantly different as compared to HC ($p=0.008$ for antiOmpC, $p\leq 0.001$ for all other markers). Combining the markers with highest predictive accuracy in a multivariate model provided a higher predictive accuracy than each marker alone (estimated AUC based on cross-validation: 0.756, 0.803, and 0.795 at 3Y, 2Y, and 1Y before dx). Specifically, 3 of the 5 markers, anti-Fla2, anti-OmpC and CRP were found to significantly predict CD in the model, with an Odds Ratio of 2.80 (90% CI: 1.8, 4.4), 1.83 (90% CI: 1.2, 2.7) and 1.78 (90% CI: 1.2, 2.5) respectively at 3Y before diagnosis. In the survival analysis, for all markers (except antiOmpC), a pre-clinical positive result was associated with a greater chance of developing IBD (Figure 1).

Conclusions: Circulating antibodies and markers of systemic inflammation can be detected in the serum of patients with IBD years before diagnosis, indicating that immune dysfunction precedes detectable tissue injury. Accurate prediction of disease at this preclinical stage could pave the way for preventive strategies.

P122

Magnetic resonance index of activity (MaRIA) and Clermont score are two MRI indices which are highly and equally effective in detecting mucosal healing in Crohn's disease

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Background: Mucosal healing is hitherto the most popular therapeutic endpoint in Crohn's disease (CD) and is currently defined as no endoscopic ulcers. Magnetic resonance imaging (MRI) is an accurate examination for assessing activity in CD. To date, magnetic resonance index of activity (MaRIA) and Clermont score (CS) are the two main MRI indices available in grading CD severity. In the present study, we aimed to compare the performances of Clermont score [1] and MaRIA [2] in assessing mucosal healing in CD.

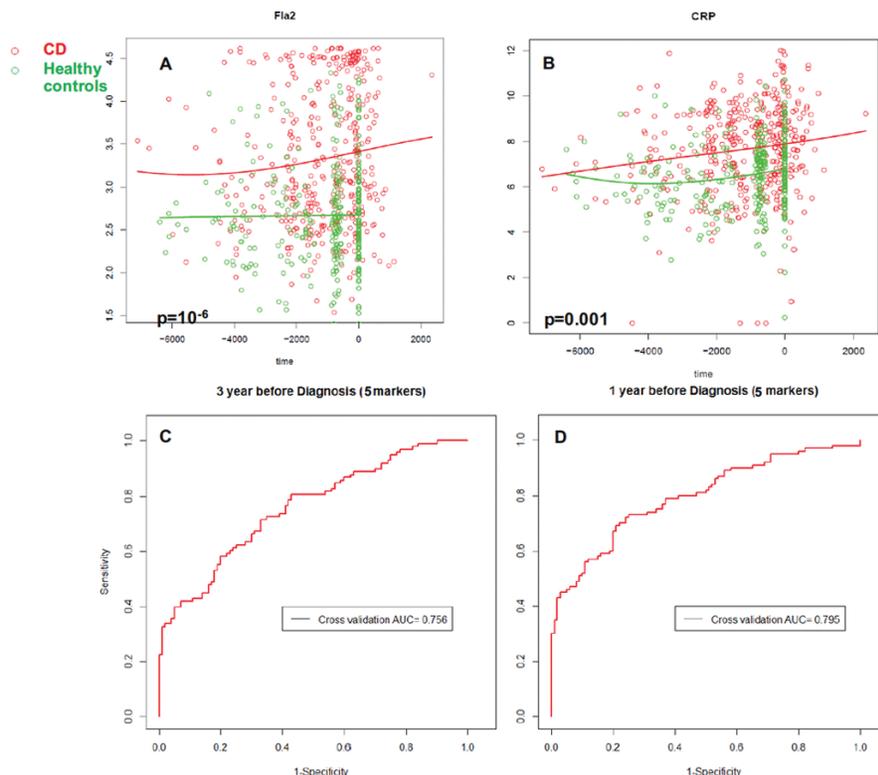


Figure – Results from functional PCA depicting the trajectory of anti-Fla2(2A) and CRP (2B) in the years before CD diagnosis. Red curve and red dots represent CD cases; green dots represent healthy controls. 2C and 2D show the AUC for the model combining several markers (antiFlaX, antiFla2, antiOmpC, ASCA IgG and CRP)

Methods: In this prospective study, all the patients underwent consecutively magnetic resonance entero-colonography (MREC) including diffusion-weighted sequences with no bowel cleansing and with no rectal enema, and colonoscopy (with CDEIS and SES-CD calculation) within 4 weeks (mean interval=17±11 days). Radiologists were blinded from endoscopic findings and endoscopists were blinded from radiologic findings.

Results: Overall, 44 CD patients were included (Table 1).

Table 1: Characteristics of the Crohn's disease patients (n=44) included in the study.

Age at diagnosis, mean (±SD)	27.9 (±15.0)
Disease duration at inclusion, median [IQR]	5.5 [0.4 – 14.2]
Male gender, n (%)	21 (47.7)
Tobacco use, n (%)	
Non smokers	25 (56.8)
Former smokers	7 (15.9)
Active smokers	12 (27.3)
Previous intestinal resection, n (%)	9 (20.5)
Montreal Classification	
Disease location	
L1, n (%)	7 (15.9)
L2, n (%)	10 (22.7)
L3, n (%)	27 (61.4)
L4, n (%)	4 (9.1)
Behaviour	
B1, n (%)	22 (50.0)
B2, n (%)	12 (27.3)
B3, n (%)	9 (20.5)
Perianal lesions, n (%)	10 (22.7)
Concomitant therapies	
5-ASA, n (%)	2 (4.6)
Corticosteroids, n (%)	13 (29.6)
Budesonide, n (%)	4 (9.1)
Thiopurines, n (%)	5 (11.4)
Infliximab, n (%)	4 (9.1)
Adalimumab, n (%)	4 (9.1)
Ustekinumab, n (%)	1 (2.3)
CDAI, median [IQR]	188 [106 – 266]
Total CDEIS, median [IQR]	4.8 [1.8 – 9.3]
Total SES-CD, median [IQR]	7 [4 – 13]
CRP, median [IQR]	11.4 [3.5 – 38.8]
Faecal Calprotectin, median [IQR]	1555 [384 – 1800]

SD: standard deviation; IQR: interquartile; n: number; CDAI: Crohn's disease activity index; CDEIS: Crohn's disease endoscopic index of severity; SES-CD: simplified endoscopic score for Crohn's disease; CRP: C-reactive protein.

Considering the 194 segments (ileum=37, colorectal=159), CS correlated with segmental CDEIS (0.48; $p<0.001$) and segmental SES-CD (0.44; $p<0.001$). MaRIA correlated also with segmental CDEIS (0.48; $p<0.001$) and segmental SES-CD (0.45; $p<0.001$). According to the established cut-off values i.e. MaRIA >7 and CS >8.4, the sensitivity of each index was 0.53 and 0.56, and the specificity was 0.80 and 0.82, respectively. The sensitivity for detecting deep ulcerations was 0.90 and 0.91 for the MaRIA and Clermont indices, respectively, with a specificity of 0.79 and 0.80.

Taking into account the 44 included patients, deep MRI remission predicted mucosal healing with sensitivity=0.60, specificity=0.76 and negative predictive value=0.85 according to Barcelona criteria (no segmental MaRIA >7), and sensitivity=0.50, specificity=0.88 and negative predictive value=0.86 according to Clermont criteria (no Clermont score >8.4). In addition, MRI remission predicted mucosal healing with sensitivity=0.50, specificity=0.85 and negative predictive value=0.85 according to Barcelona criteria (no segmental MaRIA >11), and sensitivity=0.50, specificity=0.80 and negative predictive value = 0.84 according to Clermont criteria (no Clermont score >12.5).

Conclusions: MaRIA and Clermont score are equally effective in detecting endoscopic ulcerations in Crohn's disease. Accordingly, MRI remission or deep MRI remission defined according to Barcelona or Clermont criteria are highly predictive of mucosal healing supporting their use in clinical trials and daily practice.

References:

[1] Hordonneau et al., (2014), Am J Gastroenterol

[2] Rimola et al., (2009), Gut

P123

MRI remission after therapeutic intervention is associated with more time spent in clinical corticosteroids-free remission and decreased risk of surgery in Crohn's disease

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Background: Endoscopic mucosal healing should be the therapeutic goal in Crohn's disease (CD) as it is associated with more favourable outcomes. Alternative non-invasive approach, such as magnetic resonance imaging (MRI), is able to detect morphologic changes under therapy [1]. However, whether achieving MRI remission is associated with favourable outcomes remains unknown.

We aimed to investigate whether MRI remission after therapeutic intervention could predict clinical corticosteroids-free remission (CFREM) and CD related-surgery.

Methods: We performed a posthoc analysis from pooled data of two prospective trials. All the patients undergoing MRI to monitor therapeutic response were included. Patients were excluded from this study if follow-up was <6 months. Objective sign of inflammation

Table 1: Characteristics of the 63 Crohn's disease patients at inclusion (=time of MRI examination)

Characteristics	Overall population (n=63)
Female gender	43 (68.3%)
Smokers	32 (50.8%)
Age at diagnosis, years, (mean +/- sd)	26.4 +/- 12.6
Age at inclusion, years, (mean +/- sd)	34.8 +/- 14.5
Disease duration, years, (mean +/- sd)	8.7 +/- 9.5
Montreal classification	
Location	
L1	19 (30.2%)
L2	18 (28.6%)
L3	26 (41.2%)
L4	6 (9.5%)
Behaviour	
B1	29 (46.0%)
B2	22 (34.9%)
B3	12 (19.0%)
Perianal lesions	20 (31.7%)
Prior intestinal resection	21 (33.3%)
CDAI, median [IQR]	189[80-243]
CDAI > 150	39 (61.9%)
CRP, median [IQR]	14.0[2.9-35.5]
CRP > 5g/L	37 (56.9%)
Current therapies at inclusion	
Corticosteroids	25 (39.7%)
Thiopurines	23 (36.5%)
Methotrexate	1 (1.6%)
Anti-TNF	30 (47.6%)
Infliximab	12 (19.0%)
Adalimumab	18 (28.6%)
MRI remission according Clermont criteria	21 (33.3%)
MRI remission according Barcelona criteria	19 (30.1%)
Deep MRI remission according Clermont criteria	16 (25.4%)
Deep MRI remission according Barcelona criteria	14 (22.2%)

on colonoscopy, CTscan or MRI before treatment has to be available to include the patients. All the patients underwent diffusion-weighted magnetic resonance enterocolonography with no bowel cleansing and no rectal enema. MRI evaluation was performed using 5 segments (ileum, right colon, transverse colon, left/sigmoid colon and rectum). MRI remission was defined using Clermont criteria [2] (no segmental Clermont score >12.5) or using Barcelona criteria [3] (no segmental MaRIA >11). Deep MRI remission was defined as no segmental MaRIA >7 or no segmental Clermont score >8.4. Clinical CFREM was defined as absence of CD flare (=reappearance or worsening of clinical manifestation leading to therapeutic modification, hospitalization or CD-related surgery). For each of the patients CFREM were assessed by semesters.

Results: Overall, 63 patients were included (Table 1) with a median follow-up of 4 semesters.

Overall, 300 semesters were considered. In multivariate analysis taken into account the impact of CDAI, CRP and current therapy at inclusion, deep MRI remission was associated with more time spent in CFREM according to Barcelona (85.7% vs 44.9%, $p=0.01$) or Clermont criteria (69.3% vs 46.9%, $p=0.049$). MRI remission was also associated higher proportion of semester spent in CFREM according to Barcelona (66.7% vs 47.3%, $p=0.042$) or Clermont criteria (69.4% vs 42.7%, $p=0.049$). Patients achieving deep MRI remission or MRI remission had an increased time to CD-related surgery compared to those with persistent MRI activity ($p<0.05$, for all criteria).

Conclusions: MRI remission after therapeutic intervention is associated with favourable outcomes and should be considered as non-invasive therapeutic endpoint in CD. A dedicated prospective trial should be led to confirm our data.

References:

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- [2] Hordonneau et al. (2014), *Am J Gastroenterol.*
- [3] Rimola et al. (2009), *Gut.*

P124

Disagreement among gastroenterologists in the endoscopic evaluation using the Mayo endoscopic score and the Rutgeerts postoperative score

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Background: Endoscopic evaluation is an integral part in the evaluation of patients with Inflammatory bowel disease (IBD). Endoscopy is routinely used to evaluate disease severity and guide important clinical decisions. Therefore, variability in the interpretation of endoscopic findings amongst different gastroenterologists represents a problem of the utmost importance, which can severely impact the management of these patients. We aimed to study the inter-rater variability using the Mayo endoscopic subscore (MS) and Rutgeerts score (RS) amongst gastroenterologists.

Methods: Several gastroenterologists were invited to participate in an online survey including pictures and video recordings from colonoscopies of patients with Crohn's disease (CD) and Ulcerative Colitis (UC) (total of 20 questions). Participants were asked to assess the mucosal appearance of the colorectal mucosa in UC using the MS (0–3), and the mucosal aspect of the neo-terminal ileum, anastomosis, and proximal colon in operated patients with CD using the RS

(0–4). To assess the impact of clinical information on scoring, two identical questionnaires were distributed, only differing on the clinical information provided on six cases. In the second part of the survey, participants were able to consult the endoscopic scores before answering the questions. The inter-rater concordance (IRC) was assessed using Krippendorff's alpha test.

Results: A total of 58 gastroenterologists accepted to participate in this study. Nineteen participants (32.8%) stated to be more experienced in IBD (>10 patients/week), 50 (86.2%) stated to commonly perform endoscopy in patients with IBD, and 52 (89.7%) routinely used the scores. The IRC for the MS and RS was 0.47 95% CI (0.41–0.54) and 0.33 95% CI (0.28–0.38). Clinical information did not influence IRC for the MS ($p=0.762$) or RS ($p=0.147$). Consultation of scores slightly improved IRC for the MS [0.50 95% CI (0.42–0.58) vs 0.45 95% CI (0.38–0.51)], but not RS [0.16 95% CI (0.10–0.21) vs 0.41 95% CI (0.35–0.46)]. The IRC for mucosal healing ($MS\leq 1$) and deep mucosal healing ($MS=0$) was 0.57 95% CI (0.40–0.72) and 0.89 95% CI (0.73–1). The IRC for postoperative recurrence ($RS\geq 2$) was only 0.44 95% CI (0.24–0.62) and for severe recurrence ($RS\geq 3$) 0.54 95% CI (0.36–0.71). Considering only the 18 more experienced participants, the IRC increased for the MS [0.54 95% CI (0.46–0.60)] and RS [0.42 95% CI (0.37–0.47)]. The IRC for $MS\leq 1$ [0.62 95% CI (0.45–0.78)], $MS=0$ [0.89 95% CI (0.75–1)], $RS\geq 2$ [0.58 95% CI (0.39–0.76)] and $RS\geq 3$ [0.59 95% CI (0.42–0.75)].

Conclusions: Our study confirms a high rate of disagreement using the MS and RS, even amongst experienced physicians. Worryingly, there was only a moderate concordance for the most important outcomes- mucosal healing and postoperative recurrence.

P125

Rapid increase in pan-treatment refractory Crohn's disease after transition to adult services: a regional cohort study

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Background: Inflammatory bowel disease (IBD) presents in childhood in up to 15% of cases. Paediatric onset IBD (PIBD) has a more extensive and dynamically changing phenotype and a faster rising incidence than adult-onset IBD. We aimed to evaluate rates of treatment refractory disease at and then following transition to adult services.

Methods: A prospective PIBD database identified a cohort of all patients discharged from our regional service since 01/01/07. A retrospective study of patients graduating from paediatric to adult IBD services through a transition process, transition event (single joint clinic) or transfer until 31/12/13 was conducted with post transfer follow-up (FU) data at a minimum of 1 year to last adult FU (LAFU). Pan-treatment exposure (PTE) was defined as exposure to all of azathioprine (AZA) or mercaptopurine (MP), methotrexate (MTX), infliximab (IFX) and adalimumab (ADA). Pan-treatment refractory (PTR) disease as those refractory (primary non-response [PNR], loss of response [LOR] or intolerance) to all of these therapies. We used the Montreal classification to describe disease location (L) and behaviour (B) phenotypes. Psychological co-morbidity was defined as

a formal psychiatric diagnosis, regular psychiatry/psychology input (or intention for this if repeated family refusal), documented anxiety or depression and deliberate self-harm.

Results: 138 patients graduated to adult services, 69% (95/138) had Crohn's disease (CD); 59% (56/95) male, 76% (72/95) with extensive disease (L3 or L3+L4) and 22% (21/95) B2 or B3 disease at time of transfer. Median (IQR) age at transfer 17.8 years (17.3, 18.4) and median (IQR) disease duration at transfer 5.4 years (4.6, 7.6). Median (IQR) length of FU post-transfer was 3.3 years (2.1, 5.1). 12% (11/95) had PTE with 4% (4/95) having PTR disease by time of transfer. PTE rates increased significantly to 26% (21/82) $p=0.009$ at LAFU and PTR disease to 18% (15/82) $p=0.003$; 13 patients lost to follow-up. 90% (19/21) of those with PTE had extensive disease and 48% (10/21) had B2 or B3 disease by LAFU. 80% (12/15) patients with PTR disease required bowel resection or a defunctioning stoma by LAFU, compared with 37% (30/82) of the whole CD cohort $p=0.002$. 24% (5/21) of those with PTE had significant psychological co-morbidity by LAFU.

Conclusions: Our novel data show that pan-treatment exposure in paediatric-onset CD is already significant by time of transfer to adult services and continues to increase to affect 26% of this regional cohort within a relatively short period of adult follow-up. 18% of paediatric-onset CD patients have failed all medical treatments by LAFU and 71% with PTE require resectional or defunctioning surgery to manage disease.

P126 Experience of 3D modelling in perianal fistula disease and survey of international surgical interest

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Background: Perianal Crohn's fistulas are often complex, translating to difficult surgery and worse outcomes. MRI is the reference stan-

dard for assessment of complex perianal fistula, being effective at defining anatomy and guiding surgery. [1] However, communication of radiologist's understanding of MRI findings to the surgeon remains challenging. 3D models can aid understanding of the complex relationship between sphincter anatomy and fistula, guiding surgical decisions and improving outcomes.

We presented case vignettes where 3D reconstruction has improved surgical comprehension of complex disease and surveyed an international cohort of surgeons to assess current practice and to gauge interest in 3D modelling of perianal fistulas.

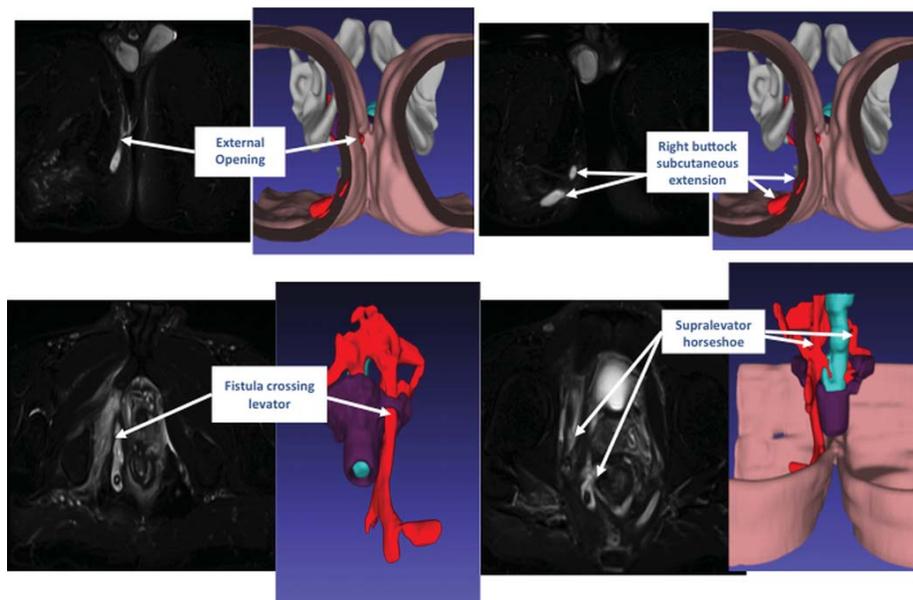
Methods: During an international gastrointestinal conference, participants were asked to complete either an online or paper-based survey following presentation of perianal Crohn's fistula 3D models. Content validity of the questionnaire was performed using the IBD multi-disciplinary team and contained multi-category scales and binary (yes/no) questionnaires. Data collected included respondents' current fistula practice, their use of MRI in operative planning and whether they would be interested in 3D modelling in their institution.

Results: Thirty-four participants completed the survey including 17 (50%) based in the UK, 4 (12%) from Denmark with the remaining participants from Canada, China, Finland, Germany, Greece, Spain, Saudi Arabia and Sri Lanka. Experience of perianal fistula surgery varied with 35% (12/34) having >10 years' experience and 30% and 35% having 5–10 and ≤ 5 years' experience respectively. 41% of the participants operate on complex perianal fistulas, whilst 65% also refer complex fistulas and 15% were from tertiary centres.

The majority (88%) of surgeons review the patient's MRI pre-operatively with 24% using MRI peri-operatively and 44% using endoanal ultrasound. However, only 18% review the images with a radiologist all of the time, whilst 62% review 50–75% of the time and 12% never review the MRI with a radiologist.

In total, 85% of respondents expect 3D modelling to be useful for perianal fistula surgery and 88% would use 3D modelling if available.

Conclusions: There is an international appetite for use of 3D modelling of complex perianal Crohn's fistula, which supports our local experience. 3D reconstruction has potential to improve surgical understanding, improve surgical decision-making, augment training and aid patient comprehension for informed consent.



Abstract P126 – Figure 1. 2D vs. 3D complex perianal fistula.

References:

- [1] Szurowska E, Wypych J, Izycka-Swieszewska E, (2007), Perianal fistulas in Crohn's disease: MRI diagnosis and surgical planning: MRI in fistulizing perianal Crohn's disease, *Abdom Imaging*, 705–718, 32(6)

P127

An assessment of a pancolonic adaptation of the ulcerative colitis endoscopic index of severity in comparison to clinical and biochemical markers of disease activity in paediatric ulcerative colitis

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Background: The ulcerative colitis Endoscopic Index of Severity (UCEIS) is an endoscopic index of disease activity, applied to the most severely affected region of the rectosigmoid, developed for use in adult ulcerative colitis (UC) patients. Given that most paediatric UC cases involve extensive colitis, we hypothesized that a pancolonic adaptation of the UCEIS may be more appropriate for children. We aimed to compare such an adapted version and the traditional UCEIS to clinical and biological markers of disease activity in this population.

Methods: In this single-centre prospective study, Paediatric UC Activity Index (PUCAI), physician global assessment (PGA), fecal calprotectin (FC) and C-reactive protein (CRP) were measured in consecutive paediatric UC patients undergoing colonoscopy. Colonoscopies were scored by 2 blinded IBD physicians using the traditional rectosigmoid UCEIS and a pancolonic adaptation derived by summing individual UCEIS scores applied to the rectum, left colon, transverse colon and right colon, and dividing by the number of visualized segments. Spearman correlations were calculated between variables. The ability of both UCEIS versions to discriminate between disease activity, reflected by PUCAI, was assessed graphically.

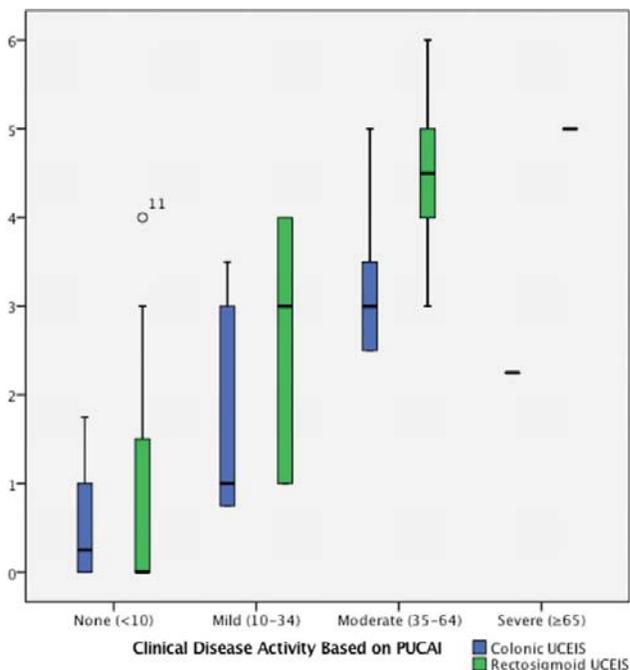


Figure 1. Box plots illustrating the distribution of the rectosigmoid and pancolonic UCEIS per disease activity category based on PUCAI.

Table 1. Spearman correlations between traditional and pancolonic UCEIS and clinical and biochemical markers of UC activity

	Rectosigmoid UCEIS	Pancolonic UCEIS
Clinical physician global assessment	0.65 (p<0.001)	0.71 (p<0.001)
PUCAI	0.82 (p<0.001)	0.79 (p<0.001)
Fecal calprotectin	0.70 (p<0.001)	0.62 (p=0.003)
C-reactive protein	0.58 (p=0.005)	0.39 (p=0.07)

Results: 35 UC patients were enrolled (53% male, median age 12.7 years, 72% pancolitis). Median PUCAI score, FC and CRP were 15 (range 0–75), 1435 (range 29–16782) $\mu\text{g/g}$ and 1.4 (range 0.1–17.1) mg/L , respectively. Spearman correlations are shown in Table 1. Both versions of the UCEIS demonstrated similar correlations with PGA, PUCAI, FC and CRP. Both scores were most highly correlated with PUCAI, and moderately correlated with PGA and FC. Correlations were lower with CRP. The boxplot in Figure 1 illustrates the distribution of the rectosigmoid and pancolonic UCEIS per disease activity category defined by established PUCAI cut-offs. Based on this, the rectosigmoid UCEIS appears to discriminate disease activity better than the colonic UCEIS.

Conclusions: The traditional UCEIS applied to the rectosigmoid region and an adapted pancolonic version performed similarly in this paediatric UC cohort when compared to various symptom-based and biological markers of disease activity. This likely relates to the usually homogeneous pattern of disease in paediatric UC in the rectum and more proximally in the colon.

P128

Diagnostic accuracy of faecal calprotectin in Crohn's disease – Does disease location matter?

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Background: Faecal calprotectin (FC) is a highly sensitive disease activity biomarker in Inflammatory Bowel Disease. However there are conflicting reports on whether the diagnostic accuracy in Crohn's disease (CD) is influenced by disease location. The aim of this study is to undertake a systematic review of published literature to compare the sensitivity and specificity of FC to accurately measure disease activity at small bowel (SB) vs large bowel (LB) location.

Methods: Databases (Medline, Embase, Web of Science and Cochrane) were searched from inception to November 8th 2016 for cohort and case control studies which had data on FC in patients with isolated SB and LB CD. Similarly, relevant conference proceedings were searched from 2005–2016. There was neither age nor language restriction. The reference standard for activity was either endoscopy, magnetic resonance imaging, computed tomography, technetium scan or a combination of these. We excluded studies reporting on post-operative CD or on a specific disease location in isolation. Screening was done independently in duplicate (EGS, RW), with any disagreements resolved by 2 other authors (GWM, SS). EGS & GWM independently completed data extraction form. To assess the risk of bias; EGS & GWM used QUADAS-2, a research tool to check the quality of systematic reviews of diagnostic accuracy studies. Any disagreement was resolved by consensus with co-authors. Communication was undertaken with all lead authors in order to obtain miss-

ing data sets. Whenever possible, sensitivities and specificities were obtained from the raw data or as reported in the publication.

Results: 5619 records were identified at initial search. 2098 duplicates were removed and 3521 records were screened. From the latter, 61 full text articles were then assessed for eligibility. 45 studies were later excluded and 16 studies were included in the final review, with sensitivities and specificities per disease location available from seven studies. The sensitivity of FC in the SB location ranged from 42.9% to 100% with a median of 75%, while that in the LB location ranged from 78.9% to 100% with a median of 94%. FC specificity in the SB location ranged from 50% to 100% while that in the LB location ranged from 28.6% to 100% with similar median specificities of 75% and 71% respectively.

Conclusions: The sensitivity of FC to accurately measure disease activity for CD in the SB appears to be lower than that in the LB. Limitations of the study include heterogeneity associated with the cut offs of FC, disease spectrum, study design, gold standard used and quality of studies as well as insufficient raw data.

P129

Persistent intestinal inflammation leads to surgical intervention in Crohn's patients: a nested case-control study

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Background: Disease flares and hospitalisations have been associated to the need for surgery in patients with Crohn's disease (CD). Endoscopically evident intestinal inflammation one year after diagnosis has been associated with poorer outcomes while a "top down" therapy has been shown to be more beneficial than a step-up approach. Assessing for mucosal healing endoscopically may not be feasible though in daily, routine practice while further evidence is required to support the argument that treating to target alters the disease course. In this study, we aimed to test the hypothesis that ongoing intestinal inflammation as measured by the non-invasive biomarker faecal calprotectin (FCAL) is associated with surgical resection in CD.

Methods: From a large IBD cohort of patients currently under follow up at King's College Hospital, London, UK, we identified all the CD patients who were diagnosed locally and had serial FCAL in the context of their routine care (at routine appointments and during flare-ups). Utilising prospectively kept electronic patient records we identified 20 patients, meeting these monitoring criteria, who required a bowel resection for CD ≥ 12 months after diagnosis (cases) and matched them in a 1:2 ratio with controls based on disease duration. Flares were identified based on the physician assessment and endoscopic or radiologic findings. Continuous variables are summarised as medians followed by interquartile range. The Fisher exact test was used to compare categorical variables, the Mann-Whitney test for continuous variables and the ROC curve for diagnostic analysis.

Results: Median time to surgery was 9.5 years (8, 11) [control group follow up: 8 (7, 10), $p=0.28$]. Right hemicolectomy was the commonest procedure (14, 70%) followed by panproctocolectomy (2, 10%), small bowel resection (2, 10%) and stricturoplasty (2, 10%). Cases and controls did not differ in clinical characteristics or anti-TNF use. Flares and hospitalisations were more common in the cases group

[20 (100%) vs. 23 (56%), $p=0.0005$ and 19 (95%) vs. 19 (48%) $p=0.0002$, respectively]. The baseline median FCAL, between flares, was 348 (240, 656) in cases and 92 (52, 164) in controls ($p<0.001$). When measured at 1 year after diagnosis the FCAL (FCAL1) was 549 (52, 1115) and 68 (26, 184) respectively ($p<0.001$). The area under the curve for FCAL1 to predict surgery was 0.83, 95% CI (0.73, 0.95) while a cut off at 600 μ g/g provided the highest likelihood ratio [18 (15, 69)].

Conclusions: Persistent intestinal inflammation is associated with flares, hospitalisations and surgery. Our results suggest that controlling intestinal inflammation in CD may alter the natural course of the disease. FCAL performed one year after diagnosis may identify high risk patients.

P130

Ingestion of 100ml and 300ml blood mimicking upper gi bleeding leads to significant calprotectin elevation in healthy volunteers – results from the "Vampire study"

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Background: Faecal calprotectin (fC), a calcium binding protein abundant in neutrophils, is increasingly gaining importance as a noninvasive biomarker for intestinal inflammation. It correlates with histological and clinical activity in inflammatory bowel disorders (IBD) and predicts IBD relapse. However, gastrointestinal (GI) bleeding might induce elevated fC levels, erroneously suggesting intestinal inflammation. To the best of our knowledge, the interference of intraluminal blood in the GI tract on fC values has not yet been systematically assessed.

Methods: 15 healthy volunteers (HV) (mean age 25 years, range 23–33 years) without GI symptoms or known GI disease and normal fC baseline values ingested 100 and 300ml of their own blood in a randomized order by drinking or via nasogastric tube, with a 28 day wash out period. fC and fecal occult blood test (FOBT) as well as the occurrence of visible melena were assessed at baseline, on day 0–7 and 14. fC was measured by a commercially available particle-enhanced turbidimetric immunoassay (Buehlmann Laboratories Ltd, Switzerland). fC >50 μ g/g was defined elevated.

Results: Ingestion of blood was tolerated well by all HV with only slight symptoms such as nausea in 7/15 HV (46%), lasting <24 hours. Melena was reported by all 15 HV after 300ml and by 10 out of 14 HV after 100ml blood ingestion (71%). Upon ingestion of 300ml blood mean fC levels rose significantly within 5 days compared to baseline ($p=0.0025$) and at least one fC value above 50 μ g/g was observed in 9/15 (60%) of HV.

Increase in fC levels after ingestion of 100ml was also significant over baseline ($p=0.028$); calprotectin levels above 50 μ g/g were observed in 7/15 (46%) of HV. Pronounced increases in fC levels above 200 μ g/g were rarely observed (1 individual (6%) after 100ml, none after 300ml ingestion).

FOBT testing became positive in 14/15 (93%) after 300ml and 6/14

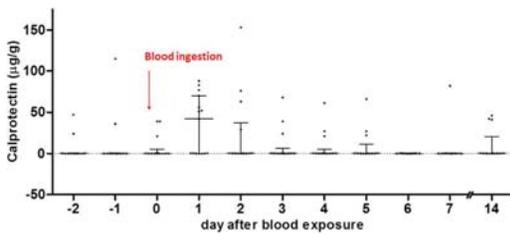


Figure 1. Scatter dot plot with median (wide line) and interquartile range (narrow line) of fecal calprotectin values on each day after 300ml blood ingestion.

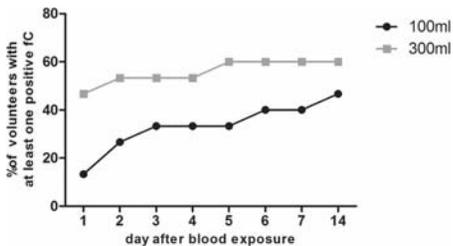


Figure 2. Cumulative fraction of patients with at least one elevated fecal calprotectin test (>50µg/g) after ingestion of 100ml (black dots) and 300ml (grey squares) blood.

(40%) after 100ml blood, respectively. FOBT and fC levels showed a positive correlation, fC levels being significantly higher in FOBT-positive samples than FOBT-negative ($p < 0.0001$).

Conclusions: Ingestion of 100ml and 300ml blood led to significant fC rise in the majority of participants. Very high fC levels (>200µg/g) were rarely observed (6% of participants). We conclude that upper GI-Bleeding should be considered as a potential reason for otherwise unexplained mild fC elevation.

P131

Fecal micro-RNAs indicate disease activity in ulcerative colitis

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Background: micro-RNAs (miRNAs) are promising biomarkers for personalised medicine owing to their tightly regulated expression and their stability in extracellular environments, suitable with non-invasive sampling methods. In this study, we investigated the expression of fecal miRNAs in Crohn's disease (CD), ulcerative colitis (UC) and *Clostridium difficile* infection (CDI).

Methods: A Nanostring screen for 800 different human miRNAs was applied to stool samples from 6 controls and 6 active CD patients. Levels of selected miRNAs were further measured by RT-qPCR in stool samples from 24 controls, 23 CD, 24 UC, and 8 CDI patients; in intestinal biopsies from 10 controls, 18 CD, and 23 UC patients; and in serum samples from 29 controls, 30 CD and 20 UC patients.

Results: 97 different miRNAs were detected in fecal samples, with miR-1246 being the most prominent miRNA in both controls and patients. A distinct fecal miRNA profile, with higher levels of miR-223 and miR-1246, was observed in the most active CD patients with colonic involvement. RT-qPCR indicates that expression levels of these two miRNA are mostly elevated in UC patients while levels of fecal miR-1246, but not miR-223, are higher in CDI pa-

tients. In UC patients, fecal miR-223 and miR-1246 levels correlate with fecal Calprotectin ($r_s = 0.61$ and 0.51 , $p < 0.001$) and CRP ($r_s = 0.56$ and 0.46 , $p < 0.001$). Fecal miR-223 and miR-1246 levels very efficiently differentiate between endoscopically inactive (endoscopic Mayo Score 0/1) versus active disease (endoscopic Mayo Score 2/3). ROC curve analysis show the following area under the curve (AUC) results: Calprotectin 0.95, $p < 0.001$; miR223 0.92, $p < 0.001$; CRP 0.88, $p < 0.01$; miR-1246 AUC 0.87, $p < 0.01$; SCCAI 0.83; $p < 0.01$. In biopsies, only miR-223 expression is increased in UC patients and serum levels of miR-223 and miR-1246 are not different between controls and patients.

Conclusions: Fecal miR-223 and miR-1246 are markers of active UC and fecal miR-223 has the potential to differentiate between active UC and CDI.

P132

Cooperation to improve quality of IPAA surgery in IBD: south Netherlands experience

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Background: Total proctocolectomy and ileal pouch-anal anastomosis (IPAA) for IBD is low volume surgery. In The Netherlands from 2009 quality and volume indicators have been defined for low volume oncologic procedures and since 2015 also for IPAA surgery following the ECCO guidelines. The two South Netherlands IBD centers (The Zuyderland Hospital [ZH], Maastricht University Medical Center [MUMC]) started to collaborate to meet the volume norm on IPAA surgery and deliver optimal quality. The present study describes the outcome of surgery in this cooperation and aims at defining further priorities in surgical care.

Methods: Data were collected from the prospective South Limburg IBD cohort which includes all newly diagnosed IBD patients of the two centers since 1991. All non-surgical data and the core surgical data are included in this database. More specific surgical information was collected retrospectively.

Results: Fifty-four patients were included that received an IPAA between January 2010 and December 2015. In 2015 the volume norm of >10 was reached, contrary to the 3 preceding years. Mean age was 39.6 (17–82) and mean disease duration 7.5 yrs (1–22.5). 35 patients (62%) previously underwent a subtotal colectomy, 13 in an open procedure, 22 laparoscopically. 41 (76%) of IPAA's were performed laparoscopically, 93% were stapled and in 44% a temporary ileostoma was performed. Three ileostomies were given due to postop complications. Postop diagnosis was UC in 52 patients, IBD-U in 1 and CD in 1. Major early complications were small bowel obstruction ($n=14$), partial anastomotic dehiscence ($n=7$), pouch bleeding ($n=2$), distal anastomotic stricture occurred in 9 patients. Pouch failure occurred in 5 patients resulting in 4 permanent ileostomies, two of which due to chronic pouchitis. Conversion from laparoscopic to open procedure was positively associated with anastomotic dehiscence. Stool frequency at follow-up was median 7.6/24hrs; 41% of patients used no antidiarrheal medication. Full continence was

achieved in 77%. No data on sexual function could be retrieved. From 2015, one team (EB and LS) operated all patients. Incidence of leakage seemed lower after cooperation, although conclusions require a larger cohort.

Conclusions: The cooperation resulted in increase from a low- to a medium volume center. Several focus points have been defined based on the results observed: progressive cooperation and optimal multidisciplinary approach to optimize timing of surgery and outcome; continue implementation of novel techniques; prospective registration of all surgical parameters including quality of life and sexuality; evolve as a regional referral and expert center and increase patient numbers.

P133

A novel candidate pathway for development of neoplasms with serrated morphology in patients with ulcerative colitis

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Background: Patients with ulcerative colitis (UC) are at increased risk of development of colorectal cancer (CRC). CRC in patients with UC, termed colitis-associated CRC (CAC), develops through an inflammation–dysplasia–carcinoma sequence. Neoplasms with serrated morphology have been reported in UC patients; however, their features are yet to be fully elucidated. Here, we clarify the clinical, histopathological and molecular features of such neoplasms and investigate a possible novel neoplastic pathway in UC patients.

Methods: We analysed seven neoplasms with serrated morphology that had been endoscopically or surgically resected from five patients with UC and compared them with those of 35 other patients with canonical CAC/dysplasias (including 13 CACs, 13 high grade and nine low grade dysplasias). We reviewed these patients' clinical features and performed morphological, histopathological and immunohistochemical analyses of these lesions. We used a laser micro-dissection

system (LMD) to accurately isolate atypical glands from formalin-fixed paraffin embedded (FFPE) sections and frozen samples and precisely determine genomic alterations. Genomic DNA was eluted and gene mutations studied by using next-generation sequencing (NGS) analysis, a >2% mutation frequency being defined as positive.

Results: All neoplasms with serrated morphology were located in chronically inflamed mucosa. All neoplasms were of elevated type; the median size was 15 mm (range, 5–40). Their pathological features were atypical of canonical CAC/dysplasias, sporadic sessile serrated adenoma/polyps (SSA/P) or traditional serrated adenomas (TSA). The patients with neoplasms with serrated morphology at diagnosis of UC were significantly younger than those with canonical CAC/dysplasias (median 26.4 years [range, 19.1–62.7] vs. 36.6 [15.3–66.1], $p=0.06$). Immunohistochemical analysis showed most neoplasms with serrated morphology and CAC/dysplasias had similar mucin expression profiles. Genomic mutations were identified in three neoplasms with serrated morphology (one adenocarcinoma *in situ* with SSA/P, two TSAs) by NGS. KRAS mutation was detected in all of them. APC and BRAF mutations were not detected and TP53 mutation was found in only one case (adenocarcinoma).

Conclusions: In this study, neoplasms with serrated morphology in association with UC developed in chronically inflamed mucosa, and had atypical macroscopic and microscopic morphology and genomic mutations. These findings, suggest that neoplasms with serrated morphology in patients with UC do not develop through an inflammation–dysplasia–carcinoma sequence, but through an alternative novel serrated neoplasia pathway.

P134

Point of care ultrasound accurately distinguishes inflammatory from non inflammatory disease in patients presenting with abdominal pain and diarrhea

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Background: There is a considerable overlap between symptoms of irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). It is important to have access to non-invasive, safe, low cost diagnostic tools to differentiate IBD from functional abdominal symptoms such as IBS, and avoid unnecessary invasive investigations including endoscopy. Point of care ultrasound (POCUS) of the bowel is not widely accessible in North America, but is routinely used in Europe. The aim of this study was to evaluate the accuracy of

Abstract P134 – Table 1. Demographics

Demographic Information:	
Number of Patients (N)	86
Female	59(69)
Male	27(31)
Median Age (IQR)	36 (28-48)
Median BMI (N=31)	22.7
Clinical Information:	
Reported Symptoms	
Diarrhea	66 (76.7%)
Abdominal Pain	54 (62.8%)
Weight Loss	16 (18.6%)
Nocturnal Symptoms	13 (15.1%)
Incontinence	10 (11.6%)
Median CRP (N=54)	2.5
Median CRP (Patients with Endoscopic Activity) (N=8)	6.90

Abstract P134 – Table 2. Sensitivity, specificity, accuracy, PPV and NPV of POCUS relative to ileocolonoscopy

	Overall	Ileum	Colon
Sensitivity% (CI%)	83.33 (55.20-95.30)	100.00 (64.57-100.00)	60.00 (23.07-88.24)
Specificity% (CI%)	100.00 (95.06-100.00)	100.00 (95.06-100.00)	100.00 (95.06-100.00)
Accuracy% (CI%)	97.67 (91.91, 99.36)	100.00 (95.47-100.00)	97.47 (91.23-99.30)
PPV% (CI%)	100.00 (72.25-100.00)	100.00 (64.57-100.00)	100.00 (43.85-100.00)
NPV% (CI%)	97.37 (90.90-99.28)	100.00 (95.06-100.00)	97.37 (90.90-99.28)

POCUS in the detection of luminal inflammation compared to gold standard ileocolonoscopy in patients presenting with undifferentiated lower gastrointestinal symptoms.

Methods: A prospective, single-center study of consecutive patients presenting to the GI clinic with symptoms high risk for IBD were evaluated to differentiate IBD from IBS. POCUS was performed, clinical data recorded and C-reactive protein measured prior to ileocolonoscopy, which served as the gold standard. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for POCUS.

Results: Eighty-six patients with undifferentiated symptoms of diarrhea (76.7%), abdominal pain (62.8%) and weight loss (18.6%) were evaluated. Nocturnal symptoms (15.1%) and incontinence (11.6%) were infrequent (Table 1). Ileocolonoscopy was negative in 72 patients confirming IBS, 2 patients had diverticulosis, while 12 revealed findings of active endoscopic disease consistent with IBD, confirmed on pathology, 11 with CD and 1 with UC, as well as microscopic colitis (N=8), diverticulosis (N=1), ischemic colitis (N=2) and one solitary rectal ulcer. The overall sensitivity, specificity, PPV and NPV of POCUS were 83.0%, 100%, 100%, and 97.37%, respectively. In cases where POCUS was positive, POCUS predicted the severity of inflammation as seen on ileocolonoscopy accurately with correlate findings of 90% (9/10 cases accurately predicted severity). The accuracy of POCUS for predicting IBD was much better than CRP, as the sensitivity of CRP was only 37.5%, specificity 76.2%. Wait time for endoscopy for patients with a positive POCUS was shorter with a median of 3.5 weeks, compared to 4 weeks for those with a negative POCUS.

Conclusions: Bedside POCUS is a useful triage tool, better than CRP in disease prediction, helpful to accurately detect the presence and severity of inflammation in the bowel and thus differentiate IBD from IBS. The detection of ileal disease was more accurate compared to colonic disease and future studies should be completed with addition of fecal calprotectin to optimize detection rates and overall accuracy.

P135

The early course of Crohn's disease: prognostic and treatment modalities during the first year of disease

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Background: Crohn's disease (CD) is a chronic immune-mediated disorder with a high risk for surgery. Although the natural history of CD has been extensively described in previous studies, the evolution during the first year after diagnosis has not been adequately described. The aim of this study was to Crohn's disease (CD) is a chronic immune-mediated disorder with a high risk for surgery. Although the natural history of CD has been extensively described in previous studies, the evolution during the first year after diagnosis has not been adequately described.

Methods: Retrospective analysis of a cohort of patients with an established diagnosis of CD from a tertiary referral center. Demographic and clinical data were retrieved and compared for prediction of outcomes across two time cohorts (before and after 2005).

Results: 648 patients with CD, mean age 31.3±13.9 years, were included in this study. In the first year following diagnosis, 179 (27.6%) required therapy with thiopurines, 43 (6.6%) with an anti-TNF, and 147 (22.7%) underwent surgery. Patients with perianal disease were more likely to receive a thiopurine (OR 1.977 95% CI 1.370–2.852) or an anti-TNF (OR 2.190 95% CI 1.162–4.125) on the first year of disease, but not patients with younger age at diagnosis, stricturing/penetrating behavior, and upper gastrointestinal disease. Smoking (OR 1.029 95% CI 1.012–1.046) and structuring/penetrating behavior (OR 9.556 95% CI 5.526–16.526), but not age at diagnosis, disease location or perianal disease were associated with the need for early surgery. Patients diagnosed before 2005 were less likely to receive thiopurine (12.9% versus 39.3%, p<0.001) or anti-TNF therapy (1.4% versus 10.4%, p<0.001). This fact could explain the fact that although patients diagnosed before and after 2005 showed similar rates of first surgery (25.0% versus 20.6%, p=0.110), a second surgery was less likely in patients diagnosed after 2005 (OR 0.172 95% CI 0.054–0.552, p=0.003).

Conclusions: There is a high heterogeneity in the severity and management of patients with CD during the first year of disease. Early initiation of immunosuppressive therapy is associated with a lower incidence of postsurgical recurrence.

P136

Sporadic adenomas in IBD patients over 50 years old and average risk population – Is there a difference?

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Background: Adenoma is the major precursor of colorectal carcinoma (CRC) in general population.

Patients with ulcerative colitis (UC) and Crohn's disease (CD) are at risk of developing CRC in relation to chronic inflammation. However, they can also develop adenomas, but the prevalence of sporadic adenomas in inflammatory bowel disease (IBD) patients is unknown.

Methods: We performed a retrospective medical review of all colonoscopies performed in our center in IBD patients (UC ou CD) ≥50 or more years old between January 2008 and November 2016.

The presence of colitis or proctitis was evaluated, as well as the use of IBD medication.

The prevalence of SA in IBD patients were compared with average-risk screening colonoscopy patients in a 3: 1 ratio over the same time period. The number and time intervals between colonoscopies were reviewed. For the prevalence calculation, we considered the first colonoscopy performed ≥50 years old.

Patients with personal or family colon cancer history and personal polyp history were excluded.

Results: Two hundred and thirty-six patients with IBD, 126 male (53.4%) and 110 female (46.6%), 63.6% with UC and 36.4% with CD, performed at least one colonoscopy during the time period, 179 (75.8%) had two or more procedures during this period.

Nine hundred and fifty-three patients underwent screening colonoscopies, and 708 patients were randomly selected to comparison.

The mean patient age was 57.1 years old for those with average risk and 56.4 years old for those with IBD ($p=0.22$).

There were no significant statistically differences between the 2 groups regarding the variable gender.

SAs were detected in 30 patients with IBD (12.7%), 23 in UC (15.3%) and 7 in CD (8.1%) patients, and in 206 (30.3%) patients with average risk, $p<0.001$.

There was no significant difference in the rate of SAs according to type of IBD (UC vs CD ($p=0.1$) or age ($p=0.98$)).

There were no significant statistically differences in the prevalence of SAs and the presence or absence of colic inflammation, 14.5% vs 10.5%, respectively, $p=0.43$.

The majority of patients with IBD took IBD medication (77.1%), most of them with mesalamine.

Conclusions: We found a significantly lower prevalence of sporadic adenomas in patients over 50 years old with IBD than in control patients. This may reflect the effect of IBD medications in stabilizing the mucosa. Further studies are needed to corroborate our findings and determine which factors in IBD influence adenoma-carcinoma sequence.

P137

Ulcerative colitis in the elderly – Different disease course?

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Background: The reported prevalence of ulcerative colitis (UC) in patients aged 60 years or older is 15%. Several studies have evaluated the differences between disease course in younger and older patients.

Methods: Retrospective analysis of patients with UC followed in an inflammatory bowel disease outpatient clinic, with follow up >2 years. Patients were divided in 2 groups; patients with UC diagnosed before the age of 60 years-old (adult-onset UC) and patients with diagnosis with ≥ 60 years (late-onset UC). Demographic data, disease extent, colectomy rates, need for hospitalization, treatment and infections were evaluated and compared between the two groups. Statistical analysis performed using SPSS 21, considering statistical significance, $p<0.05$.

Results: 115 patients, 60 males, 29 patients (25%) in the late-onset group. Mean time follow-up was 12,7 years in the adult-onset versus 9,8 years in the late-onset group. There were no differences between the 2 groups regarding family history of IBD ($p=0.712$) and smoking habits ($p=0.193$). Regarding disease extent, in the adult-onset group 25% had proctitis, 48% had left-sided disease and 27% had extensive disease versus 28%, 48% and 24% respectively in the late-onset group ($p=0.932$). Progression of disease extent occurred in 9.6% in the late-onset group and 10.3% in the late-onset group ($p=0.912$). Colectomy was performed in only 1 patient, with adult-onset UC.

There were no differences in the need for hospitalization (29% in the adult-onset; 21% in the late-onset group; $p=0.379$) or in the corti-

costeroids use (57% versus 48% respectively, $p=0.315$). There was a significant higher use of immunosuppression in the adult-onset group (27%) than in the late-onset group (6.9%), $p=0.025$. Biologic therapeutic was used in 10.6% in the early onset group and 3.4% in the late-onset group but there was no statistical difference $p=0.243$. There were no differences in the Cytomegalovirus and *Clostridium difficile* infections ($p=0.658$; $p=0.904$, respectively).

Conclusions: Although several studies have shown that late-onset UC has a more favorable clinical course, in our series there were no significant difference in the disease course between the late-onset and adult onset, except for the use of immunosuppression, which was higher in the adult-onset group.

P138

Does depression at IBD diagnosis impact on disease outcomes in Crohn's?

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Background: There is growing interest in how psychological disturbances can impact on disease activity in IBD through neuro-humoral mechanisms, but research in this field is limited and conflicting. The impact of co-existing depression at the time of IBD diagnosis and its impact on subsequent disease activity through IBD medication usage and surgery has not previously been studied. We aimed to investigate whether baseline depression in patients diagnosed with Crohn's disease (CD) affects the requirement for steroids, thiopurines and intestinal surgery using a nationally representative UK research database.

Methods: We used the Clinical Practice Research Datalink to identify incident cases of patients with CD between 1998–2014. Demographic data including age at diagnosis, sex, body mass index, social and smoking status were extracted as well as prescription data for IBD medications including 5-aminosalicylic acids (5ASA), corticosteroids (CS) and thiopurines (TP). Additionally, prescribing data for the most commonly used anti-depressant medications (ADM) were obtained. A patient was considered to have baseline depression if they had either a prescription for ADM or a Read code for depression within the period 6 months prior to and up to 3 months after the formal IBD diagnosis using an established methodology [1]. We compared the proportion of patients receiving 5ASA, CS and TP at 6 and 12 months from IBD diagnosis between patients with and without a diagnosis of depression at diagnosis. We generated a Cox regression model to estimate the risk of CS use, TP use and requirement for surgery in patients with baseline depression.

Results: We identified 6237 patients with CD in the study period. Depression at IBD diagnosis was present in 13%. Amongst CD patients with depression at diagnosis there was a higher proportion of females (72% vs 51%, $p<0.001$), a higher proportion of smokers (39% vs 29%, $p<0.001$) and a higher proportion of IBS co-diagnosis (25% vs 16%, $p<0.001$) compared to those without depression. There were no significant differences in medication usage at 6 months between patients with and without baseline depression (5ASA: 45% vs 47%, CS: 19% vs 20%, TP: 17% vs 16%). Similarly, there were no differences in medication usage at 12 months between patients with and without baseline depression (5ASA: 48% vs 50%, CS: 24% vs 25%, TP: 21% vs 22%). In the multivariate regression analysis, depression at baseline was not significantly associated with CS use (HR 0.93, 95% CI 0.72–1.19, $p=0.55$), TP use (HR 1.13 95% CI 0.94–1.35, $p=0.20$) or intestinal surgery (HR 0.72 95% CI 0.48–1.10, $p=0.13$).

Conclusions: In patients with CD, depression at IBD diagnosis does not appear to impact on medication usage or the need for surgery in the first year after diagnosis.

References:

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P139

Articular manifestations in inflammatory bowel disease – results from Northeastern Romania

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Background: The presence of extraintestinal manifestations (EIM) in inflammatory bowel disease (IBD) is a common and well known finding. Among these, joint involvement is one of the most frequently associated.

Methods: Using the national database IBD Prospect, we conducted a prospective case-control study that included 325 patients diagnosed with Crohn's disease (CD) or ulcerative colitis (UC). Between these cases, 81 (24.92%) were classified in the group CD, 242 (74.46%) having UC and 2 cases (0.62%) were classified as having undifferentiated colitis. Among them, 30 patients (9.23%) had EIM including 24 cases of articular manifestations. Regarding joint events, we found 5 cases of arthritis, 10 cases having axial manifestations like sacroiliitis or ankylosing spondylitis and 9 cases of multiple EIM including articular damage.

Results: In both study arms, articular manifestations occupy the first place into EIM (14/17 CD vs 10/13 UC, 82.35% vs 76.92%, p=0.927). Into the group of CD patients, joint manifestations first correlated with the ileo-colonic form of CD (8/14; 57.14%) followed by the colonic involvement (4/14; 28.57%). Into the UC arm, joint damage was associated with an extended colonic involvement (4/10; 40%) followed by proctitis and left side colitis. Both groups of patients with articular manifestations were associated with a moderate form of IBD activity - 10/14 CD vs 5/10 UC (71.43% vs 50%, p=0.199).

Conclusions: In Northeastern Romania predominate UC cases. Most patients included in this study and having EIM belong to CD phenotype. Articular manifestations occurred at a higher frequency in patients with CD as compared to those diagnosed with UC. The most common articular manifestation is the axial involvement, followed by peripheral arthritis.

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Use of vedolizumab in a transplanted liver patient: a case report of the first experience in a liver transplant referral center in Argentina

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Background: Vedolizumab is a humanized monoclonal antibody directed against the $\alpha 4\beta 7$ integrin and it is indicated for induction and maintenance of remission of moderate to severe inflammatory bowel disease (IBD), either naive or refractory to anti TNF agents. Little is known about the use of Vedolizumab in patients with liver transplantation.

Methods: We report the first patient with IBD and liver transplantation being treated with vedolizumab in a liver transplant referral center in Latin America.

Results: A 20-year-old male with a history of ulcerative colitis (UC) and primary sclerosing cholangitis, both diagnosed in the childhood, referred for liver transplantation in May 2012 to our hospital. He had a pancolitis since he was 6 month old treated with mesalamine, with frequent relapses and treatments with corticosteroids. He presented a flare-up of severe active colitis in September 2015 in France that required treatment with infliximab, with lost of response after 2 months. He was switched to vedolizumab in December 2015 with a positive clinical and endoscopic response. His blood tests done previously and after the vedolizumab infusion showed an improvement of inflammatory parameters and stability of the liver enzymes. In April 2016, he returned to Argentina and a control colonoscopy was performed showing remission of UC (Mayo score 1). So far he is still receiving vedolizumab through an especial regimen of compassionate use, because this drug has not been approved yet by the local health authorities.

Conclusions: Little is known about the use of vedolizumab in liver transplantation patients. A case series of 10 pre and/or post liver transplantation patients has recently been published showing that vedolizumab was well tolerated. In our experience we conclude that vedolizumab could be a safe option for treating refractory ulcerative colitis in liver transplant patients. More experience is needed to determine the efficacy and safety of this drug in these particular complex group of patients.

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Characteristics and outcomes of acute colitis presenting via the emergency department in an Irish academic medical centre

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Background: A significant proportion of Emergency Department presentations with gastrointestinal symptoms, resulting in the performance of cross-sectional imaging, receive a radiological diagnosis of colitis. Data are few on the demographics and natural history of this patient cohort. We aimed to review the characteristics, outcomes and final diagnoses of new emergency department presentations with colitis diagnosed on cross-sectional imaging

Methods: An institutional radiology database was interrogated to identify cross-sectional imaging, which demonstrated a colitis, performed on patients admitted in 2015 via the Emergency Department of St James's Hospital. Radiology reports were reviewed to confirm the presence of colitis and exclude patients with known diagnoses of gastrointestinal disease. Baseline demographic data, information on inpatient investigations, final diagnoses and outcomes were recorded.

Baseline data was analyzed for to look for significant predictors of mortality or adverse outcomes. Adverse outcomes were defined as death, colectomy, or ICU admission during the inpatient stay.

Results: N=118 subjects were deemed eligible for inclusion: Age [median, range] 64 years [16.9–101.2]; 67% female. Proportions admitted under medical, surgical, gastroenterology and other services were 33%, 34%, 9% and 25% respectively. Median [range] admission duration was 10 days [1–241]. Laboratory parameters (median [range]) at admission were WCC $9.7 \times 10^9/L$ [0.1–55], haemoglobin 11.8 g/dL [5.8–17.7], platelets $261 \times 10^9/L$ [10–757], albumin 34 g/L [14–71], CRP 54 mg/L [1–307] and lactate 1.8 mmol/L [0.7–15]. Final colitis diagnoses were: undefined (35%), infectious (25%), reactive to other intra-abdominal pathology (13%), new IBD diagnosis (11%), ischaemic (9%), chemotherapy-associated (3%), diverticular (3%) and medication associated (1%). Colonic perforation, colectomy and mortality occurred in 1%, 5% and 13% of the cohort respectively. No clinical or laboratory variable associated significantly with mortality. Univariate analysis of baseline data showed Male Gender, Haemoglobin, Albumin and Lactate associated with adverse outcomes.

Table 1. Univariate analysis – Baseline clinical and biochemical factors associated with adverse outcome (n=118)

Variable	Odds Ratio (95% CI)	p value
Age (years)	1.00 (0.98–1.03)	0.530
Male gender	3.09 (1.23–7.77)	0.019
WCC	1.00 (0.95–1.06)	0.990
Haemoglobin	0.67 (0.52–0.87)	0.002
Platelet count	1.00 (1.00–1.00)	0.503
CRP	1.00 (0.99–1.01)	0.95
Albumin	0.86 (0.80–0.93)	0.0002
Lactate	1.65 (1.13–2.42)	0.009

Conclusions: There is a broad differential for patients presenting with an acute colitis via the Emergency Department with a significant proportion having no clearly defined aetiology following hospital admission. Considerable morbidity and mortality is observed in this patient cohort. Male gender, serum albumin and lactate concentrations are associated with adverse outcomes.

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Postoperative course of laparoscopic subtotal colectomy is not affected by preoperative medical treatment in patients with acute colitis complicating inflammatory bowel disease

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Background: Medical treatment of severe acute colitis (SAC) complicating inflammatory bowel disease (IBD) is given in order to avoid surgery, but in 20 to 50% of cases colectomy remains necessary. This study aimed to determine the impact of the different lines of medical therapy (i.e. steroids, anti-TNF or ciclosporin) on postoperative course after laparoscopic subtotal colectomy (LSTC) for SAC complicating IBD.

Methods: All the patients who underwent LSTC for SAC were included, and divided into 2 groups: those who presented with postoperative morbidity (Group A) and those with an uneventful course (Group B). Preoperative physical, endoscopic and radiological data, and medical treatment were compared between groups.

Results: From 2006 to 2015, 65 patients (32 males, median age =35

[17–87] years) operated for SAC were included. Postoperative morbidity occurred in 20 patients (31%, Group A), and was mainly represented by surgical morbidity (n=16), including ileus (n=10), stoma-related complications (n=8) and intra-abdominal abscess (n=5). Major morbidity was noted in 8/65 patients (12%). No mortality occurred in the two groups.

Number of previous episode of SAC, Lichtiger score, endoscopic and radiological evaluation were similar between groups. There was no significant difference between groups regarding preoperative steroid treatment alone (40 vs 29%, p=0.57), steroids with another immunosuppressive drug (40 vs 35%, p=1.00) or steroids with two other immunosuppressive drugs (10 vs 9%, p=1.00).

Conclusions: This study suggests that postoperative course after LSTC for SAC is not affected by any preoperative medical treatment.

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From biopsies to fecal samples: challenging *Faecalibacterium prausnitzii* and related phylogroups as potential biomarkers for IBD

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Background: Both, *Faecalibacterium prausnitzii* (Fpra), and Fpra phylogroups (PGH-I and PHG-II), combined with *Escherichia coli* (Ecoli), are an accurate biomarker to distinguish healthy (H) from diseased, and also among different clinical manifestations and disease locations (López-Siles et al, 2016). The purpose of this study was to verify this capability in faecal samples, in order to develop a non-invasive system for diagnostic support.

Methods: A Spanish cohort consisting of 23 IBD (10 CD and 8 UC) and 12 H was enrolled. Sixty seven faecal samples (26 CD, 30 UC and 11 H) fecal samples were obtained during their treatment. Fpra total, PHG-I, PHG-II and Eco abundances were quantified by qPCR. **Results:** Fpra and PHG-II were less abundant in IBD patients, compared with healthy subjects (p=0.046 and p=0.009, respectively). In turn, abundance of Ecoli was higher in IBD patients (p=0.007) (with sensitivities and specificities between 60%-85%). As compared to H, CD patients displayed lower abundance of Fpra I, PHG-I and PHG-II (p=0.014, 0.045 and 0.004) and higher of Eco (p=0.001). Finally, PHG-II loads were lower for Fpra and higher for Eco in samples from UC patients (p=0.050 and p=0.047).

Concerning disease localization, significant differences were observed in CD. Fpra and PHG-I abundances were lower in the colon (p=0.046 and p=0.026), whereas PHG-II was significantly higher in the ileum (p=0.032).

UC and CD with colon affectation could also be distinguished; a lower abundance of PHG-I and Eco (p=0.020 and p=0.048) was observed in samples of colon CD, with sensitivities and specificities between 70%-100%.

Conclusions: Fecal loads of total Fpra and related phylogroups correlate with those describe on biopsy samples.

Ecoli and PHG-I seem to be good markers to discriminate between patients with UC and CD with colonic affectation.

References:

[1] Mireia López-Siles, (2016), Changes in the Abundance of *Faecalibacterium prausnitzii* Phylogroups I and II in the Intestinal

Mucosa of Inflammatory Bowel Disease and Patients with Colorectal Cancer, Inflammatory Bowel Diseases

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Protozoa and bacterial infections are relevant for clinical outcomes in ulcerative colitis: a study from Latin American country

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Background: Few epidemiological studies have shown that enteric infections are associated with exacerbations of ulcerative colitis (UC). Patients with active UC have higher frequency of parasitic stool pathogens. The aim of this study was to evaluate the frequency of stool pathogens including: parasites, organisms grown in stool cultures and presence of *Clostridium difficile* in Mexican patients with UC, and clinical outcomes related to the presence of pathogens.

Methods: We studied 303 with diagnosis confirmed UC patients from the IBD Clinic from the period of January 2014 and December 2015. Disease extension, severity, medical treatment, extra-intestinal manifestations, hospitalizations, length of hospital stay, and stool tests were analyzed. Statistical analysis was performed by SPSS v.21 program. A P value <0.05 was considered significant.

Results: A total of 303 UC patients were evaluated from 2007 to 2016. We evaluated 160 men and 143 women, with a mean age of 46.6±14.2 years-old. 35 active and 368 remission patients were found. 46.5% of patients had pancolitis. 247 of 303 patients had stool tests performed. 61.4% of active patients had a positive stool test. A positive parasite test (51.6% of active patients) was associated to: current activity (p=0.002) and severity (p=0.006); number of parasites isolated in test had a trending association to UC extension (p=0.051). Most isolated parasite was *Blastocystis hominis* in 15.8%. A positive stool culture was found in 13.2% of patients, most isolated pathogen was *Clostridium difficile* in 4.6% of patients. Having any positive stool test was associated to current activity (p=0.001) and severity (p=0.003), and with a trend in need for hospitalization caused by exacerbation (p=0.056). We found 85 steroid-dependent patients, of which 38 had a positive stool test (p=0.14), and 29 had a positive parasite stool test (p=0.35), with no association. Negative stool test and negative parasite stool test were significantly associated to clinical (p<0.001 & p=0.001), biochemical (p=0.001 & p=0.003) and endoscopic remission (p=0.025 & p=0.018), but not with histological remission.

Conclusions: A high frequency of 61.4% of positive stool tests were found in active UC patients. Presence of stool pathogens was associated to several important clinical outcomes such as activity and severity of UC as well as hospitalizations related to this disease.

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Measuring access and quality of care indicators in inflammatory bowel disease in a tertiary referral center

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Background: To achieve clinical remission and endoscopic healing in inflammatory bowel diseases (IBD) a multidisciplinary approach

combined with optimized patient stratification, monitoring strategies and re-evaluating clinical care pathways is needed constituting to quality of care (QoC). The aim of this study was to evaluate structural, access/process components and link these to outcome quality indicators (QIs) in our tertiary referral IBD center.

Methods: In the first phase structural/process components of our IBD center were assessed, followed by the second phase of formal evaluation of access and management on a set of consecutive IBD patients with and without active disease (248 CD/125 UC, 52/52% females, median age 35/39 years). Ileocolonic location, complicated disease behavior and perianal disease was 62.1, 49.6, and 45.9% of CD patients, 72.1% of UC patients had extensive disease.

Results: Structural components of our IBD center met the requirements (3 gastroenterologists with IBD interest, access to surgeon and radiology, regular multidisciplinary meetings) with the exception of the IBD nurse. Process indicators are part of standard operational processes (e.g. urgent outpatient access for suspected flare, evaluation of newly diagnosed patients, tracking of medications and surgical history, latent TB testing before immunosuppression or biologicals). Initial assessment: all patients underwent a full colonoscopy while ileocolonoscopy/gastroscopy was performed in 81.8/45.5% of CD patients, CT/MRI in 66.1/49.6% of CD patients and pelvic MRI in 83.1% in patients with perianal disease. Patients with a flare (CD/UC: 50.6/54.6%) after 2014, had an outpatient consultation with specialist at the IBD clinic within a median of 1 day with same day laboratory testing and abdominal US, CT scan/surgical consult and change in medical therapy if needed. Medical therapy was changed in 51.9/59.4% of CD/UC patients (initiation of steroids: 41.5/69.8%, AZA: 18.1/7.5% anti-TNF/dose intensification: 29.6/19.7% and 25.5/21.4%). 20.1% of CD patients required any surgery, 1.4% colectomy in UC, 17.3/3.2% of CD/UC patients required hospitalization. A total of 86.7% of CD patients had any imaging evaluation after 2014 (US: 49.7%, CT: 5.6% and MRI: 39.3%, colonoscopy: 45.5%), while 51.1% and 35.9% of UC patients underwent colonoscopy and abdominal US. The median waiting time for non-emergency endoscopy/CT/MRI was 16, 14 and 22 days.

Conclusions: Prospective continuous tracking and formal evaluation of structural, process/access and outcome parameters of QoC in IBD centers is important. Measurement of QIs and patient satisfaction improves healthcare delivery and efficiency and leads to improved patient outcomes.

P146

Primary intestinal Epstein-Barr virus-associated NK/T-Cell lymphoproliferative disorder: a disease mimicking IBD

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Background: Primary gastrointestinal Epstein-Barr virus (EBV)-associated NK/T-cell lymphoproliferative disorder (LPD) (PIEBV+NK/T-LPD) is quite rare. Moreover, it has strong heterogeneity in clinical manifestation and course progression among individuals. In most cases, this disorder mimics the corresponding presentation of inflammatory bowel disease (IBD). It has become a clinical challenge to confirm its diagnosis on time. We summarize and analyze the clinicopathological features and differential diagnosis of 11 Chinese PIEBV+NK/T-LPD in order to raise knowledge about it.

Methods: Patients, who were diagnosed with PIEBV+NK/T-LPD in

West China Hospital between 2014 and 2016, were included in this study. The clinical, endoscopic, surgical and histopathological characters were reviewed and the differential diagnosis was analyzed for these patients.

Results: In total 11 cases with confirmed PIEBV+NK/T-LPD were enrolled. The ratio of male to female was five to six, the median age of diagnosis was 37.3 years and the mean disease course was 2.7 years before a definite diagnosis was confirmed. Initial symptoms mainly included occasional fever (10/11), abdominal pain (8/11), hematochezia (7/11), diarrhea (3/11). At its advanced stage, complications in gut mainly comprised perforation (5/11), hemorrhage (2/11), obstruction (2/11). Endoscopy commonly revealed segmental ulcers or extensive inflammation of mucosa. Terminal ileum and colon were most likely involved.

At early stage, this disorder could present a mild to moderate infiltration of small or medium-sized lymphoid cells in lamina propria. Its main immunophenotypes included positivity for CD3, TIA-1 and Granzyme B and deletion of CD5. *In situ* hybridization was positive for EBER 1/2 in all cases, whereas peripheral blood EBV-DNA and EBV-capsid antigen-IgA were positive in 9/11 and 2/8 cases, respectively. Nine patients had ever been misdiagnosed with ulcerative colitis (UC) (4/9), Crohn's disease (CD) (3/9), or tuberculosis (TB) (2/9) because of mimicking histopathological performance. Moreover, two case who had ever been misdiagnosed as UC was further misdiagnosed as CD. The median endoscopic examination before confirmation of diagnosis was 3.5 times, and even four cases were confirmed until surgical specimens were examined after failure to multiple endoscopies.

Conclusions: PIEBV+NK/T-LPD could be challenging in diagnosis due to its resemblance to IBD endoscopically and pathologically. Thus EBV test and immunophenotype assessment together with repeated endoscopy or even reasonable surgery are essential to make an accurate diagnosis

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Metabolomics discriminate children with Crohn's disease from ulcerative colitis and from healthy controls – preliminary study

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Background: Ulcerative colitis (UC) and Crohn's disease represent inflammatory bowel disease (IBD) with multifactorial pathogenesis. Metabolic profiling might be used to understand interactions between nutrients, the intestinal metabolism and the microbiota composition in these diseases. The aim of our study was to determine the usefulness of untargeted metabolomics in detection of metabolic differences and similarities between children with Crohn's disease (CD) or ulcerative colitis (UC) in comparison to healthy individuals.

Methods: Metabolic fingerprinting of serum samples was estimated with liquid chromatography coupled to mass spectrometry (LC-QTOF-MS) in newly diagnosed children with CD (n=9, median age 14 years), ulcerative colitis (n=9, median age 13.5 years) and controls (n=10, median age 12.5 years). Statistical analysis was used to find metabolic differences between Controls and IBD patients as well as between UC and CD groups. Depending on data distribution t-test

or U-test were used to select significant metabolites. Multivariate statistical analysis was used for samples classification.

Results: Detected metabolites were used to build good quality partial least square discriminant analysis model (R²=0.99, Q²=0.76) which showed clear separation between studied groups. 46 metabolites were significantly discriminating between IBD patients and Controls. Several lysophospholipids – lysophosphatidylcholine (LPC), lysophosphatidylethanolamine (LPE) were found decreased (from 30 to 60%) in IBD patients (p-value 0.005–0.03). Phosphatidylcholine (PC) 42:6 was 46% increased (p=0.02) in IBD group. 44 metabolites were significantly discriminating CD from UC patients. Among them phospholipids (Phosphatidylethanolamine, PE 38:5 +271%, p=0.003 and PC 35:5 +46%, p=0.03) and anandamide (+48%, p=0.02) were increased in UC group. While PC 42:6 (+40%, p=0.00006) and LPC 15:0 (+79%, p=0.0006) were increased in CD group.

Conclusions: Metabolic fingerprinting allows for discrimination between Controls and two studied inflammatory bowel diseases. Obtained results indicate for disruption mainly of lysophospholipids metabolism in IBD patients. On the other hand phospholipids and anandamide were mainly responsible for discrimination between CD and UC groups. Although promising, obtained results are preliminary and require validation on larger group of patients and with the use of targeted analysis of significant metabolites.

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Fecal calprotectin as a noninvasive indicator for ulcerative colitis disease activity in the Korean cohort

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Background: The aim of this study was to evaluate the diagnostic role of fecal calprotectin (FC) as a noninvasive marker for the disease activity of ulcerative colitis (UC) in the Korean cohort.

Methods: A total of 168 fecal samples were collected from 168 UC patients (April 2015-September 2016). FC was measured using the Quantum Blue[®] Calprotectin rapid test (Bühlmann Laboratories AG, Schönenbuch, Switzerland). The results of laboratory tests, partial Mayo score and colonoscopic imaging conducted at the time of fecal calprotectin measurement were retrospectively reviewed. Mayo endoscopic subscore and UC endoscopic index of severity (UCEIS) were graded by two certified endoscopists after training on another 50 cases.

Results: The mean (± standard deviation, SD) FC level was 3619.2±5344.5 µg/g and the median (interquartile range, IQR) partial Mayo score, Mayo endoscopic subscore, and UCEIS were 5 (3–6), 3 (2–3), and 4 (3–6), respectively.

The FC levels were significantly correlated with partial Mayo score (Spearman correlation coefficient r=0.387, p<0.001), Mayo score (r=0.383, p<0.001), and UCEIS (r=0.378, p<0.001). The correlation with FC was significantly greater for UCEIS than for Mayo endoscopic subscore (Meng's z=-3.057, p=0.002). Among the laboratory values, FC levels had significant correlations with C-reactive protein (r=0.368, p<0.001) and serum albumin (r=-0.393, p<0.001) (see Figure 1).

In the receiver-operating-characteristics (ROC) curve analyses, the

Table 1. Demographic and clinical characteristics of the study subjects

Variables	UC (N =168)
Sex	
Male	97 (57.7%)
Female	71 (42.3%)
Age at diagnosis (years), median (IQR)	35.7 (26.5-48.6)
Age at fecal calprotectin measurement (years), median (IQR)	40.8 (29.3-54.1)
Disease duration before fecal calprotectin measurement (months), median (IQR)	18.2 (2.0-58.6)
Maximum extent of UC	
Proctitis	31 (18.4%)
Left-sided colitis	43 (25.6%)
Extensive colitis	94 (56.0%)
Smoking status at diagnosis	
Never smoker	94 (56.0%)
Former smoker	44 (26.2%)
Current smoker	30 (17.8%)
Family history of IBD at diagnosis	
No family history	158 (94.0%)
First degree relative	9 (5.4%)
Second degree relative	1 (0.6%)
Ever use of medication at calprotectin measurement	
Oral 5-ASA	144 (85.7%)
Topical 5-ASA	109 (64.9%)
Topical corticosteroids	31 (18.5%)
Systemic corticosteroids	116 (69.0%)
Thiopurines	55 (32.7%)
Cyclosporine	4 (2.4%)
Anti-TNF agents	28 (16.7%)
Fecal calprotectin (µg/g), mean ± SD	3619.2 ± 5344.5
Hematocrit (%), mean ± SD	36.9 ± 6.5
Serum albumin (g/dL), mean ± SD	3.4 ± 0.7
Erythrocyte sedimentation rate (mm/hr), mean ± SD	33.4 ± 25.4
White blood cell count (x10 ³ /uL), mean ± SD	8.1 ± 3.9
Platelet count (x10 ³ /uL), mean ± SD	330.6 ± 115.2
C-reactive protein (mg/L), mean ± SD	2.1 ± 3.7
Partial Mayo score, median (IQR)	5 (3-6)
Mayo endoscopic subscore, median (IQR)	3 (2-3)
Mayo score, median (IQR)	7 (4-9)
UCEIS, median (IQR)	4 (3-6)

Table 2. Inter-rater agreement of endoscopic indices on 168 study subjects

Variables	Weighted Kappa	95% CI
Mayo endoscopic subscore	0.76	0.68-0.84
UCEIS	0.60	0.54-0.67
Vascular	0.65	0.52-0.78
Bleeding	0.38	0.28-0.47
Erosions and ulcers	0.72	0.65-0.79

[CI] 0.506–0.744), 0.695 (95% CI 0.577–0.813), and 0.708 (95% CI 0.625–0.791), respectively (see Figure 2, p. S152).

Conclusions: FC level showed significant correlation with the disease activity of UC, endoscopic indices and other serum inflammatory biomarkers in the Korean cohort. UCEIS showed a better correlation with FC level than Mayo endoscopic subscore. Fecal calprotectin could be used as a reliable noninvasive indicator to evaluate the disease activity and mucosal healing of UC.

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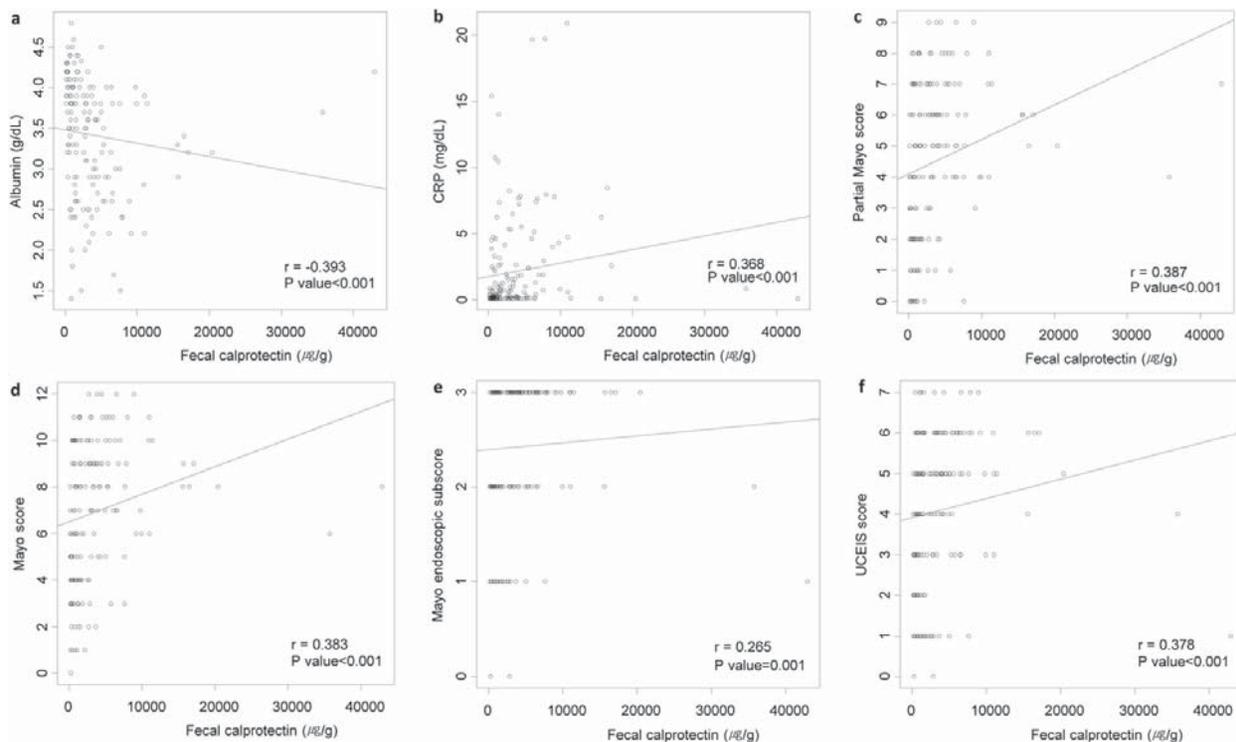
Urban life is an independent risk factor for psychological symptoms of the Chinese patients with Crohn’s disease

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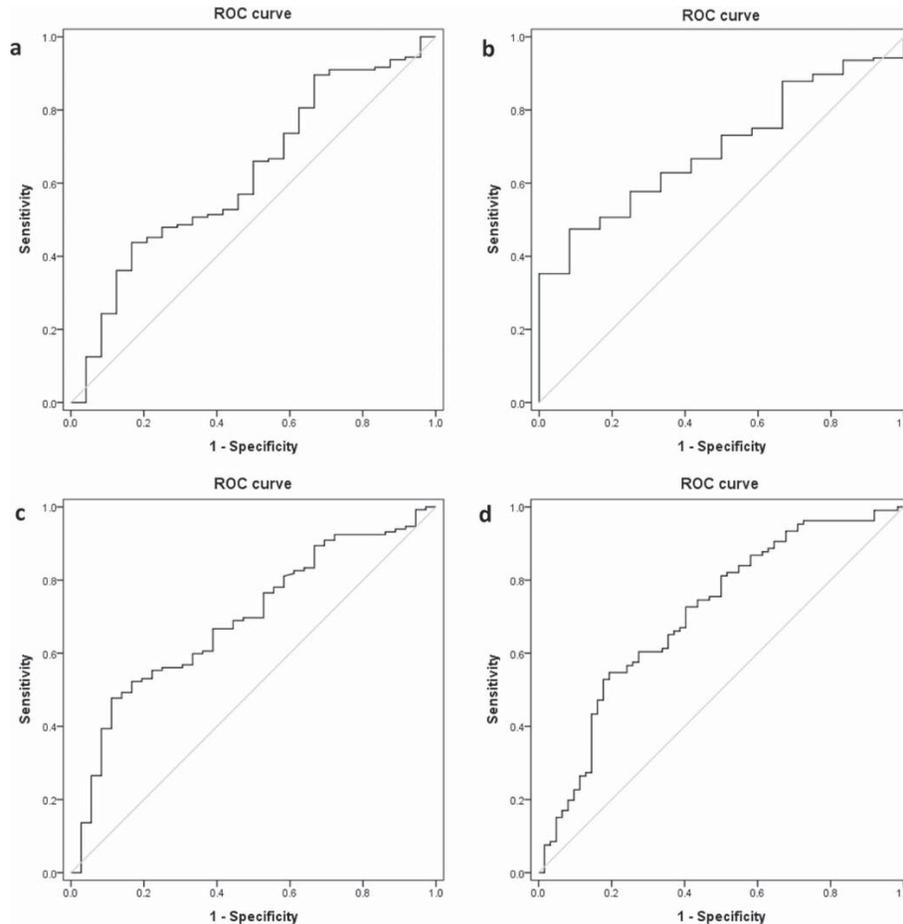
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Background: Previous studies have demonstrated that patients with inflammatory bowel disease (IBD) have increased vulnerability for psychological symptoms. However, the further investigation of the

area under the curve (AUC) of FC for discriminating mucosal healing (Mayo endoscopic subscore 0–1), clinical remission (Mayo score 0–2), and UCEIS score 0–3 were 0.625 (95% confidence interval



Abstract P148 – Figure 1. Correlation between FC and a) serum albumin (r=–0.393, p<0.001); b) CRP (r=0.368, p<0.001); c) partial Mayo score (r=0.387, p<0.001); d) Mayo score (r=0.383, p<0.001); e) Mayo endoscopic subscore (r=0.265, p=0.001); f) UCEIS (r=0.378, p<0.001).



Abstract P148 – Figure 2. In the ROC curve analysis, AUC of FC for discriminating a) Mayo endoscopic subscore 0–1 was 0.625; b) Mayo score 0–2 was 0.695; c) UCEIS score 0–2 was 0.693; d) UCEIS score 0–3 was 0.708.

psychological symptoms and impaired daily function in Chinese patients with Crohn's disease (CD) is not well described. Our aim is to estimate the psychological symptoms and daily function of the patients with CD comparing with health controls and the risk factors for psychological symptoms of the Chinese patients with CD.

Methods: A cross-sectional study was undertaken including 169 patients with CD and 174 healthy controls. The Research Electronic Data Capture (REDCap) were adopted to perform web-based surveys. Sociodemographic variables including age, gender, employment state, marriage state, education, place of residence and fertility, clinical variables including surgery history, stoma, course of disease, therapy and disease activity estimated by the Harvey-Bradshaw Index (HBI), psychological symptoms measured by the Depression Anxiety Stress Scales (DASS-21), daily function measured by the Work and Social Adjustment Scale (WSAS) were estimated in both patients with CD and healthy controls. Chi-square test was performed to identify differences of psychological symptoms and daily function between the patients with CD and the controls. Logistic regression was performed to identify the risk factors associated with psychological symptoms in patients with CD.

Results: The median age of the patients with CD and the controls was 30.75 ± 10.79 and 30.99 ± 8.48 years old, respectively. The patients with CD experienced elevated depression symptoms (10/169, 14.8%), anxiety symptoms (40/169, 23.6%) and impaired daily function (92/169, 54.5%) than the controls (10/174, 1.4%; 14/174, 8.0%; 14/174, 8.0%, respectively). The patients with active CD experienced elevated anxiety symptoms (25/72, 34.7%) and impaired

daily function (49/72, 68.1%) than the patients in remission (15/97, 15.5%; 38/97, 39.2%). Urban life (OR=2.631, 95% CI: 1.176 to 5.885) is the independent risk factor for psychological symptoms.

Conclusions: The Chinese Patients with CD experience elevated psychological symptoms and impaired daily function, particular the Patients in activity diseases state. Urban life is the independent risk factor for psychological symptoms. So the Chinese Patients with CD need psychological assessment and support.

P150 Pregnancy complications and outcomes in patients with inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD) is a chronic relapsing and remitting immune disorder with morbidities that impair function and quality of life. The disease has an increasing prevalence, and is frequently diagnosed at childbearing age. Given that IBD requires life-long medication, it is important to monitor and manage disease activity for successful pregnancy outcomes. We were

interested to better understand the effect of IBD on pregnancy outcomes.

Methods: Between 2011 and 2015, a total of 39 pregnant patients with IBD were reviewed. Sixteen had Crohn's disease (CD) and 23 had ulcerative colitis (UC). We retrospectively evaluated the 41 pregnancy outcomes in these 39 patients. In the CD cases, active disease was defined as CD activity index (CAI) ≥ 150 , while in the UC cases, active disease was defined as clinical activity index (CAI) ≥ 4 . The pregnancy and neonatal complications including spontaneous abortion, preterm delivery (<37 weeks), caesarean section, low birth weight (<2500g) and congenital abnormality were determined.

Results: The mean age was 33.5 \pm 4.2 years in CD patients and 32.7 \pm 5.2 years in UC patients. For most patients, IBD was inactive prior to pregnancy (84%, n=33). Elemental diet (n=9 cases) and anti-tumour necrosis factor- α biologics (n=10) were the most common drugs used during pregnancy in CD patients, while mesalamine (n=22) was the most common drug in UC patients. Flare up rate during pregnancy was higher in UC patients than in CD (62.5% vs 29.4%). Most patients relapsed in the first pregnancy trimester (28.5%) and puerperal period (60%). The rate of preterm delivery (12.2%), low birth weight (22.0%) and caesarean section (31.7%) were not significantly different from non-IBD controls (n=394; 28.4%, 32.3%, 46.4% respectively). However, the rate of congenital abnormality was higher in IBD patients than in non-IBD (7.3% vs 0.2%). The rate of neonatal and pregnancy complications was significantly higher during active disease than during quiescent period (p<0.05).

Conclusions: We found that IBD flare ups had occurred particularly in the first pregnancy trimester and puerperal period. Flare up rate was higher in UC patients than in CD patients. Accordingly, IBD patients, particularly UC patients should be diligently monitored in the first pregnancy trimester and puerperal period. Likewise, in this study the prevalence of congenital abnormality was higher in IBD patients than in non-IBD, but we did not investigate the risk factors for congenital abnormality in the IBD clinical setting.

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Spinal disorders in IBD patients 20 years after diagnosis. Results from the IBSEN study

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Background: Patients with inflammatory bowel disease (IBD) often suffer from extraintestinal rheumatic manifestations, prevalently including inflammatory back disorders like ankylosing spondylitis (AS), axial spondylarthropathy (axial SpA) and inflammatory back pain (IBP). However, few studies have estimated the prevalence of these disorders late in the disease course. The aim of this study was to describe the prevalence of inflammatory back disorders 20 years after IBD diagnosis in a well-defined IBD cohort.

Methods: All newly diagnosed cases of IBD in four counties in south-eastern Norway between 1990 and 1993 were included in the IBSEN cohort and followed prospectively. At the 20 year follow-up the patients answered a detailed questionnaire regarding their IBD disease course. Moreover, they were asked about symptoms of inflammatory back disorders and established diagnoses of rheumatic diseases. The patients were classified as having IBP or axial SpA according to the

criteria from the Assessment of SpondyloArthritis International Society (ASAS) (IBP if 4 of 5; age at onset<40, insidious onset, pain at night, improvement with exercise, no improvement with rest. Axial SpA criteria; chronic back pain (>3 months) and age at onset<45 plus either radiological sacroiliitis and ≥ 1 SpA feature or HLA-B27 positivity and ≥ 2 SpA features).

Results: In total 599 patients from the original cohort were still alive, of those 470 (78.5%) were investigated. Chronic back pain had been present during the disease course in 148 patients (31.5%), 90 (38.3%) women and 58 (24.7%) men. The ASAS criteria for IBP were met by 37 patients (7.9%), 23 women and 14 men, and 17 patients (3.6%) fulfilled the criteria for axial SpA (11 women and 6 men). Over the last 3 months 80 patients (17.0%) reported chronic back pain, leaving only 21 patients (4.5%) fulfilling the IBP criteria and 5 patients (1.1%) the axial SpA criteria. AS was diagnosed in 21 patients (4.5%), 8 women and 13 men. The total HLA-B27 prevalence was 8.7%. The prevalence was higher among patients with chronic back pain, IBP, axial SpA and AS, with 12.8%, 27.0%, 88.7% and 57.1%, respectively.

Conclusions: The prevalence of axial SpA and AS in IBD patients late in the disease course was higher than the prevalence reported in general populations (total SpA 0.4–1.9% and AS 0.1–1.8%) [1], while the prevalence of chronic nonspecific back pain amongst IBD patients was comparable to the general population (reported to be 20% in men and 25–33% in women) [2].

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P152

Reconsidering the prognostic value of traditional serologic antibodies in Crohn's disease – immunoglobulin classes to take the centre stage

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Background: The most relevant scope of serologic antibodies in Crohn's disease [CD] is to stratify the risk of complicated disease course. Significance of distinct antibody classes and their characterisation was rarely considered. We aimed to address these concerns.

Methods: Sera of 266 well-characterized CD patients (m/f: 112/154, median age: 25 years, B1: 80.1%, P1: 18.0%) and 155 controls were assayed for traditional anti-microbial antibodies (ASCA IgA/IgG, anti-OMP IgA). Endotoxin core IgA (EndoCab) and a panel of non-specific immunoglobulin A (IgA) molecules (IgA1, IgA2 and secretory [s] IgA) were also assessed by ELISA. An observational follow-up study [median, 143 months] was conducted to assess possible associations between serologic antibodies and the development of various complications and subsequent surgical interventions. A novel flow cytometry based test system was established for characterisation of IgA type ASCA to reveal possible origin of the antibody.

Results: A total of 65.7% and 46.2% of the CD patients were posi-

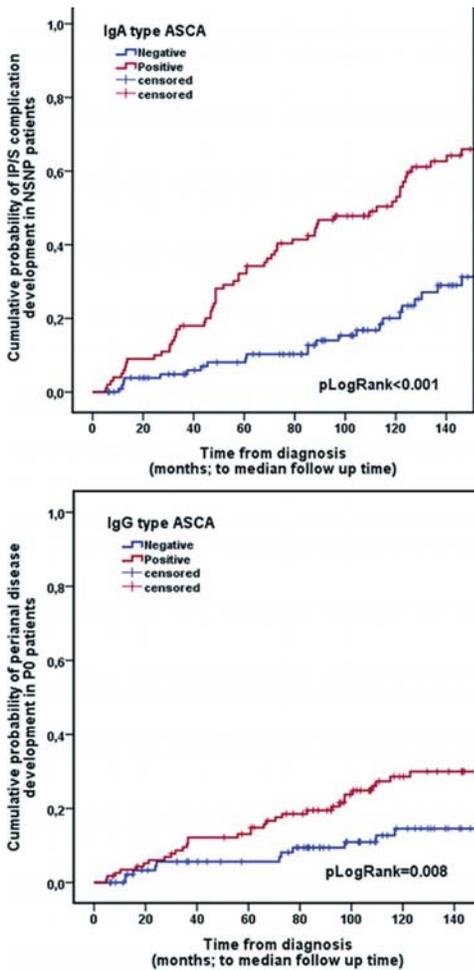


Figure 1. Kaplan-Meier survival analysis for the probability of complicated disease course.

tive for ASCA IgA/IgG and anti-OMP antibodies. Both ASCA types occurred equally. EndoCab IgA positivity was more frequent (15.4% vs. 5.4%, $p < 0.01$) and sIgA levels were increased [median, 51 vs. 29 $\mu\text{g/ml}$, $p < 0.001$] in CD compared to controls. They were also associated with presence of IgA type anti-microbial antibodies. Contrary, ratio of IgA2/A1 in CD corresponded with the value of the controls. In Kaplan-Meier analysis, development of internal penetrating and/or stenosing (IP/S) complications and resective surgery (SR) was significantly associated with IgA type, while development of perianal penetration (PP) with IgG type ASCA.

Performance of OMP and EndoCab IgA was equal to ASCA IgA, however sIgA not. Anti-microbial antibodies remained independent

Table 1. Summary of multivariate Cox regression analysis for the association of serologic antibodies with complicated disease course

HR [95% CI]; p	IP/S in B1 pts	SR in B1 pts	PP in P0 pts
ASCA IgA	2.92 [1.85–4.62]; <0.001	1.77 [1.09–2.87]; 0.021	
ASCA IgG			2.77 [0.36–5.63]; 0.005
ASCA IgA/IgG	1.76 [1.09–2.87]; 0.022	1.45 [0.86–2.45]; 0.163	2.07 [0.98–4.39]; 0.057
OMP IgA	1.66 [1.09–2.54]; 0.019	2.08 [1.28–3.38]; 0.003	1.13 [0.63–2.01]; 0.692
sIgA	1.54 [0.97–2.44]; 0.066	1.37 [0.82–2.28]; 0.23	1.25 [0.67–2.34]; 0.475
EndoCab IgA	2.60 [1.62–4.17]; <0.001	1.66 [0.96–2.87]; 0.071	0.74 [0.33–1.68]; 0.475

predictors in multivariate Cox-regression analysis comprising relevant clinical factors. Without uncoupling of Ig antibody classes yielded clearly inferior performance.

ASCA IgA subtyping assays revealed marked increase in the proportion of IgA2 subtype (29%) and presence of the secretory component (89% of total ASCA IgA) concurrently.

Conclusions: Consideration of antibody classes is an important novel parameter in serology-based prediction in CD. Involvement of gut mucosal immune system is in center of IgA type antibody formation reflecting sustained exposure and dysregulated immunresponse to bacterial constituents.

P153

Role of 3D endoanal ultrasound in perianal fistulising Crohn's disease. Preliminary results

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Background: Perianal fistulising Crohn's Disease is a challenging clinical situation; the development of appropriate diagnostic tools is crucial for correct patient's management. The role of 3D endoanal ultrasound is well established in the diagnosis of anal fistulas. In this report we investigate if these some specific endosonographic features (the Crohn's Ultrasound Fistula Sign -CUFS, a double track, the presence of debris in the fistula track or abscess, the maximum width of the fistula tract) may have a role in discriminating between cryptoglandular and Crohn's Disease related fistulas.

Methods: 48 consecutive patients with anal fistulas were included in the study from July 2015 to January 2016. Each patient underwent a 3D endoanal ultrasound (B-K Medical, 2052 transducer) and subsequent surgery. 11 patients had an established diagnosis of CD. The abovementioned ultrasonographic features were searched for and compared between the cryptoglandular fistulas group ("crypt group") and the CD related fistulas group ("CD group"). Cohen K Statistics was used to determine the agreement between ultrasound diagnosis (primary orifice, tract) and operative findings. Wilcoxon rank sum test has been used to compare the fistula width between cryptogenic and CD cases. Diagnostic accuracy of the Width of the fistula tract has also been evaluated with a ROC curve and the AUC. The role of all the abovementioned signs and ultrasonography features as diagnostic tools for perianal fistulising CD has also been investigated and Sensitivity, Specificity, Accuracy, Positive and Negative Predictive Value (PPV/NPV) and Positive and Negative Likelihood ratios (PLR/ NLR) have been calculated. Statistical analysis were performed using STATA 12 statistical software.

Results: Preoperative ultrasound and surgical findings showed a very good agreement ($k=0.96$ for primary orifice and $k=0.94$ for fistula tract). Mean width of the fistula tract was 2.7 mm in the crypt group and 5.1 mm in the CD group ($p < 0.001$, Wilcoxon rank sum Test). A width over 4 mm has been proposed as a cut-off for highly suspicious CD related fistulas. The frequency observed of the CUFS, double track, debris and width > 4 mm is significantly higher in the CD group than in the crypt group ($p < 0.01$, Fisher exact test). All of these signs show a high sensitivity, specificity, positive and negative predictive value and a high positive likelihood ratio for diagnosis of perianal Crohn's disease.

Conclusions: Endoanal 3D ultrasound is a safe and reliable tool for diagnosis of perianal fistulas; some specific ultrasonographic features have been described to discriminate between cryptoglandular and perianal CD related fistulas, with a high level of diagnostic accuracy.

P154
Complete sequence-based NUDT15 and TPMT variants for predicting thiopurine-induced leukopenia in patients with Crohn’s disease

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Background: Thiopurine-induced leukopenia is a life-threatening complication in Asians. Other than previously known thiopurine S-methyltransferase (TPMT) mutation, the NUDT15 genetic variant was recently identified to have a strong association with thiopurine-induced leukopenia. We investigated the association of NUDT15, TPMT, metabolites of thiopurines on leukopenia in patients with Crohn’s disease (CD).

Methods: We investigated the data of 168 adult patients with CD undergoing thiopurine treatment. Clinical evaluation and laboratory examinations were performed every 1–3 months. We carried out a complete sequencing analysis for evaluating NUDT15 and TPMT variants and measured thiopurine metabolites levels.

Results: Of 168 patients, 34 patients (20.2%) had NUDT15 variant alleles. NUDT15 heterozygous variants were found in 28 patients (16.7%) and NUDT15 homozygous variants were found in 6 patients (3.6%). Among the 168 patients, 35 (20.8%) patients experienced leukopenia during first year of thiopurine treatment. NUDT15 variant types were strongly associated with developing leukopenia [10.9% wild type as reference; 48.5% heterozygous variant genotype; 100% homozygous variant genotype, odds ratio (OR) 3.44 (95% CI, 1.21–9.78)].

However, TPMT genotype was not associated with developing leukopenia (OR 0.58, 95% CI 0.07–4.96). Patients with NUDT15 homozygous variant genotype developed severe early leukopenia

Table 2. Thiopurine metabolites levels and thiopurine-induced leukopenia in NUDT15 variant genotype subgroup

	NUDT15 variant type (n=22)		p-value
	Leukopenia (n=12)	Normal (n=10)	
6-TGN (pmol/8×10 ⁸ RBC)	298.5 (205–407)	280.8 (174–327)	0.344
6-MMPN (pmol/8×10 ⁸ RBC)	62.5 (35.2–78.0)	406.7 (212–745)	0.124

with average 88.2% (range, 84–94%) reduction from baseline WBC count at 4 weeks.

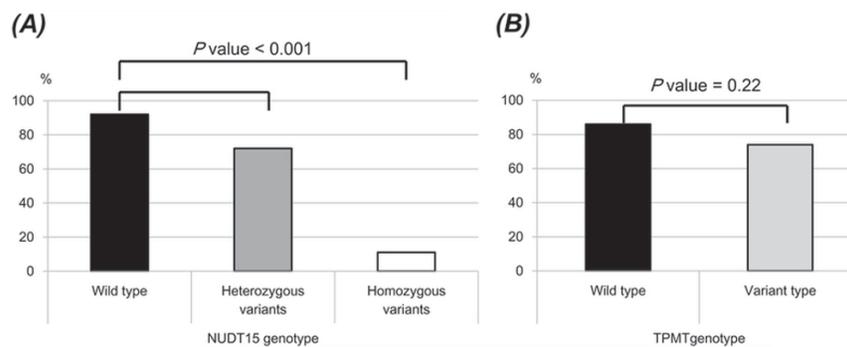
In subgroup of NUDT15 variant type, there was no significant difference of 6-TGN levels between patients with and without leukopenia [298.5 (205–407) vs. 280.8 (174–327) pmol/8×10⁸ RBC, p=0.344].

Conclusions: This is the first complete sequence-based analysis for NUDT15 variants in Asian populations. Our findings suggest that NUDT15 genotype should be detected rather than TPMT before initiating thiopurines. Thiopurines treatment should not be recommended to patients with NUDT15 homozygous variant genotype due to severe early leukopenia.

P155
A retrospective analysis of Clostridium difficile infection in patients with ulcerative colitis

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Background: Many reports have documented the increasing impact of Clostridium difficile infections (CDI) in patients with inflammatory bowel disease (IBD) in the latest years. To determine the prevalence, risk factors, clinical characteristics and prognosis of CDI in hospitalized ulcerative colitis (UC) patients, we conducted this retrospective analysis.



Abstract P154 – Figure 1. WBC count as a percentage of baseline at 4 weeks after thiopurines treatment.

Abstract P154 – Table 1. The risk of leukopenia according to NUDT15 and TPMT genotype

	Number of participants	Number of early leukopenia (0–8 weeks)	Number of leukopenia (0–48 weeks)	Early leukopenia (0–8 weeks), OR (95% CI)	Leukopenia (0–48 weeks), OR (95% CI)
NUDT15					
Wild	129	1 (0.8%)	14 (10.9%)	1.00 (reference)	1.00 (reference)
Heterozygous variant	33	8 (24.2%)	15 (48.5%)	26 (2.81–241.10)	3.44 (1.21–9.78)
Homozygous variant	6	6 (100%)	6 (100%)		
TPMT					
Wild	161	14 (8.7%)	34 (21.1%)	1.00 (reference)	1.00 (reference)
Variant	7	1 (14.3%)	1 (14.3%)	1.89 (0.21–9.98)	0.58 (0.07–4.96)

Methods: Patients with UC, hospitalized from January 2010 to December 2015 at the department of gastrointestinal in PUMCH, China were objects of this study. For all the patients suspected of CDI, stool samples were tested for toxins A and B of *Clostridium difficile* (CDAB) with enzyme-linked immuno sorbent assay (ELISA). Clinical data of CDAB positive patients were collected. Controls were CDAB negative patients by matching age, gender and the year CDAB tested at 1:2 ratios. Logistic regression was used to reveal the risk factors of CDI.

Results: In a total of 421 in-patients with UC, 34 (8.08%) were CDAB positive and diagnosed as CDI. 68 CDAB negative patients were matched. Univariate analyses revealed that risk factors for CDI were: antibiotic exposure within 3 months prior to CDAB test ($p=0.004$), prior hospitalization within 1 month ($p=0.025$), systemic use of steroids ($p=0.002$), and dose of steroids used in CDI patients was higher than non-CDI patients ($p=0.001$). At the meanwhile, the study found a correlation between active cytomegalovirus (CMV) infection and CDI in UC patients ($p=0.001$). On logistic regression analyses, active CMV infection had a significant difference between CDI and non-CDI patients (OR 13.502, 95% CI: 1.307~139.512, $p=0.029$). However, the severity of UC (evaluated on clinical criteria and endoscopic scoring system), distribution of UC, disease course, duration of disease, history of smoking and alcohol use, combination of diabetes, history of surgery, 5-aminosalicylic acid (5-ASA), proton pump inhibitor (PPI), immunosuppressants except steroids, infliximab, parenteral nutrition within 1 month didn't increase the risk of CDI in UC patients. Clinical features of CDI patients in UC had no significant differences from non-CDI patients, such as body mass index (BMI), defecation frequency, toxic megacolon incidence rate, leucocyte and neutrocyte level of peripheral blood ($p\geq 0.05$). CDI didn't increase the subsequent colectomy rate in this study.

Conclusions: The complication of IBD by *C. difficile* infection has received increasing attention. This retrospective study found that recent usage of antibiotic, a history of prior hospitalization and systemic using of steroids increase the risk of CDI. CMV infection was an independent risk factor of CDI in patients with UC.

P156

Microbiota diversity at time of surgery predict endoscopic recurrence in Crohn's disease: results of a prospective study of the REMIND group

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Background: Operative resection in Crohn's disease (CD) is not curative. After ileocecal resection, endoscopic recurrence is frequently observed on the anastomosis and/or on the neo-terminal ileum. The aim of this study was to analyze the mucosa associated microbiota at time of surgery and to look for predictors of post-operative endoscopic recurrence within the microbiota.

Methods: This is a prospective study performed in 9 centers of the

REMIND group, collecting clinical and biological data at time of surgery and of endoscopy (performed at 6 months). Bacterial composition of the ileal mucosa associated microbiota was analyzed at time of surgery in 146 patients with CD using 16S (MiSeq, Illumina) sequencing. The obtained sequences were analyzed using the Qiime pipeline to assess composition, alpha and beta diversity. Bacterial taxa associated with clinical parameters were identified using Multivariate association with Linear Models (MaAsLin) taking into account disease phenotype, clinical parameters and treatments.

Results: 146 patients were included: 73 (50%) were male, median age at surgery was 32 years (IQR 26–42). Median disease duration was 6 years (IQR 2–12). 44 patients (30%) were active smoker at time of surgery. Thirty patients (21%) had a previous resection, and 35 patients (24%) had perianal lesions. At time of surgery, 67 patients (46%) had received anti-TNF therapy within the last 3 months. After surgery, 31 patients received thiopurines, and 52 patients received anti-TNF therapy. The microbiota was mainly composed of bacteria from the Firmicutes (mean 53%, range 0.3–99%), Proteobacteria (mean 36%, range 0.5–99%) and Bacteroidetes (mean 3%, range 0–52%) phyla. As expected, antibiotics treatment within one month before surgery had a dramatic impact on microbiota composition (Anosim, $p<0.0001$) and diversity (mean observed species: 302 ± 17 vs 236 ± 14 , $p=0.005$). Taking into account only the patients who did not received antibiotics within a month before surgery, patients with endoscopic recurrence, defined by a Rutgeerts score ≥ 1 , had a lower bacterial diversity at time of surgery compared to patients in endoscopic remission (mean observed species: 276 ± 14 vs 365 ± 45 , $p=0.015$). This predictive value was lost in patients treated by anti-TNF postoperatively.

Conclusions: Ileal mucosa associated microbiota of CD patients at time of surgery is dominated by bacteria belonging to Firmicutes, Proteobacteria and Bacteroidetes phyla. Antibiotics induce major perturbations of the microbiota. Reduction in bacterial diversity at time of surgery is predictive of endoscopic recurrence but this predictive value is lost in patients treated by anti-TNF supporting the effectiveness of this post operative treatment.

P157

Fecal calprotectin correlates to endoscopic and histologic remission in ulcerative colitis: a prospective study

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Background: Endoscopic healing (EH), has become the target endpoint of successful ulcerative colitis (UC) management while the role of histology remains to be clarified. Clinical and biochemical markers are not sufficient to predict which UC patients are in EH. Fecal calprotectin (FC) has been demonstrated to be useful surrogate marker, however, there has not been a consensus for cut off values for FC for endoscopic and histologic remission.

Methods: Our prospective cohort study recruited patients with UC in clinical remission who were being followed at the McGill IBD Center between 2013–2016. Patients were recruited if they had clinical remission (partial Mayo score of ≤ 2) and were undergoing colonoscopy for disease reassessment. At the time of colonoscopy, fecal calprotectin

(FC) was collected, as well as full and endoscopic Mayo score, Geboes histology score and record of basal plasmacytosis.

Results: 163 patients were recruited (88 males, 75 females; mean age 49 years; IQR 39–59). Based on endoscopic scores, 65% (n=106), 24% (n=39), 11% (n=18) patients were Mayo 0, 1, 2 respectively. There was a statistically significant difference in fecal calprotectin based on endoscopic mayo score ($p<0.0001$). The area under the curve (AUC) in receiver operator characteristic (ROC) analysis of FC to predict Mayo 0 (from Mayo 1–2) was 0.747 (CI 95% 0.65–0.83, $p<0.01$) with a cut off value of FC 150mcg/g yielding 65% sensitivity and 72% specificity.

Table 1. Fecal calprotectin and mayo endoscopic score 0 (versus Mayo 1–2)

	Sensitivity	Specificity
FC <50	86%	40%
FC <100	75.4%	56%
FC <150	65%	71%
FC <200	60%	78%
FC <250	58%	83%

Similarly, there was a statistically significant difference between fecal calprotectin based on histologic Geboes score and presence or absence of basal plasmacytosis ($p=0.005$). The AUC in ROC analysis of FC to predict Geboes <3.1 (remission) was 0.582 (CI 95% 0.481–0.683, $p=0.119$). The AUC in ROC analysis of FC to predict basal plasmacytosis was 0.64 (CI 95% 0.51–0.766, $p=0.02$), with a cut off value of FC 140 mcg/g yielding 60% sensitivity and 72% specificity.

Table 2. Fecal calprotectin and basal plasmacytosis

	Sensitivity	Specificity
FC <50	74%	44%
FC <100	63%	60%
FC <150	57%	72%
FC <200	54%	75%
FC <250	51%	80%

Conclusions: Our study demonstrates that fecal calprotectin below 150 mcg/g predicts endoscopic Mayo 0. In addition to correlating with the endoscopic score, fecal calprotectin below 140 mcg/g correlates with absence of basal plasmacytosis. Using non-invasive testing, these predictive values have potential to identify patients with ulcerative colitis in remission, but further validation is needed.

P158

Pouchitis in paediatric ulcerative colitis: a multicentre longitudinal cohort study from the Porto IBD working group of ESPGHAN

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Background: Risk factors associated with the development of pouchitis in adults after formation of an ileal pouch anal anastomosis (IPAA) include severe inflammation at diagnosis, upper gastrointestinal (UGI) involvement, backwash ileitis, pancolitis, and extra-intestinal manifestations (EIM), all of which are more common in paediatric-onset ulcerative colitis (UC). We thus aimed to assess outcomes and explore risk factors for pouchitis in children who underwent IPAA before the age of 18 years.

Methods: Data were retrospectively collected from 17 paediatric IBD centres from the Porto group of ESPGHAN. Electronic REDcap system was used, including explicit baseline characteristics, management, surgical information and medical short and long term follow up.

Results: A total of 129 children who underwent IPAA were included (50% male; 93% UC and 7% IBDU, mean age at diagnosis 10.5±4.2 years, median disease duration to colectomy 17 months (IQR 8–35.5 months) and median follow-up after pouch formation 36 months (IQR 21–64 months). Eighty-six children (67%) developed pouchitis during follow-up. In 33 (26%) the pouchitis was chronic, 10 of whom (8%) had Crohn's-like disease of the pouch. Median time from pouch formation to the first episode of pouchitis was 10.5 months (IQR 6–22); in 54% of cases the first episode occurred within one year.

The experience of the surgeon was strongly associated with development of chronic pouchitis (8/54 (15%) in surgeons with ≥10 surgeries/year vs 11/27 (41%) in surgeons with <10/year, $p=0.013$). There was no significant added benefit to surgeon experience greater than 10 surgeries/year.

Other variables that were associated with development of pouchitis included: younger age at diagnosis (mean 9.9±4.3 vs 11.7±3.7 years; $p=0.014$), longer disease duration prior to colectomy (median 22 (IQR 10–39) vs 13 (6–29) months; $p=0.026$), and Ashkenazi Jewish ethnicity (7/15 Ashkenazi patients with chronic pouchitis vs 21/103 patients of other ethnicity; $p=0.046$). The following variables did not predict pouchitis: UGI involvement, disease extent, backwash ileitis, EIM, pANCA positivity, IPAA type, and high PUCAI score at diagnosis/surgery). Multivariate logistic regression showed that chronic pouchitis was associated with male gender (HR=4.3, 95% CI 1.2–14.7) and surgeon experience (<10surgeries per/year) (HR=5.2, 95% CI 1.5–18.6) while controlling for age and disease duration.

Conclusions: UC patients who underwent IPAA during childhood developed pouchitis at a higher rate than usually described in adults. Surgeon experience seems to be an important controllable predictor of chronic pouchitis and should be taken into consideration in paediatric patients.

P159
Real-time endoscopic-guided measurement of rectal mucosal admittance: a novel and safety method for prediction of relapse in ulcerative colitis

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Background: Previously, the association between inflammatory bowel disease (IBD) and the mucosal paracellular permeability change has been reported. A novel catheter that can measure mucosal admittance (MA) has been developed recently. In this study, we aimed to clarify the usefulness of measuring MA for predicting the prognosis of ulcerative colitis (UC) patients in remission.

Methods: Patients with UC in remission had been carried out real-time measurement of MA during colonoscopy and subsequent clinical follow up prospectively. The measurement of MA was taken by using the new device, Tissue Conductance Meter (TCM, AsahiBiomed Co., Ltd.), which can measure the mucosal permeability change electrophysiologically. Relapse was defined as moderate to severe clinical flare during the follow up period. We examined the relations between mucosal admittance, clinical parameters, and disease relapse during follow up period by the COX proportional hazards model.

Results: Fifty-four UC patients in remission were measured MA at baseline and studied for a median of 14 months. At baseline, the mean age was 44.8±13.8 years and 69% were males. The mean rectal MA of the patients was 906.7±264.3, and no complications were encountered by MA measurement. In this prospective study, 23 patients (31.5%) relapsed, and in those patients, two patients (3.7%) underwent surgery during follow up period.

In the multivariate analysis, rectal MA in relapse group (801.2±207.1) was significantly lower than rectal MA in remission group (955.2±275.9, hazard ratio 0.998, 95% CI 0.996–1.000, p=0.046). The ROC curve analysis showed that the optimal cut-off value of rectal MA for relapse was 781.0 (AUROC =0.679, 95% CI:

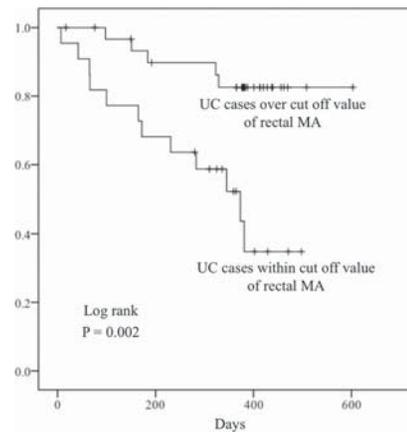


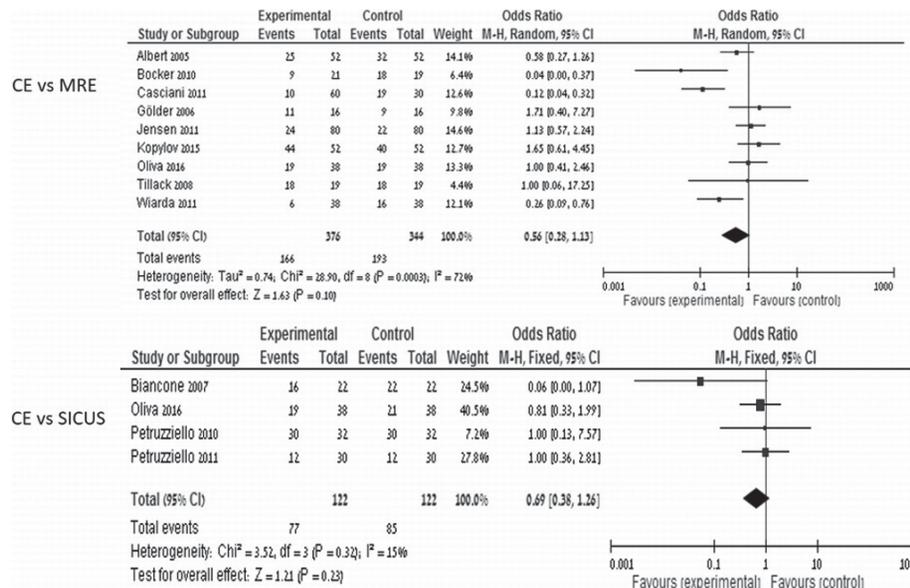
Figure 1. Kaplan-Meier survival analysis showed that relapse during follow up period was significantly correlated with rectal MA cut-off values (Log rank test, p=0.002).

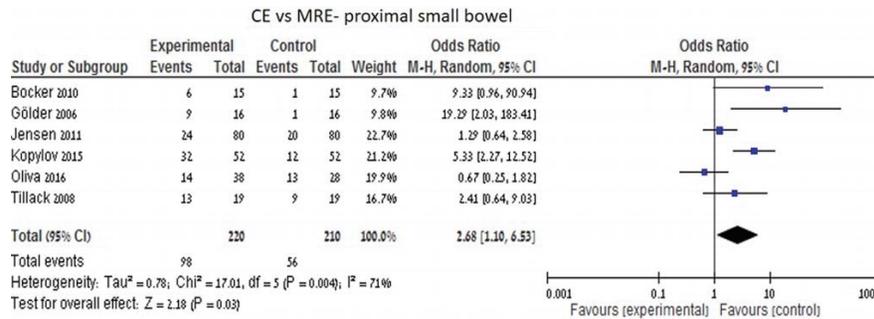
0.529–0.829, p=0.036). In patients whose rectal MA was below the cut-off value, relapse rate was significantly more than for the other patients (Log rank test, p=0.002, Figure 1).

Conclusions: Our results showed that low levels of rectal MA are associated with relapse rate. Real-time measurement of rectal MA using a novel endoscopy-guided catheter could be safety and useful for predicting the prognosis of patients with UC in remission.

P160
Diagnostic yield of capsule endoscopy versus magnetic resonance enterography and small bowel contrast ultrasound for evaluation of small bowel Crohn's disease: a systematic review and meta-analysis

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Abstract P160 – Figure 2

Background: Crohn’s disease (CD) involves the small bowel (SB) in at least 70% of those affected. Capsule endoscopy (CE), magnetic resonance enterography (MRE) and SB intestinal contrast ultrasound (SICUS) are the modalities of choice for SB evaluation. In CD, proximal SB disease is associated with worse long-term outcomes. This study aimed to compare the diagnostic yield (DY) of CE, MRE and SICUS in detection and monitoring of SB CD by performing a systematic review and meta-analysis of the available literature.

Methods: MEDLINE and EMBASE searches were performed using the search terms “capsule endoscopy”, “ultrasound”, “magnetic resonance enterography” and “Crohn’s disease”. We retrieved prospective trials comparing the accuracy of CE, MRE and SICUS for detection of active SB disease in patients with suspected and established CD. Only prospective studies comparing CE with at least one additional diagnostic modality were included. Odds ratios (ORs) for DY with 95% confidence intervals (CIs) were calculated. Where data were available, DY was also analyzed separately for proximal and distal SB.

Results: A total of 138 studies were retrieved by the literature search; 12 studies were eligible for analysis. The DYs of CE, MRE and SICUS were similar for the overall population. The OR for DY of CE vs MRE was 0.56 (95% CI 0.28–1.13, p=0.1; I²=72%; 9 studies, 376 patients). The OR for CE vs SICUS was 0.85 (95% CI 0.69–1.38; p=0.23; I²=15%| 4 studies, 122 patients) (Fig. 1). The DY for distal SB disease was similar to the overall analysis, OR 1.58 (95% CI 0.56–4.46; p=0.41; I²=71%; 6 studies, 220 patients). Segmental analysis was not possible for SICUS due to a low number of studies. DY was similar in suspected and established CD. Comparing CE to MRE, CE had superior DY for proximal SB disease with OR 2.62 (95% CI 1.10–6.53; p=0.03; I²=71%; 6 studies, 220 patients) (Fig. 2).

Conclusions: CE, MRE and SICUS have similar DY for detection of SB CD in both suspected and established CD. CE was superior to MRE for detection of proximal SB involvement; this may have important practical implications due to the prognostic impact of SB disease.

P161
Crohn’s disease risk prediction model appropriately stratifies patients’ risk for developing disease related complications

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Background: A model has been developed to predict the risk of patients with Crohn’s disease experiencing a disease related complica-

tion [1]. Although the model was validated retrospectively in additional patient cohorts, it had not been tested prospectively to determine if high-risk patients actually experience more complications than those with predicted low-risk disease. The aim of this study was to determine the proportion of patients experiencing Crohn’s disease related complications stratified by predicted risk category.

Methods: Patients with Crohn’s disease are being prospectively recruited from 15 medical practices across the US (8 academic, 7 community based). To meet inclusion criteria, all patients have to be within 15 years of diagnosis, without any current or prior disease complications, not currently on immunomodulators or biologics but considered a candidate for these treatments by their provider. Upon study entry, based on serologic and genetic testing, disease phenotype and demographic information, an individualized risk profile is generated for each subject using the validated risk prediction tool, PROSPECT [1]. PROSPECT predicts a patient’s risk of developing a complication (stricture or fistula) or progression to surgery over the next 3 years. We report clinical outcomes after the first year of follow-up.

Results: 154 patients have been recruited in total, of which 122 patients have been followed for 6 months, 91 for 1 year, and 28 for 2 years. Median age of patients is 31 (range 18–69) and 55% of patients are women. 18% of patients were predicted to have a low risk of developing disease related complications, 57% at moderate risk, and 25% were predicted to be at high risk. Overall, 21 patients experienced complications and 6 progressed to surgery. 10/21 complications occurred within 6 months of enrollment and 19/21 occurred within one year of enrollment. Among patients that experienced complications, 10% were predicted to be at low risk of developing a complication; 50% were at moderate risk and 40% were predicted to be at high risk. Of all patients predicted to be at low risk, 10.0% developed a complication; of all patients at moderate risk, 15.2% had a complication; and of all patients at high risk, 26.7% had a complication.

Conclusions: The PROSPECT tool predicted that over 80% patients with Crohn’s disease are at moderate to high risk of disease related complications within 3 years. Within the first year of follow-up, as predicted, more patients at moderate to high risk developed disease related complications compared to those at low risk.

References:
 [1] Siegel CA, et al. AP&T 2015.

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Early onset of disease and higher risk for colorectal dysplasia in IBD patients with coincidental primary sclerosing cholangitis – evidence from a large cohort study

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Background: Inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD) and Ulcerative colitis (UC), are characterized by chronic remittent intestinal inflammation and carry the risk for extraintestinal manifestations including primary sclerosing cholangitis (PSC). There is conflicting data on the possible impact of PSC on the course of IBD. Therefore, aim of our study was to compare the disease course in IBD patients with and without coincident PSC.

Methods: A cohort of 1814 patients with histologically confirmed IBD was evaluated. In detail, medical records from 705 UC patients and 1022 CD patients as well as from 77 UC-PSC patients and 10 CD-PSC patients were assessed. In matched-pair analyses IBD patients without and with PSC were matched at the ratio of 3:1 by sex, disease entity, age at diagnosis, time from diagnosis to hospital presentation, and duration of follow-up. Time to event analyses were performed using survival analytic methods (Kaplan-Meier method and the Log-rank test).

Results: PSC was diagnosed in 77 and 10 patients out of 781 UC patients (9.9%) and 1033 CD patients (0.96%), respectively. While average age at diagnosis was 32 years in UC patients without PSC, UC-PSC patients were diagnosed significantly earlier at the age of 26 years ($p < 0.001$). In CD patients, average age at diagnosis was found to be of 27 years vs. 24 years of age in CD-PSC patients. While extensive disease manifestation was observed in 46% of UC patients, pancolitis was more frequently diagnosed in UC-PSC patients (75%). Colorectal high grade intraepithelial neoplasia (HGIEN) and CRC were detected in 25 IBD patients without PSC and in 7 IBD-PSC (4 UC and 3 CD) patients (1.45% vs. 8.05%). Importantly, in IBD-PSC patients HGIEN/CRC occurred significantly earlier than in IBD patients without PSC (32 years vs. 50 years; $p = 0.019$). Biological therapy including vedolizumab and antibodies targeting TNF was initiated in 37.3% of IBD patients and in 27.9% of IBD-PSC patients. Interestingly, there was a trend to commence biological therapy earlier in IBD patients as compared to IBD-PSC patients (median 20.4 vs. 28.6 years after onset, $p = 0.087$). No significant differences between IBD and IBD-PSC patients were observed with respect to the time to first surgical intervention.

Conclusions: In our large cohort study, we found that IBD patients with coincident PSC show a distinct disease course with earlier disease onset and higher risk for extensive disease manifestation in UC. Furthermore, the risk for colorectal dysplasia development in IBD patients with coincident PSC was markedly increased as compared to IBD patients without PSC. Therefore, regular surveillance colonoscopies are essential in the clinical management of IBD patients suffering from PSC.

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Performance of ASAS criteria for inflammatory back pain in patients with inflammatory bowel disease

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Background: Axial spondyloarthritis (axSpA) is a common extraintestinal manifestation of inflammatory bowel diseases (IBD). It is recommended to be diagnosed in patients with IBD by association of clinical features, such as Inflammatory Back Pain (IBP), and imaging, such as MRI and X-ray. In axSpA patients without IBD, Ankylosing Spondylitis Assessment Society (ASAS) criteria are used for defining IBP. Their diagnostic performance in patients with association of axSpA and IBD is not clear. The goal of the study was to evaluate the prevalence of Inflammatory Back Pain (IBP) in patients with IBD, and to explore the prognostic value of ASAS criteria for IBP in patients with IBD compared with imaging (MRI, X-ray) and ECCO consensus requirements for axSpA diagnosis in patients with IBD.

Methods: The study included 70 patients with IBD (Ulcerative Colitis (UC) - 45 patients (64.3%), Crohn's disease (CD) - 25 (35.7%), mean age 44 ± 1.34 years). IBP was defined by ASAS criteria (2009). Patients, who fulfilled the ASAS criteria, or had back pain duration over 3 months and fulfilled 2–3 out of 5 ASAS criteria, imaging of lumbar spine and sacroiliac joints was performed (X-ray - 44 patients, including 21 with IBP; MRI (T1, STIR) - 25 patients, including 19 with IBP). Imaging was considered positive, if patients had at least unilateral sacroiliitis stage 2 or higher according to accepted grading system on X-Ray, or bone marrow oedema in sacroiliac joints on MRI.

Results: Low back pain was observed in 60 (85.7%) patients with IBD, 25 (35.7%) patients fulfilled the criteria ASAS for IBP. Radiographic changes were observed in 11 patients, 6 patients fulfilled the requirements of the modified New York classification criteria for ankylosing spondylitis. Osteitis on MRI was detected in 16 patients. Performance of the ASAS criteria was the following: sensitivity 76.2%, specificity 64.3%, PPV 61.5%, NPV 78.3%, LR+ 2.13, and LR- 0.37 (ECCO consensus definition used as the "gold standard"). Combination of ASAS criteria with MRI provided good discriminating power. X-ray didn't have any additional predictive value in patients with signs of IBP. In contrast, MRI doesn't have any additional predictive value in patients with no IBP.

Conclusions: IBP is a common finding in patients with IBD. The ASAS criteria for IBP were proved to be a valid instrument in patients with IBD. Performance parameters of the ASAS criteria in patients with IBD was comparable to the following in the general population of patients with axSpA.

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FOX04 gene expression in colonic mucosa is a potential marker associated with histological remission in patients with ulcerative colitis

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Background: Ulcerative colitis (UC) is a chronic and inflammatory disease that affects the colon of unknown etiology. The genetics factors play an important role in the pathogenesis of UC. FOX04 is a transcription factor that regulates the immune response by inhibition of nuclear factor kappa B (NF- κ B). The NF- κ B regulates the expression of pro-inflammatory cytokines and proteins from tight junctions such as occludins. The aim of this study was to measure the gene expression of FOX04 in patients with UC and normal controls as well as to determine their association with clinical outcomes.

Methods: We included a total of 37 patients with confirmed diagnosis of UC and 20 controls without endoscopic evidence of any

type of colitis or neoplasia. All colonic biopsies were taken by colonoscopy. The histological remission was defined according Riley and Geboes index. The relative quantification of the gene expression was performed by real time PCR for FOXO4: forward: cgagggactggactcaact; reverse: ggctcaagggtaaagtagatatga and the glyceraldehyde-3-phosphate dehydrogenase (GAPDH): reverse 3'-agccatcgtctcagacac and forward 5'-gcccaatacaccacaaatcc, as house-keeping gene was analyzed for normalization. Statistical analysis was performed using the program SPSS Ver. 17. Statistical significance was considered when P value was <0.05.

Results: Of the 37 patients with UC (17 male and 20 female) with a mean age at diagnosis of 42 years and 20 normal control individuals with a mean age of 44 years. Regarding to the UC group, 22 had histological activity and the remaining 15 UC patients were on histological remission. The extent of UC was pancolitis (74%), distal colitis (23%) and left side colitis (3%) and clinical course was distributed as follows: 37% were initially active and then inactive; 30% had intermittent activity and 33% had continuous activity. The gene expression of FOXO4 was increased in patients with remission UC compared to active UC patients ($p < 0.002$) and normal control group ($p < 0.001$). No significant differences were found between patients with active UC and normal controls. The overexpression of FOXO4 gene was associated significantly with histological remission ($p < 0.05$, OR=8.5, 95% CI: 0.83–87.8).

Conclusions: The gene expression of FOXO4 in colonic mucosa was increased in patients with remission UC. FOXO4 could be a potential marker of histological remission and its over-expression in remission UC might suggest an anti-inflammatory mechanism as inhibitor of the production of NF kappa B.

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Impact of double balloon endoscopy on management of small bowel Crohn's disease

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Background: Since Double Balloon Endoscopy (DBE) enables us to examine deep small bowel either oral or anal it could be of great utility in the management of Crohn's disease (CD) patients. Aim: To evaluate the diagnostic yield and therapeutic impact of DBE on small bowel CD.

Methods: The medical records of 180 CD patients, from October 2009 to April 2015, were retrospectively analyzed. Patients were included if they had known CD based on clinical, colonoscopic and histological findings and had been subjected to DBE. If one patient underwent more than one DBE examination only the first evaluation was considered. The primary end point of our study was to evaluate small bowel involvement that is beyond the reach of conventional colonoscopy. The secondary endpoints were to determine the impact of DBE findings on management strategy of CD. The diagnostic yield of DBE in small bowel CD was determined. In addition, the changes in medical treatment, endoscopic intervention and surgical procedures, within three months after DBE, were analyzed.

Results: Among 180 patients with CD, 90 patients underwent 168 DBE examinations and included. The mean age of included patients was 40±13.6 years. They were 63 males and 27 females. Eighty-two (91%) patients with established CD underwent DBE for evaluation

of small bowel involvement and 8 (9%) patients underwent DBE because of suspicion of CD and had been newly diagnosed. The overall diagnostic yield of DBE was 69%. Within 3 months after DBE examination the management strategy of CD changed in 47 (52.2%) patients, based on DBE findings. The medical treatment escalated in 20 (32%) patients, and decreased in 7 (11%). 14 (24%) patients underwent DBE assisted balloon dilatation, and 6 (9.6%) patients underwent CD-related surgery.

Conclusions: DBE is able to uncover small bowel involvement in a significant proportion of CD patients. The DBE findings modified the management strategy in at least one half of CD patients.

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Decreased expression of elafin in peripheral blood and intestinal mucosa in inflammatory bowel disease

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Background: Elafin is an endogenous serine protease inhibitor that has diverse functions such as anti-inflammation, immunoregulation, anti-microbe and so on. The cause of inflammatory bowel disease (IBD) is still unclear. Recently, the destruction of balance between proteases and antiproteases become the focus in the pathogenesis of IBD. Several studies have reported the expression of elafin in colonic tissue of IBD patients or murine models, although the results are controversial, its therapeutic implication is noteworthy. Here, we detect the expression of elafin in peripheral blood and colonic tissue of IBD patients, then, explore its role and value in assessing the activity and severity of IBD.

Methods: Real-time PCR and ELISA were respectively performed to quantitate elafin mRNA and plasma concentration in a total of 106 peripheral blood samples from 106 patients (41 UC, 27 CD, 38 controls). Compare the expression of elafin between groups and among each stage of IBD. Analyze the correlation between elafin and other markers (ESR, CRP, IBD activity score). Histological inflammation was scored, and elafin was localized and semiquantified by immunohistochemistry in a total of 49 colonic paraffin sections (17 inflamed, 13 noninflamed, 19 controls) from 36 patients (12 UC, 5 CD, 19 controls).

Results: Elafin mRNA levels decreased significantly in active UC group, but increased in remission UC group. However, in CD, we did not detect the above significant differences. Moreover, elafin mRNA levels had tendency to decrease with increasing disease severity both in UC and CD. At the same time, elafin plasma concentration decreased both in UC and CD, but the differences among each stage were not significant. Extensive expression was detected in the colonic mucosa and gland cells in healthy controls, whereas in UC and CD, both in inflamed and noninflamed tissue, immunostaining of elafin weakened, especially in inflamed mucosa.

Conclusions: The expression of elafin in peripheral blood and colonic inflamed tissue from active IBD patients decreases and correlates with the activity of IBD to some extent, suggesting that it may play a protective role in IBD and may predict disease activity and severity.

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Diagnostic accuracy of neutrophil-lymphocyte ratio in suspected paediatric inflammatory bowel disease

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Background: Faecal calprotectin has an established role in the investigation of paediatric inflammatory bowel disease (PIBD) but may not be available. Availability is often hampered by non-provision of samples or delayed by long turnaround times. Exploration of other indices which may indicate a strong likelihood of PIBD in the absence of faecal biomarkers remains important. The neutrophil-lymphocyte ratio (NLR) can be calculated from a full blood count (FBC) and has been proposed as a marker of inflammation. We aimed to determine the diagnostic accuracy of NLR in suspected PIBD patients prior to their first endoscopic assessment.

Methods: Children (aged <18 yrs) undergoing endoscopic assessment for suspected PIBD were identified from our prospective regional IBD database and local endoscopy lists. Review of laboratory records identified the FBC performed closest and prior to endoscopy. Patients were eligible for inclusion if complete FBC data was available within 6 months prior to endoscopy, during the initial diagnostic cycle. Statistical analyses were performed using Vassarstats and EasyROC v1.3.

Results: 182 patients met the inclusion criteria; 89 cases of PIBD and 93 cases with non-IBD diagnoses or normal investigations. The PIBD group were older (12.6yr vs 8.8yr; $p < 0.0001$) with no difference in sex ratio ($p = 0.575$). Median time from blood sample to endoscopy was 16 days (IQR 0–49) and was lower in the PIBD group (4d vs 37d; $p < 0.0001$). NLR was significantly higher in PIBD (median 3.04, IQR 2.03–4.18) than in non-IBD patients (1.4, 0.95–2.03) ($p < 0.0001$). Area under the receiver operator curve (AUROC) for NLR as a diagnostic test for PIBD was 0.81 (95% CI 0.75–0.88). Using an optimal cut-off of 2.37 gave a sensitivity of 67% (95% CI 57–77) and specificity 85% (95% CI 76–92). In patients with otherwise normal blood markers (CRP, ESR, albumin, WCC, platelets), median NLR remained significantly higher in PIBD (2.32 [1.74–3.28] vs 1.43 [1.01–1.97]; $p < 0.001$, AUROC 0.77 [95% CI 0.65–0.89]). Using any abnormal test from CRP, ESR, albumin and NLR, sensitivity was 86% (95% CI 77–92), specificity 66% (95% CI 54–76), positive predictive value 74% (95% CI 64–83) and negative predictive value 80% (95% CI 68–89).

Conclusions: NLR is significantly higher in patients with PIBD compared to cases with non-IBD diagnoses or normal investigations. This remains the case in patients with normal inflammatory markers. NLR provides moderate sensitivity and specificity for the diagnosis of PIBD and sensitivity is improved by combination with other readily available blood parameters. We propose that NLR has a useful place in the diagnostic work-up of patients with PIBD, especially in the resource-poor setting and where there are barriers to obtaining faecal samples.

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Validation of the red flags index for early referral of patients with symptoms and signs suggestive of Crohn's disease

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Background: Crohn's disease (CD) is a systemic chronic debilitating inflammatory disease affecting the gastrointestinal tract. The delay in diagnosis is common and this can have severe clinical consequences. Recently, a simple 8 symptom index "The Red Flags Index" has shown high specificity and sensitivity in identifying patients with symptoms suggestive of CD who should be referred to a specialist for further evaluation. We sought to validate this score in a cohort of Portuguese patients.

Methods: The previous score (S. Danese et al Journal of Crohn's and Colitis, 2015, 601–606) was prospectively applied in a cohort of patients with an established diagnosis of CD. Healthy subjects and patients with irritable bowel syndrome (IBS) were used as controls. Patients with CD were asked to recall the symptoms and signs that they had experienced during the 12 months previous to the date of diagnosis. Patients with IBS and healthy subjects were asked about symptoms and signs present during the 12 months before the visit.

Results: 132 patients (66 with CD) were included in this study. Subjects with CD had higher scores than controls (3.5 ± 0.78 versus 2.1 ± 1.4 , $p < 0.001$). In ROC curve analysis (AUC 0.961), a score > 2 showed sensitivity of 96.97% and positive and negative predictive values were 83.1% and 95.7%, respectively. A score > 7 showed 100% specificity and positive predictive value for diagnosing CD.

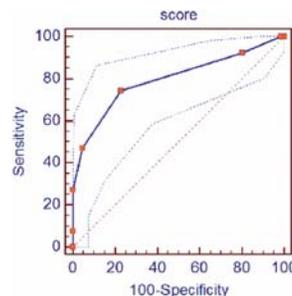


Figure 1. AUROC.

Conclusions: The Red Flags Index showed good sensitivity and specificity for selecting patients with Crohn's disease in a cohort of Portuguese patients. Its routine use in primary care may allow early diagnosis and referral of patients with CD.

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Usability of a home-based test for the measurement of fecal calprotectin in IBD patients

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Background: Fecal calprotectin (FC) correlates well with mucosal healing and risk of relapse in inflammatory Bowel Disease (IBD). An obstacle for a broader use of FC measurement in routine practice is the need to bring stool samples at the hospital or the send them by mail. The aim of our work was to test the usability of a home-based test for the measurement of FC in IBD patients.

Methods: IBD patients in clinical remission or mild disease activity and declaring motivation to perform home-based FC measurements were prospectively recruited in three IBD centres in Oslo, Barcelona and Liège. They received a standardized training. They were instructed to collect and extract stools and to measure FC with a dedicated tool and smartphone application, 5 times at two weeks

intervals over a 8 weeks period. The included patients had to fill in a usability questionnaire made of simple questions and Linkert scales at the first and the last FC measurement. Two global scores were calculated integrating the different aspects of usability: the System Usability Scale (SUS: 0–100) and the Global Usability Score (GUS: 0–85). FC was also centrally measured by ELISA.

Results: 58 patients were recruited, including 18 ulcerative colitis (UC) and 40 Crohn's disease (CD), 30 females. Median (IQR) age was 35 yrs (27–40), median (IQR) HBI in CD was 0 (0–4), median (IQR) Clinical Mayo in UC was 0 (0–1). Over the 58 included patients, 42 performed at least one FC measurement and 27 performed all the FC requested measurements. The median (IQR) GUS (0–85) at the first and last use were 74 (69–80) and 77 (68–83), respectively; the median (IQR) SUS (0–100) at the first and last use were 85 (78–90) and 81 (70–88), respectively. Adherence to the planned measurements and usability of the tool were higher in females and in less severe disease. The inter-class correlation coefficient between home-based and centrally measured FC was 0.85.

Conclusions: Around three quarters of the patients who declared themselves motivated to use home-based test of FC measurement actually did it, but only half of them fully adhered to the planned measurements. Usability scores for the home-based test were high. There was a very good correlation with the centrally measured FC by ELISA.

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Integrated psychological care in outpatients with inflammatory bowel disease

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Background: Psychological issues are prevalent in people with Inflammatory Bowel Disease (IBD). Anxiety and depression are associated with reduced quality of life and may even worsen disease course and impede medical management. However, psychological support is not routinely provided to people with IBD in outpatient settings. Here the need for and acceptability of integrating psychological support was examined.

Methods: Potential participants were recruited in the IBD service of a large tertiary hospital via post and in-person at scheduled outpatient appointments. Screening data were gathered by questionnaire: mental health with the Hospital Anxiety and Depression Scale (HADS) and the Kessler 6 Scale (K6), medication adherence with the Morisky Medication Adherence Scale (MMAS-8) and quality of life by the Assessment of Quality of Life measure (AQoL-8D). Psychological therapy was offered where scores indicated likely need.

Results: 500 patients were approached: 67% participated in psychological screening, 38% scored within clinical ranges, and 17% accepted psychological support. Gender was a significant predictor of participation in screening; women were 62% more likely to participate than men. Analgesia and/or mental health medication significantly increased the likelihood of scoring within the clinical range nearly fivefold (analgesia OR=5.32, p=0.030; psych OR=6.04, p=0.001). Significant predictors of accepting psychological intervention included older age (OR=1.03, p=0.041), anxiety (OR=1.09,

p=0.045), general distress (OR=1.11, p=0.003) and lower quality of life (OR=0.93, p=0.042).

In addition, there were small-to-moderate negative, correlations between medication adherence and anxiety (r=-0.323, p=0.000), depression (r=-0.200, p=0.000) and general distress (r=-0.250, p=0.000). There were also large, negative correlations between overall quality of life and anxiety (r=-0.708, p=0.000), depression (r=-0.787, p=0.000) and general distress (r=-0.801, p=0.000). Anxiety, depression and general distress were not related to IBD disease activity.

Conclusions: Psychological issues were prevalent in patients with IBD and were associated with lower quality of life and reduced medication adherence. Integrating psychological screening into outpatient care was widely accepted, although women were more likely to participate. Furthermore, high proportions of patients reported clinical levels of distress (irrespective of IBD activity) and accepted psychological intervention. These outcomes support the need for psychological screening and intervention in routine IBD care. Follow-up data are currently being collected to determine whether targeted psychological care improves mental health, physical health and/or health-care utilisation.

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Reliable assessment of ultrasound parameters during transabdominal ultrasonography in inflammatory bowel disease

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Background: The inflammatory activity of chronic inflammatory bowel disease (IBD) may effectively be controlled by means of intestinal ultrasound (IUS). Although IUS is considered to be safe and inexpensive, it is criticised for being dependent on the examiner. The aim of this study was to evaluate whether ultrasound parameters are interpreted in the same way by examiners with experience in this diagnostic procedure.

Methods: 40 participants (38 IBD specialists, including 27 gastroenterologists with professional experience between <5 years and >10 years) from nationwide IBD centres were included. Using a standardised questionnaire, the participants assessed 20 ultrasound images and videos of IBD patients. In addition, all study participants independently performed “simulator” investigations of 3 IBD-specific pathologica (Schallware simulator, Germany). Overall, the participants all received the same questions for the exact assessment of US image recordings. The questions related to both the assessment of the technical image quality, the methodology of imaging and the evaluation of specific parameters such as bowel wall thickness, vascularisation, etc. were used as reference results for the consensus of a group of experts (n=3). The parameters were evaluated according to the correspondence between the cases and the conformity of the participants. Mann-Whitney U test and Kappa coefficient were used for the statistical evaluation.

Results: The inter-observer variability, as measured by the kappa coefficient, determined moderate agreement between 0.36 to 0.59 with regard to all parameters assessed by the participants. The evaluation of the specific IBD activity parameters revealed a good match with an average of 60.9%. The relevant parameters for an IBD as

assessment (bowel wall thickness, etc.) were recognised by all participants. The heterogeneity of agreement with regard to interpretation of the findings ranged between 88.5% (item “extraintestinal air”) and 35.6% (item “unevenly altered bowel wall stratification”). Subgroup analyses using the Man-Whitney U test showed that examiners with greater experience reached a higher degree of consensus.

Conclusions: The examiners were able to equally interpret images derived during intestinal ultrasound. In particular, examiners were able to reliably interpret ultrasound parameters relevant for the assessment of IBD activity and complications. The reliability of the assessment increased with the experience of the examiner. Further studies with a larger number of participants to evaluate the reliability of assessment would be meaningful

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Abstract has been withdrawn

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Risk stratification of patients with Crohn’s disease: a retrospective analysis of clinical decision-making and its impact on long-term outcome

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Background: Complications such as need for small bowel resections and hospitalization due to Crohn’s disease (CD) occur when disease activity persists due to ineffective therapy. Certain high-risk features require early introduction of anti-TNF therapy to prevent such complications. We aim to evaluate the prevalence of high-risk features among a cohort of patients with CD and examine the association between discordance of early therapy with baseline risk stratification and disease outcome.

Methods: All adult patients with CD were retrospectively identified and their medical records were reviewed. Clinical, endoscopic, laboratory and radiological data were collected. Patients were divided into “low” and “high” risk groups according to the presence or absence of penetrating disease, perianal involvement, foregut involvement, extensive disease seen on endoscopy or cross sectional imaging, young age at the time of diagnosis (<40), persistent cigarette smoking and frequent early requirements for corticosteroid therapy. Initial treatment selection and treatment approach (“step up” vs. “accelerated step-up” vs. “top-down”) within 6 months of diagnosis was recorded. Rates of CD-related bowel resections and hospitalization within 5 years of diagnosis were calculated. Logistic regression analysis was used to examine the association between “discordance” of early treatment selections and risk stratification categories with outcomes.

Results: Eighty-five CD patients were included. Mean age and duration of disease were 27.1 (+11.7) and 6.4 (+ 4.8) years, respectively. Sixty five percent were females and 66% were native Saudi’s. Smoking was reported in 12% of patients and perianal disease in 18%. “High-risk” features were identified in 51% of which only 14% were treated with “top-down” therapy and 16% “accelerated step-up” care. “Discordance” occurred in 34% of cases. Bowel resection was required for 15/85 (18%) patients and 32/85 (38%) required at least one hospitalization within 5 years of diagnosis. Logistic regression analysis identified a statistically significant association between “discordance” and need for bowel resections (Odds ratio (OR) = 6.50, 95% confidence interval (CI): 1.59–26.27, p=0.009), and hospital-

izations (OR=3.01, 95% CI: 1.08–8.39, p=0.035) within 5 years of diagnosis.

Conclusions: “Discordance” between patient risk-profile and treatment selection early in the course of CD has a significant influence on disease outcome, specifically need for bowel resection and hospitalization. Early identification of “high-risk” features could help prevent long-term complications.

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Optimal time interval required for correlation between fecal calprotectin test and endoscopy

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Background: Fecal calprotectin (FC) concentration has been reported to show good correlation with the degree of inflammation observed in endoscopy, in both Crohn’s colitis (CD) and ulcerative colitis (UC). For more precise correlation between FC and endoscopic inflammation, patients need to provide a stool sample at the same time of endoscopy. However, in real practice, two tests can be hardly performed at the same time. Therefore, we aimed to investigate the time interval between FC test and endoscopy to have a good correlation in assessment of IBD activity.

Methods: Fifty eight patients with IBD (ileocolonic or colonic CD, n=10; UC, n=48) who had undergone endoscopy and FC test were retrospectively analyzed. FC test performed within 3 months were included in evaluation. FC level >200 ug/g was defined relapse of quiescent IBD. Degree of inflammation was assessed using endoscopy-based classification of inflammation for CD and Mayo endoscopic subscore for UC. After assessing concordance between FC and endoscopic score, correlation to the time interval was assessed by receiver operator curves (ROCs).

Results: Median FC levels were 1050 (range 93–6000) ug/g in CD and 305 ug/g (range 6–6893) in UC. Mean time interval between FC test and endoscopy was 18.1±24.4 days. Endoscopic score and FC level were well correlated ($r=0.694$, $p=0.026$) in CD patients. In UC, Mayo endoscopic subscore showed a weak positive correlation to FC level ($r=0.381$, $p=0.008$). ROC analysis suggested that the best cut-off of the time interval for separation of non-correlation and correlation between endoscopic activity and FC level was 48 hours with a sensitivity of 68.4% and a specificity of 51% (AUC, 0.616; 95% CI 0.464–0.768).

Conclusions: FC level within 48 hours could reflect endoscopic activity in patients with IBD. In case of endoscopic examination for treatment decision in IBD patients with high level FC, 48 hours of time interval is recommended.

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A novel small-caliber deep enteroscope can overcome technical difficulty of insertion in patients with Crohn’s disease

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Background: Balloon-assisted enteroscopy is a useful modality for the evaluation of the small intestinal lesions in patients with Crohn’s

disease (CD). Not infrequently, deep insertion of the enteroscope carries difficulty due to adhesion, stricture, or other causes. Deep insertion is required especially for accurate assessment of mucosal healing and treatment of stricture in CD. The novel device (SIF-Y0006; Olympus Co. LTD., Tokyo) is a single balloon enteroscope, with distal tip diameter of 5.4mm and active/passive bending mechanism. The aim of this study is to investigate improvement of insertion ability with the new device, as compared to the standard single balloon-assisted enteroscope (SBE).

The study protocol was approved by each research ethics committee and registered in the University Hospital Medical Information Network as UMIN00017835.

Methods: The patients with CD in whom insertion difficulty existed in the past or expected due to adhesion or stricture are recruited for this study. The standard SBE (SIF-Q260) was inserted per rectally for usual clinical indication. All procedures were performed by expert endoscopists with sufficient experience with enteroscopy. The length of small intestinal insertion less than 1m was regarded as insertion failure, and the scope was removed after crystal violet marking at the deepest portion. Then SIF-Y0006 was re-inserted by the same expert endoscopist. Insertion time to the marking, length of small intestinal insertion, accomplishment of procedure objectives, and patient's acceptance were assessed.

Results: Thirty eight patients were enrolled for this study. Nine patients in whom the length of small intestinal insertion was more than 1 m with the standard SBE were excluded, and remaining 29 patients (CD 25, suspicious of CD 4) were included. With SIF-Y0006, the scope was inserted to the marking in all cases, and beyond the marking in 26. The small intestinal insertion length (24±19 vs. 44±27 cm) and the insertion time to the marking (12±7.5 vs. 5.5±5.6 min) with Y0006 were significantly superior to those with Q-260. Procedure objectives were attained in 81% with Y0006. The patient's acceptance was also better with Y0006.

Conclusions: The new prototype small-caliber enteroscope is useful in patient with CD in whom small intestinal insertion is difficult.

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Correlation of biomarkers to PET/MRI and endoscopy in patients with Crohn's disease with special focus on small bowel involvement

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Background: The combination of positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG) with magnetic resonance imaging (MRI) as integrated PET/MRI in one examination is a new cutting-edge technology for the non-invasive assessment of disease activity in patients with inflammatory bowel disease not accessible for routine diagnostic. In Crohn's disease (CD) a manifestation throughout the gastrointestinal tract is possible. Therefore, a comprehensive diagnostic work-up including endoscopy and an extended exploration of the small intestine is recommended. Non-invasive biomarkers like Lactoferrin and Calprotectin are increasingly

popular and used in all-day patient care. Aim: To compare the performance of non-invasive biomarkers to PET/MRI and colonoscopy in patient with CD with a special focus on small bowel involvement.

Methods: In every patient, a PET/MRI including the maximum standardized uptake value ratio gut/liver (rSUV) and a colonoscopy including an endoscopy index (SES-CD) was performed. The PET/MRI was rated as pivotal for the small bowel and colonoscopy for the colon. Lactoferrin (LF; >7.25 µg/g; TechLab), CalprotectinIMUN (Call; >50 µg/g; Immundiagnostik - monoclonal), CalprotectinCALPREST (CalP; >50 µg/g; Eurospital - polyclonal), PMN-elastasis (PMN-e; >0.062 µg/g; Immundiagnostik), S100A12 (Immundiagnostik) as well as CRP (≥0.5 mg/dl) were correlated to the SUVQuot and the SES-CD using nonparametric correlation analyses and median levels in active and inactive patient groups were calculated.

Results: 50 patients (32 female), mean age 43.1±13.4 years (range 20–67) with known CD (mean years since first diagnosis 12.8±11.5) were included in the study. N=28 patients showed signs of active disease in colonoscopy and/or PET/MRI, n=14 patients showed at least one stenosis. N=17 patients showed exclusively small bowel involvement. rSUV range was 0.5–11.5, SES-CD median in active disease was 4.5 (range 0–12) indicating mild to moderate disease. rSUV was correlated significantly with the SES-CD (rs(45)=0.505; p<0.001) and with LF (r(50)=0.33; p=0.026) and S100A12 (r(50)=0.30; p=0.04), but not with PMN-e, CalP, Call and CRP (all p>0.05). The median levels (inactive/active) of LF were: 3.5/9 µg/g, Call: 96.3/122.4 µg/g, CalP: 195/238 µg/g; PMN-E: 0.115/0.15 µg/g, S100A12: 47.3/55.1 µg/g, CRP: 0.25/0.4 mg/dl. In the patient group with exclusively small bowel involvement rSUV was correlated significantly only with LF (r(50)=0.676; p=0.003).

Conclusions: Lactoferrin and S100A12 levels were significantly correlated to rSUV and Lactoferrin levels remained significantly correlated to rSUV for exclusively small bowel activity. Further studies are warranted to assess the performance of fecal biomarkers in IBD identified by PET/MRI.

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Histological features in paired ileal resections in Crohn's disease patients

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Background: Post-operative recurrence after ileo-colonic resection for stricturing Crohn's disease (CD) is common. The ileal wall in CD can be pathologically heterogeneous, featuring variable combinations of smooth muscle, fibrous and lymphoid tissue as well as edema and lymphatic dilatation. The clinical significance of its composition with respect to disease recurrence is unknown. This study sought to determine whether the composition of recurrent strictures recapitulate those of the primary ileal disease.

Methods: Patients with Crohn's ileitis that required 2 resections, occurring >6 months apart were identified from our archives. The most representative sections of the inflamed ileum in H&E slides were reviewed. For each layer [mucosa, muscularis mucosae (MM), submucosa (SM), muscularis propria inner (MP-I) and outer layer (MP-O), and subserosa (SS)], histological abnormalities were evaluated using a semi-quantitative graded scale (scored -1 to +3). The parameters assessed included layer thickness, expansion of smooth muscle and adipose tissue, and the presence of fibrosis, dilated lymphatics or vessels, inflammatory cells, granulomas, edema, and lymphoid aggregates. All histological analysis was performed by an expert gastroenterology pathologist, who was blinded to the clinical information. Statistical analysis of the paired data was done with equivalence and weighted Cohen's Kappa tests. Correlation (r) value >0.3 was considered meaningful. Cluster analysis was used to identify groups of variables that showed similar results.

Results: Forty four ileal resection specimens from 22 patients (64% were men; mean age at 1st surgery: 32±13y) were retrieved. All surgical specimens presented with expansion of the MM and MP-I. Using the equivalence test, most of the histological features were similar between primary and secondary specimens. The features with highest correlation between the first and second resections were: MP-O inflammatory cells (r=0.78), MP-O and MP-I dilated lymphatics (r=0.46 and r=0.43, respectively), MP-O and SS granulomas (r=0.37 and r=0.35, respectively), SS lymphoid aggregates (r=0.33) and MP-I inflammatory cells (r=0.32). There was a significant clustering for granulomas in different layers between first and second specimens (p<0.05).

Conclusions: To the best of our knowledge, this is the first report describing the histologic features in paired ileal resections in CD patients. The overall histological composition of the specimens was similar between surgeries. MP inflammatory cells and dilated lymphatics, MP-O and SS granulomas and SS lymphoid aggregates were the pathological features that were most likely to be found at reoperation. The presence and severity of granulomas is similar between paired surgical specimens.

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Validation of the clinical utility of IFI16-based markers in IBD

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Background: Although the exact cause of IBD remains unknown, available evidence suggests that an abnormal immune response against the intestinal microorganisms is responsible for the disease

in genetically susceptible individuals. Recent advances in immunology and genetics have clarified that the innate immune response is as important as adaptive immunity in inducing gut inflammation in IBD patients. Significant alterations in the expression and function of pattern recognition receptors (PRRs), including the IFI16 protein, were indeed described in colonic mucosal biopsies from active ulcerative colitis (UC) patients versus healthy controls (Vanhove et al., *Inflamm Bowel Dis* 2015). We have recently extended these analyses to Crohn's disease (CD) patients (Caneparo et al., *Inflamm Bowel Dis* 2016). Furthermore, because we have previously demonstrated that IFI16 protein is a target for autoantibodies, this study aimed to evaluate its specific seroresponse in a large and heterogeneous cohort of patients with IBD.

Methods: To date, we have measured anti-IFI16 antibodies (IgG and IgA subtypes) in the sera of 157 patients with IBD: 113 patients with CD and 44 patients with UC, prospectively harvested before and after therapy. The patient antibody statuses were qualitatively and quantitatively associated with disease phenotype and response to therapy, and compared to those for anti-GP2 antibodies.

Results: In a cohort of patients undergoing Infliximab (IFX) treatment, we have recently observed significantly higher titers of anti-IFI16 IgG in both CD and UC patients compared with healthy controls. Anti-IFI16 IgA titers were also present in patients with CD. Finally, significant changes in anti-IFI16 IgG subtype titers after IFX therapy were demonstrated in patients with CD, which correlate with clinical remission. In the present study, we have extended this analysis to a larger IBD cohort including patients with therapy other than IFX. The results substantiate that anti-IFI16 autoantibody titers are significantly higher in IBD patients than in controls. Moreover, IgG and IgA titers correlate with different specific clinical features in CD patients.

Conclusions: Our recent results have highlighted the importance of IFI16 in IBD pathogenesis showing that its *de novo* overexpression in the gut epithelial cells may lead to the development of specific autoantibodies (Caneparo et al., *Inflamm Bowel Dis* 2016). Furthermore, our recent results in a larger cohort of IBD patients substantiate our reasons to focus on the biological and clinical significance of the IFI16 protein and specific antibodies, and their clinical utility with the potential to ameliorate the diagnostic/prognostic stratification of IBD.

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Diagnostic performance of low haemoglobin density (LHD%) for detecting iron deficiency in IBD patients

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Background: In the absence of a feasible, non-invasive gold standard, iron deficiency anaemia (IDA) is best measured by the use of multiple indicators. However, the choice of an appropriate single iron biomarker to replace the multiple-criteria model for screening for IDA at the population level continues to be debated. Recently low haemoglobin density (LHD%) from Coulter counters has been suggested as a useful tool to detect iron deficiency [1]. Its diagnostic performance in an IBD population has not been evaluated. Using the mathematical sigmoid transformation $LHD\% = 100 \times \sqrt{[1 - (1/(1 + e^{1.8(30 - MCHC)}))]}$ this study investigated the reliability of LHD% for the assessment of iron status in iron deficiency

anaemia (IDA), anaemia of chronic inflammation (ACD) and mixed IDA/ACD.

Methods: The study population consisted of 84 patients (34 male, 50 female) with IBD (age, 36.40±13.14 years, 40% male), who consecutively attended the Crohn Colitis Centre Frankfurt for routine evaluation between October 2014 and September 2016. Blood count, transferrin saturation (TSAT), serum ferritin (SF), C-reactive protein and ZPP were determined by routine assays. Patients with anaemia were classified as having IDA if active inflammation (CRP <5mg/L) was absent and TSAT <20% and ferritin level <30 µg/L; Patients were classified as having ACD if active inflammation was present (CRP ≥5mg/L) and TSAT <20% and ferritin level ≥100µg/L; Patients were classified as having IDA/ACD if active inflammation was present and TSAT <20% and ferritin level >100µg/L [2]. Receiver operator characteristic (ROC) curves were constructed to evaluate the performance of LHD.

Results: In ferropeonic IBD patients (IDA and IDA/ACD), the values obtained for LHD% showed no statistical difference ($p>0.5$). Significant differences were detected when patients with ACD (LHD% 10.5%) were compared with the ACD/IDA group (LHD 24.1%, $p=0.0001$). ROC analysis for LHD% in the detection of iron deficiency showed the following: area under curve 0.903; cut off 5.5%, sensitivity 88.6%, specificity 76.9%.

Conclusions: These results clearly demonstrate that LHD% is a reliable biomarker for the detection of iron deficiency in IBD patients with anemia in both the presence and absence of inflammation. Our findings indicate that LHD can provide added value in diagnosing iron deficiency in anaemic IBD patients.

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Investing in workability of patients with IBD: results of a pilot project Activ84worK (Activate for work)

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Background: Inflammatory bowel diseases (IBD) are chronic gastrointestinal conditions mainly affecting young people. The symptoms of these diseases often make it difficult to actively participate in the workplace especially during periods of flare. Activ84worK was a pilot project to stimulate professional activity and reduce absenteeism in IBD patients by providing them with more flexible working conditions including teleworking.

The aim of Activ84worK was to improve both the well-being of the patient as well as his/her employer, and to contribute to a reduction in absenteeism.

Methods: Activ84worK was a collaboration between Abbvie, Mensura, Proximus, SD Worx and University Hospitals Leuven (UZ Leuven) with the support of the patient association “Crohn- en Colitis Ulcerosa Vereniging (CCV vzw) in Flanders, Belgium”. Since April 2015, IBD patients were recruited by CCV and the gastroenterology department of UZ Leuven. Patients who showed interest, were contacted by Novellas healthcare for screening and follow-up in the

program. Informed consent was signed and both the employee and employer were followed for 6 months by face-to-face meetings and intermediate phone contacts. The project was evaluated from 3 perspectives: the benefit of teleworking for the employer, the employee, and the effect on society.

Results: Between April 2015 and October 2016, 71 patients showed interest in the Activ84worK program, 19 were eligible to participate and 14 completed the program (29% male, 29% private companies). Over the period of 6 months, all patients expressed their enthusiasm for tailored and flexible working conditions thanks to the option of teleworking. The case studies, based on interviews conducted with participating employees, indicated that removing work-related stress factors (such as not having a toilet nearby, not being able to take a rest when needed) resulted in employees feeling much more at ease. Concretely, this led to fewer days of sick leave for most patients, a higher degree of workability and focus of employees, and a decrease in costs of absenteeism for employers and society. The pilot project was seen as a very positive experience by both parties. In addition, more openness was created between the employee and the employer, the taboo on the disease was lifted, and this had an overall positive impact on the work-life balance of patients.

Conclusions: This pilot project showed that teleworking and flexible working hours improved labor participation of patients with IBD. The results of this project are now used to inspire policy-makers and employers to gain maximum support for the chronically ill eager to work. We feel this initiative should be extended to a larger cohort of patients and should also be tested in other chronic diseases.

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Home smart-phone based measurement of fecal calprotectin by IBD patients: correlation with laboratory assay and applicability as patient-friendly monitoring tool

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Background: Fecal calprotectin is an important tool for monitoring disease activity in IBD. As patient-tailored therapy continues to develop, we aimed to examine the efficiency and accuracy of a smartphone-based fecal calprotectin home-test in comparison to the established calprotectin Quantum-Blue assay.

Methods: Prospectively-followed adalimumab-treated IBD patients performed a fecal calprotectin home-test (Buhlmann - IBDoc), consisting of fecal collection, extraction and measurement by a smartphone app using the phone's camera. Each patient performed the test under guidance by qualified personnel. The Quantum-Blue laboratory assay was performed simultaneously using the same stool sample for each patient.

Results: 52 patients performed both tests (median age 35.5 years, 50% females, 92% Crohn's patients, 33% high school education or less). In 27/52 tests there was >25% difference in quantitative result of the paired tests. However, there was significant and strong correlation between results from both assays ($\rho=0.924$, $p<0.0001$, figure 1). Educational status and age did not affect the correlation between tests results ($\rho>0.92$, $p<0.0001$, for both comparisons).

Conclusions: Despite some numeric quantitative divergence, the results of the home fecal calprotectin test (IBDoc) correlate well with values-ranges obtained using conventional lab-based calpro-

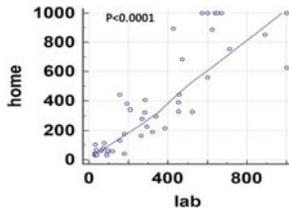


Figure 1. Correlation between widely applied laboratory test & smart-phone-based home test.

tectin test. Smart-phone based fecal calprotectin test may be a useful patient-friendly tool for monitoring of IBD patients at home, with minimal interference to their routine.

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Assessing the effect of ethnicity on urinary metabolic profiles in inflammatory bowel disease

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Background: Urinary metabolic profiling can distinguish patients with inflammatory bowel disease (IBD) from healthy controls (HC) and can also separate ulcerative colitis (UC) from Crohn's disease (CD). Clinical phenotype varies between Caucasians (Cau) and South Asians (SA) however discriminatory metabolites have not been studied in different ethnic populations. The aim of this study was to compare the urinary metabolic profiles of IBD patients and HC in Cau and SA backgrounds.

Methods: Samples from 405 IBD patients (283 Cau and 122 SA) and 137 HC (98 Cau and 48 SA) were analysed by H¹NMR spectroscopy. Clinical and dietary data were collected. Orthogonal partial least squares discriminant analysis (OPLSDA) was performed to examine whether there were differences in metabolic data between Cau and SA. R² (variance), Q² (quality assessment) and p values (validity) for each model were described. Targeted profiling was performed using integral regions of 19 metabolites relating to the gut microbiota, TCA energy cycles and amino acids, as identified in published literature on IBD metabonomics in Cau.

Results: The phenotype of SA CD was not significantly different to Cau CD in this cohort. In the SA UC group there was more pancolitis (p=0.051) and less proctitis (p=0.008). There were more vegetarians in the SA group. OPLSDA was able to separate patients with IBD from HC, and also UC from CD, in the Cau cohort, but this separation could not be replicated in SA (negative Q² values).

OPLSDA models also separated SA HC from Cau, and SA CD from Cau CD, but in UC no robust model could be made. In targeted analysis 4-cresol and hippurate were lower in SA compared to Cau regardless of IBD or HC. In IBD patients trimethylamine-N-oxide and succinate were different between ethnicities in both subtypes of

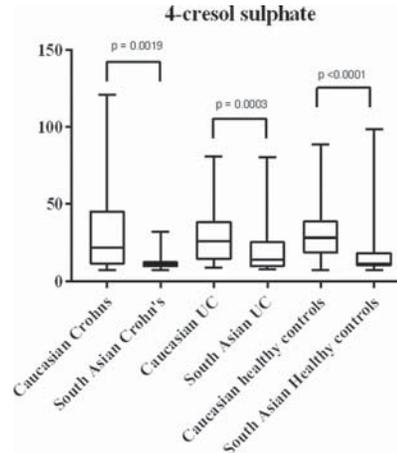


Figure 1. Targeted analysis of 4-cresol sulphate.

IBD, alanine and methanol were different between Cau and SA controls.

Conclusions: SA manifest IBD phenotypically differently and display a different metabolic profile to Cau with IBD. Differences are also present between SA and Cau HC, and a combination of genetics, diet and microbiome may account for these differences. IBD has been sparsely studied in populations other than Cau, but with an incidence in SA migrants superseding that of the native UK population, it is important to better understand and interpret IBD metabolic profiles of different ethnicities.

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Psychosocial impact of inflammatory bowel disease and its practice management as perceived by patients and physicians in Spain. The ENMENTE Project

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Abstract P182 – Table 1. OPLSDA models examining HC vs CD, HC vs UC, and UC vs CD in Cau and SA cohorts. Implicated discriminatory metabolites identified from loadings plot of each model

	R ² Cau	Q ² Cau	p value (1000 permutation testing) Cau	Implicated metabolites Cau	R ² SA	Q ² SA
HC vs CD	0.63	0.63	0.003	Beta-aminoisobutyrate (3-aminoisobutyrate), Hippurate, Glycine, Creatine	0.60	-0.21
HC vs UC	0.82	0.80	0.012	Fatty acyl chain protons, Hippurate, Citrate, Cholate	0.34	-0.15
UC vs CD	0.88	0.46	0.008	N-Acetylglutamate, Hippurate, Alpha-hydroxyisobutyrate (2-hydroxyisobutyrate),	0.22	-0.07

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Background: Inflammatory Bowel Disease (IBD) may cause psychological morbidity. The ENMENTE project aims to improve the identification and initial management of psychological problems affecting IBD patients in the gastroenterology clinic. The aim of the study was to describe the patients' and physicians' perception about the emotional impact of IBD and its approach by gastroenterologists.

Methods: During April 2016 two surveys were made available online, one for IBD patients, on the ACCU Spain website (Confederation of IBD Spanish Patients' Associations) and another one for physicians (n=665) members of GETECCU (Spanish Group for IBD treatment). Both invited their members to participate by email and the patients' survey was announced in social networks. Patients and physicians were asked closed questions about a) how they perceive the impact of IBD on psycho-social aspects, b) how they think the initial management should be and 3), physician behaviours during patients follow-up. A Mann-Whitney test was used to compare 165 valid physicians' questionnaires with a random sample of 165 patients' questionnaires.

Results: 912 patients (mean age 39 (\pm 10) years, 67% women, mean duration of IBD 11 (\pm 9) years) and 170 physicians (mean age 44 (\pm 10) years, 58% women, 98% public hospital practice) responded. A high percentage of physicians and patients agreed that IBD influences patients' psychological status, personal relationships and everyday life, and that IBD activity can be influenced by patients emotional status (Table 1, a). Similarly, a high percentage of physicians and patients reported that patients psychological evaluation should be addressed as routine clinical practice in the IBD clinic, and that a clinical psychologist should be part of the IBD clinical team, however the role of the nurse as helping the patients to cope with their disease was less valued by patients than by doctors (Table 1, b). Although >50% of physicians declare to address psychological and social aspects always/nearly always during patients regular visits, this was only perceived by 15–20% of the patients (Table 1, c).

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Table. Proportion of physicians and patients who responded "agree/totally agree" (a,b) or "always/nearly always" (c).

	Physicians (n=165)	Patients (n=165)	P-value
a) Influence of IBD on different patient's facets			
IBD Influences psychological status	90	77	<0.05
IBD influences personal relationships	80	61	<0.05
IBD influences every-day life	86	72	<0.05
Stress worsens IBD	79	84	ns
Sadness or depression worsen IBD	76	69	ns
b) Perception on how the initial management of psychosocial comorbidities should be addressed			
Physician should inquire on patient's psychological status	93	80	<0.05
Psychological treatment should be part of the therapy.	93	77	<0.05
The psychologists should be part of the medical team	95	81	<0.05
The psychologists would be helpful for patients to cope with their disease	77	71	ns
The nurse may help patients to cope with their disease	68	40	<0.05
c) Percentage of physicians who address several aspects of psychosocial comorbidity of IBD			
Emotional status	60	21	<0.05
Working life	62	16	<0.05
Social life	47	16	<0.05
Family life	51	21	<0.05
Sexual life	12	4	ns

Conclusions: Patients and physicians agree on the impact of IBD on patients' psychosocial aspects and on the importance of addressing it together with a psychologist. However, patients indicate that physicians address these aspects less frequently than doctors perceive. An optimal patient-physician communication would help to refocus on IBD-related morbidity.

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Photoprotective behaviours in inflammatory bowel disease patients on azathioprine and TNF- α inhibitors

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Background: Azathioprine and TNF- α inhibitors are widely used immunosuppressants in Inflammatory Bowel Disease (IBD). It has been reported that such treatments increase the risk of developing all types of skin cancer. Patients on combination therapy have been shown to have up to five times the relative risk of non-melanoma skin cancer. The British Association of Dermatology (BAD) has published preventative guidelines for patients on immunosuppression, but specific gastroenterology recommendations are lacking.

Our aim was to assess knowledge of skin cancer risk factors and preventative strategies in an Irish at risk IBD cohort.

Methods: A prospective pilot cohort study. Following ethical ap-

proval and informed consent, a self-assessment questionnaire was given out to patients attending our IBD clinic over a twelve week period. Clinical data was recorded including diagnosis, immunosuppressants, skin cancer risk factors and photoprotective behaviours.

Results: To date, 178 patients completed the questionnaire. Patients were excluded as follows; 21 (12%) with an unconfirmed diagnosis or indeterminate colitis and 58 (33%) not on azathioprine or TNF- α inhibitors.

Data was therefore analysed on 99 (56%) patients. Of these 52 (53%) were women, mean age 40 years (range 17–72 years). In total 78 (79%) had Crohn's disease, 21 (21%) ulcerative colitis, 59 (60%) were on anti-TNFs, 25 (25%) on azathioprine and 15 (15%) were on both.

The majority of patients were a high risk phenotype with light coloured eyes (62% n=61), fair skin (51% n=50), >30 freckles (49% n=49) or had blonde/red hair (24% n=24). Of interest, one (1%) patient had a personal history and 14 (14%) gave a family history of any type of skin cancer. With regard to other risk factors; 24 (24%) worked outdoors, 29 (29%) used sunbeds and 41 (41%) had previous blistering sunburn.

With reference to BAD recommended preventative measures, the majority of our cohort (71% n=70) wore sun cream, but failed to take other important measures; re-applying sun cream every 2 hours (46% n=46), wearing a hat (20% n=20) and staying in the shade at high risk times (54% n=53).

In addition, while 58% (n=57) knew what changes to look for in a suspicious mole, only 37% (n=37) performed regular self-skin checks.

Conclusions: Our pilot study highlights gaps in our at risk IBD cohort's education regarding skin cancer risk and prevention associated with immunosuppression therapy and warrants further investigation. Ideally educational interventions to enhance patient awareness should be undertaken and assessed.

P185 Validity of contrast enhanced ultrasonography and dynamic contrast enhanced MR enterography in the assessment of Crohn's disease

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Background: Increased small intestinal wall thickness correlates with both inflammatory activity and fibrosis in Crohn's disease (CD). Assessment of perfusion holds promise as an objective marker distinguishing between the two conditions. Our primary aim was to determine if relative bowel wall perfusion measurements correlate with histopathological scores for inflammation or fibrosis in CD

Methods: 25 patients were investigated prior to elective surgery for small intestinal CD. Unenhanced Ultrasonography (US) and MR Enterography (MRE) were applied to describe bowel wall thickness and ulcers.

Perfusion was assessed with Contrast Enhanced US (CEUS) and Dy-

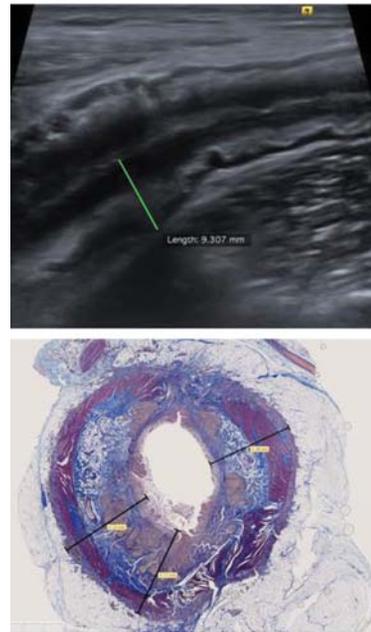


Figure 1. Top: Ultrasonography of bowel wall thickening, measured to 9.3 mm. Bottom: Histopathological stained Masson-Trichrome. Three measurements of bowel wall thickness. The greatest measurement is 9.15 mm.

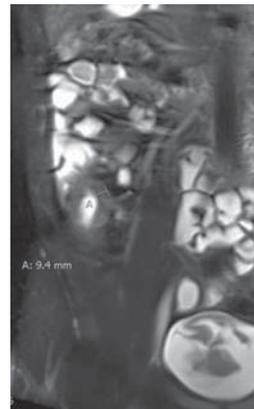


Figure 2. MR enterography (T2 HASTE fat sat): neo-terminal ileum w. edema and a thickened bowel segment, measured to 9.4 mm.

namic Contrast Enhanced MRE (DCE-MRE). Histopathology was used as gold standard.

Results: Bowel wall thickness measured on histopathology was 8.7 ± 1.6 mm, on US 9.1 ± 2.1 mm and on MRE 10.0 ± 2.6 mm. US measurements were 0.4 (–0.3 to 1.0) mm thicker, $p=0.238$ (LoA –2.7 to 3.5 mm), whereas MRE measured a mean of 1.4 (0.4 to 2.3) mm thicker bowel wall compared to histopathology, $p=0.006$ (LoA –3.0 to 5.7 mm). Ulcers defined as linear, rake, confluent, or large were present in 19 patients on histopathology. Sensitivity and specificity for ulcer detection by US and MRE are shown in Table 1.

No correlation was found between the severity of inflammation nor fibrosis on histopathology and neither DCE-MRE ($r=-0.13$, $p=0.54$ for inflammation and $r=0.41$, $p=0.05$ for fibrosis) nor CEUS ($r=0.16$,

Table 1. Accuracy for ulcer detection on cross sectional imaging

	Sensitivity	Specificity	Accuracy	p-value
Ulcers on US	18/19 (94.7%) [74.0–99.9%]	4/6 (66.7%) [22.3–95.7%]	80.7% [59.4–100%]	$p=0.005$
Ulcers on MRE	15/18 (83.3%) [58.6–96.4%]	2/6 (33.3%) [4.3–77.7%]	58.3% [35.9–80.8%]	$p=0.366$

p=0.45 for inflammation and r=-0.28, p=0.19 for fibrosis). Wall thickness assessed with US was correlated with both histological inflammation (r=0.611, p=0.0012) and fibrosis (r=0.399, p=0.048). The same was not true for MR (r=0.41, p=0.047 for inflammation and r=0.29, p=0.16 for fibrosis).

Conclusions: In conclusion, we found no correlation between relative perfusion measurements and histological grading of inflammatory activity or fibrosis. This could be due to the chosen gold standard and the complicated nature of perfusion measurements. Bowel wall thickness remains the single parameter that correlates best with both activity and fibrosis and can be reliably estimated by MRE and especially US.

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Association between anti-TNF serum levels and mucosal healing in inflammatory bowel disease

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Objectives: a) To evaluate the diagnostic accuracy of anti-TNF through levels to predict mucosal healing (MH) in inflammatory bowel disease (IBD); b) to determine the best cut-off point to predict MH in IBD patients treated with anti-TNFs.

Methods: Multicenter, prospective study. IBD patients under anti-TNF treatment for at least 6 months that had to undergo an endoscopy for medical indication were included. Patients with incomplete endoscopy, those with intestinal segments affected by the disease non-accessible to endoscopy, and those receiving anti-TNF to prevent postsurgical recurrence were excluded. MH was defined as: Simplified Endoscopic Score for Crohn's Disease (SES-CD) <3, Rutgeerts score <2 or Mayo endoscopic score <2.

Anti-TNF concentrations were measured using SMART ELISAs (Sanquin Reagents, Amsterdam, The Netherlands)

Results: 182 patients were included; 50% were male, 70% had Crohn's disease and 49% had MH. 52% of patients were under adalimumab (ADA) and 48% under infliximab (IFX) treatment; 51% of patients had previously received another anti-TNF agent. 32% of patients were on concomitant treatment with thiopurines. IFX through levels (median) were significantly higher among patients that had MH than among those who did not (4.8 vs. 3 µg/mL, p=0.04). Similarly, ADA through levels were significantly higher among patients with MH (9.8 vs. 6.6 µg/mL, p=0.04). The accuracy of anti-TNF through levels to predict MH is shown in table 1. Concomitant treatment with immunomodulators had no impact on anti-TNF drug levels. In the multivariate analysis, to have anti-TNF drug levels above the threshold (3.4 µg/mL for IFX, and 7.2 µg/mL for ADA) and to have ulcerative colitis (instead of Crohn's disease) were the variables associated with a higher probability of having MH (OR=3.1, 95% CI: 1.5–6.5 and OR=4, 95% CI: 1.7–9.5, respectively). On the other hand, to have needed an escalated dosage (OR=0.2, 95% CI: 0.08–0.45) and to be current smoker (vs. non-smoker) (OR=0.2, 95% CI: 0.09–0.52) were associated with a lower probability of MH

Table 1. Accuracy of anti-TNF through serum levels to predict mucosal healing in inflammatory bowel disease patients

Anti-TNF	Area under the ROC curve	Best cut-off point	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Infliximab	0.63	3.4	60%	60%	73%	42%
Adalimumab	0.60	7.2	65%	56%	46%	72%

Conclusions: There was an association between anti-TNF through levels and MH in IBD patients; however, the accuracy of the determination of both IFX and ADA concentrations to predict MH was suboptimal. To have IFX through levels above 3.4 µg/mL had a positive predictive value for MH of >70%.

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Differential distribution of Epstein-Barr virus and Cytomegalovirus in colonic mucosa in patients with active ulcerative colitis

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Background: Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) are members of the herpesvirus family. CMV reactivation is often complicated with ulcerative colitis (UC), and is known as the one of exacerbation factors in its pathophysiology. On the other hand, EBV is indicated on the association with oncogenesis including several cancer or lymphoproliferative disorder. However, the association between EBV reactivation and colonic inflammation is still unclear.

Methods: Sixty-four active UC patients who received colonoscopy between January 2005 and January 2015 in Kyoto University Hospital were enrolled in this study. We assessed EBV and CMV reactivation in inflamed and non-inflamed colonic mucosa of active UC patients. Biopsy specimens were obtained from both inflamed and non-inflamed colonic mucosa in each patient. Viral load of EBV and CMV was measured by real-time PCR detection of each DNA quantity more than 10 copies/µgDNA. Moreover, we examined the correlation between positivity of each viruses and patients' backgrounds.

Results: (1) Of 64 UC patients, 20 patients (31.3%) and 31 patients (48.4%) were positive for CMV and EBV, respectively. No significant correlation between EBV and CMV reactivation was observed ($p=0.33$). CMV-DNA was detected in both inflamed and non-inflamed colonic mucosa only in 5 of 20 patients (25.0%) with CMV reactivation. In contrast, 21 of 31 EBV-positive patients (67.7%) had EBV reactivation in not only inflamed but also non-inflamed colonic mucosa.

(2) There was no significant difference in patients' backgrounds between CMV-positive and CMV-negative group.

(3) Mayo endoscopic score was significantly higher in EBV-positive group than EBV-negative group (2.5 vs 2.0, $p=0.04$). Moreover, the proportion of patients treated with anti TNF- α antibody was significantly higher in EBV-positive group compared to EBV-negative group (16.1% vs 0.0%, $p=0.02$).

Conclusions: Our data suggests that a mechanism of EBV reactivation would be different from that of CMV reactivation, and might include blockade of TNF- α . Further studies are required to clarify a role of EBV reactivation on colonic inflammation in UC patients.

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Crohn's disease of the terminal ileum: PET-MRE results correlate well with biomarkers

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Background: IBD specialists often find it difficult to make treatment plans for Crohn's disease (CD) patients, due to both inflammatory and fibrotic components of diseased bowel segments. It is essential to estimate the extent, dominance, depth and overall clinical implications of these. We have preliminarily evaluated a novel imaging method, FDG-PET MREnterography (PET-MRe) and its correlation with the commonly used biomarkers.

Methods: In this exploratory study, 41 patients who were referred for colonoscopy for suspicion of CD, or evaluation of active CD, with a known prior diagnosis, underwent PET-MRe within 8 weeks of the endoscopic evaluation. A SES-CD was obtained at colonoscopy, CRP and faecal calprotectin (FC) were also measured. Imaging results were divided into: no, short-segment (<10cm) or long-segmental (>10cm) inflammation. The study was approved by the local IRB. Correlations were made between the extent of inflammation obtained by PET-MRe and the other parameters using the SAS 9.4 system, by Chi-Square and Wilcoxon tests. Univariate and multivariate analyses were performed per the above parameters.

Results: 34 patients had terminal ileal (TI) disease and 7 had no evidence of inflammation. There was good correlation between active inflammation demonstrated in the terminal ileum by PET-MRe and FC >150, $p<0.0008$. Increased CRP levels and SES-CD score, showed a trend correlating with the extent of inflammation obtained from imaging, with median values of 0.69, 0.76 and 1.35 for CRP ($p=0.26$), and SES-CD scores of 1, 4.5 and 5.5 ($p=0.32$), when compared to non-inflamed, short segment and long segment of inflamed terminal ileum, respectively.

Conclusions: This is a preliminary report of our pilot cohort of CD patients assessed by a novel imaging technique which will further enable the 3-dimensional evaluation of the burden of inflammation

in CD patients. The transmural nature of this disease necessitates a modality that incorporates deep tissues uptake of FDG. We intend to further investigate the composite score that will express this.

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Serum neutrophil gelatinase-associated lipocalin correlates with Mayo Clinic score in ulcerative colitis but fails to predict activity in Crohn's disease

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Background: Hitherto used non-invasive biomarkers to diagnose and monitor activity of inflammatory bowel disease (IBD) show many shortcomings and cannot replace endoscopy. Neutrophil gelatinase-associated lipocalin (NGAL) is a low molecular weight protein released from activated neutrophils and necrotic epithelium whose mRNA expression is increased in inflamed intestinal tissue. Our aim was to explore the relationship between serum NGAL level and endoscopic/clinical activity of IBD.

Methods: A total of 120 patients, 79 with Crohn's disease (CD) and 41 with ulcerative colitis (UC) were prospectively included into the study. In each patient the colonoscopy was performed and routine laboratory tests, serum NGAL and faecal calprotectin levels were determined. The activity of IBD was assessed either by CDAI (Crohn's Disease Activity Index) or Mayo score according to IBD form.

Results: No significant differences were found between UC and CD patients for serum level of NGAL (74.7 vs. 66.5 ng/ml, $p=0.26$), CRP (21.2 vs. 19.4 mg/l, $p=0.98$) and faecal calprotectin (425 vs. 614 mg/kg, $p=0.36$). The transition of UC inflammation activity measured by Mayo score from remission to mild-moderate-severe form was associated with respective levels of NGAL: 37.0, 52.2, 84.9 and 92.9 ng/ml ($p=0.001$), CRP: 3.2, 6.6, 17.7 and 45.9 mg/l ($p=0.004$), and faecal calprotectin: 28.1, 874, 368 and 291 ($p=0.03$). Serum NGAL correlated with CRP ($r=0.55$), but not with faecal calprotectin. In CD patients no significant differences were found between 4 categories (inactive-mild-moderate-severe) by CDAI score for NGAL ($p=0.93$) and faecal calprotectin ($p=0.43$). By contrast, growing CDAI stages were associated with increasing CRP levels (7.8, 18.8, 23.7, 47.9 mg/l, $p=0.04$). Investigated biomarkers did not distinguish between colonic and ileal form of CD.

Conclusions: In UC patients serum NGAL corresponds to disease activity and correlates with CRP concentration, showing higher predictive efficacy than faecal calprotectin. In CD patients CRP shows better relationship with clinical activity than serum NGAL and faecal calprotectin.

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Comparison of two endoscopic scores of inflammatory activity in small-bowel Crohn's disease and its correlation with clinical activity and biomarkers

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Background: Capsule endoscopy (CE) represents the non-invasive method with the highest sensitivity in the evaluation of small-bowel

mucosa in Crohn's disease (CD). Recent recommendations advocate the employment of validated CE scores for the assessment of small-bowel inflammatory activity in CD, allowing a standardized description of lesions and an objective assessment of severity and follow-up. Lewis Score (LS) and Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) are the two validated scores currently available, but comparative studies are scarce. Moreover, evidence concerning the correlation of these endoscopic scores with biomarkers and clinical activity in small-bowel CD is lacking.

The primary aim of this study was to compare LS with CECDAI and to determine cutoff values for CECDAI similar to those of LS (135 and 790). The second aim was to correlate LS and CECDAI with biomarkers and symptoms.

Methods: All patients with CD who underwent CE between March 2010 and February 2016 were included. LS and CECDAI were determined after analysis of each CE. In patients with CD confined to the small-bowel, C-reactive protein (CRP) and Harvey-Bradshaw index (HBI) were evaluated. Statistical analysis: Spearman's correlation coefficient and linear regression analysis. Significance: $p < 0.05$.

Results: Fifty-three patients were included, 60.4% ($n=32$) were women, with a mean age of 41.8 years. CD was restricted to the small-bowel in 64.2% ($n=34$) of patients and in the remaining 35.8% ($n=19$) the activity was ileocolonic. Mean values obtained for LS were 1147 (± 1453), CECDAI 11.3 (± 6.9), CRP 0.92 (± 1.5) mg/dL and HBI 2.4 (± 2.8). There was a very strong correlation between LS and CECDAI ($r_s=0.878$; $p < 0.0001$). In linear regression analysis, thresholds values of 135–790 in LS corresponded to 7.7–10.3 cutoff values in CECDAI, respectively, with an accuracy of 62.3%. Neither CRP correlated with LS ($r_s=0.068$; $p=0.72$) or CECDAI ($r_s=-0.004$; $p=0.98$), nor HBI with LS ($r_s=-0.15$; $p=0.40$) or CECDAI ($r_s=-0.10$; $p=0.23$).

Conclusions: Correlation between the two CE activity scores was very strong, with LS thresholds of 135 and 790 corresponding to CECDAI values of 7.7 and 10.3. HBI and CRP had no correlation with endoscopic activity scores in small-bowel CD.

P191 The robotic surgery in the treatment of Crohn's disease: our experience

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Background: The laparoscopic surgery became the standard of care for the treatment of Crohn's disease only in the last ten years when many studies demonstrated that the minimally invasive colectomy and proctectomy have improved not only the short-term outcomes but also the fecundity rate of patients with a comparable long-term outcomes and safety over traditional open surgery. The reason of this slowly adoption and the hesitation of the surgeons to apply this new approach for the Crohn's disease was due to some specific difficulties like: the general condition of the patients caused by their chronic disease (anemia, malnutrition and immunosuppression) and the macroscopic aspect of the tissues (thickened and inflamed mesentery with a friable and bleeding tissues, the presence of a chronically dilated bowel loops). The introduction of the robotic platform not only is useful to reduce the post-operative adherence, almost 25–45% of patients undergo to a two or operation in their life but thanks to endowrist instruments and staplers may offer a significant benefit over laparoscopy in case of deep and narrow space like pelvis.

Methods: We analyzed our first 5 cases of robotic total proctocolectomy for Crohn's disease surgery from 1st October 2015 to 1st October 2016, evaluating benefits of the robotic platform and performing a comparison between the robotic (5 cases) and laparoscopic (8 cases) approach in a matched based group on demographic, comorbidities and performance status.

Results: All the patients treated underwent to total proctocolectomy with stapled anastomosis, the overall operative time in the robotic group was higher than laparoscopy (335 vs 234 min) as well as the estimated blood loss (350 vs 195 ml). We had one conversion in the first group and 3 in the laparoscopic one. The return of first bowel movement (2.42 vs 2.88 days) and the length of hospital stay (7.46 vs 9.23 days) showed a better result in the patients treated by robotic approach. The intra and post-operative complications rate was similar in both group (1 vs 2).

Conclusions: Even if the longer operative time and the higher estimated blood loss, the robotic approach is a safe and feasible technique and can offer benefits over the laparoscopic approach in case of low rectal dissection thanks to the stable retraction and a magnified view and it can lead to a lower conversion rates. Despite the small number of patients the robotic approach is comparable to open with regard to perioperative outcomes, complications rate and short terminal functional outcomes. We believe is recommended evaluate further the impact of robotic platform in the quality of life of these patients and the impact of the new model Da Vinci Xi system with its wider range of motion in case of multiquadrant surgery.

P192 Heartburn in Crohn's disease is associated with increased disease activity, poor sleep quality and prior ileocectomy

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Background: Patients with Crohn's disease (CD) commonly report symptoms of heartburn, however the prevalence, predisposing factors, and relationship between heartburn and CD are not known. We assessed the prevalence of heartburn in patients with CD and investigated the association between gastro-oesophageal reflux disease (GORD) and CD manifestations, treatment, and sleep quality.

Methods: We recruited patients (pts) with CD from an ambulatory clinic at a tertiary care inflammatory bowel disease center. Pts completed a survey that included the validated GORD Health Related Quality of Life (GORD-HRQL) instrument and Pittsburgh Sleep Quality Index (PSQI). We abstracted clinical data from medical records including medical history, CD classification, medications, and Harvey-Bradshaw Index (HBI). Simple statistical analysis was performed for univariate associations, followed by multivariate logistic regression analysis.

Results: 111 pts with CD were included in the analysis. The mean age was 42 years, mean body mass index (BMI) was 26.31, and the population was 60.4% female. The most common Montreal classification was A2 (59.5%), L3 (55.0%, 9.9% L4), and B1 (50.5%). 63.9% of pts with CD reported heartburn. Pts with and without heartburn were of similar age, sex, smoking status, location of disease, and disease behavior. Pts with heartburn had a higher mean BMI and less frequent alcohol use (Table 1). Female sex (OR 3.06 (95% CI 1.18–7.90), $p=0.02$), BMI (OR 1.12 (1.03–1.22), $p=0.01$), alcohol use (OR 0.47 (0.24–0.90), $p=0.02$), current steroid use (OR 3.70

(1.17–11.67), $p=0.03$), and history of ileocectomy (IC) (OR 4.27 (1.41–12.89), $p=0.01$) were associated with heartburn (Table 2). Pts with heartburn reported less satisfaction with their current condition ($p=0.005$), worse sleep (PSQI mean 7.35 v. 4.63, $p<0.001$), and higher mean HBI (2.54 v. 1.20, $p=0.017$). Pts within 5 years of IC had a similar rate of heartburn as those whose surgery was more than five years prior, but of less severity (GORD-HRQL 4.30 v. 12.05, $p=0.02$).

Table 1. Characteristics of patients reporting heartburn symptoms compared to patients that do not report heartburn symptoms

	Heartburn n = 71	No Heartburn n = 40	p
Age (mean)	41.0	43.6	0.621
Female Sex (%)	64.8%	52.5%	0.229
BMI (mean)	27.2	24.7	0.036
Charlson Comorbidity Index (mean)	0.35	0.48	0.291
Age at diagnosis (mean)	23.9	27.4	0.110
Current smoker (%)	5.6%	5.0%	1.000
Alcohol use (%)			
0	66.2%	42.5%	0.034
1 to 3	31.0%	45.0%	
4 to 6	1.4%	10.0%	
7 to 10	0.0%	2.5%	
10 to 14	1.4%	0.0%	
> 14 per week	0.0%	0.0%	
HBI (mean)	2.5	1.2	0.017
Montreal classification (%)			
A1	32.4%	15.0%	0.000
A2	57.7%	27.5%	
A3	9.9%	57.5%	
L1	23.9%	15.0%	0.536
L2	22.5%	27.5%	
L3	53.5%	57.5%	
L4 modifier	11.3%	7.5%	0.743
B1	53.5%	45.0%	0.426
B2	21.1%	17.5%	
B3	25.4%	37.5%	
Perianal disease modifier	31.0%	32.5%	1.000
Number of prior surgeries (mean)	1.14	1.21	0.904
Ileostomy (%)	7.0%	12.5%	0.491
Strictureplasty (%)	7.0%	5.0%	0.671
Partial colectomy (%)	14.1%	22.5%	0.258
Total colectomy (%)	8.5%	12.5%	0.493
Small bowel resection (%)	12.7%	25.0%	0.119
Ileocectomy (%)	34.3%	17.5%	0.078
GORD-HRQL Total (mean)	12.5	1.3	0.000
PSQI Total (mean)	7.4	4.6	0.000
Sleep efficiency (mean)	86%	92%	0.030
Sleep disturbance score (mean)	8.0	4.2	0.000
Daytime disturbance score (mean)	1.8	1.1	0.006
Satisfied with condition? (%)			
Dissatisfied / Neutral / Satisfied	10.1% / 46.4% / 43.5%	0.0% / 27.5% / 72.5%	0.005

Table 2. Multivariate analysis of factors to predict the presence of heartburn symptoms in Crohn's disease determined by logistic regression

	OR (95% CI)	p
Age	0.98 (0.95–1.00)	0.10
Alcohol use	0.47 (0.24–0.90)	0.02
Sex	3.06 (1.18–7.90)	0.02
Body Mass Index	1.12 (1.03–1.22)	0.01
Steroid use	3.70 (1.17–11.67)	0.03
History of ileocectomy	4.27 (1.41–12.89)	0.01

OR = Odds Ratio; CI = Confidence Interval.

Conclusions: Heartburn in CD is associated with poor sleep quality and increased disease activity. In addition, we newly identified prior IC as a risk factor for heartburn in CD, which may reflect motility alterations due to surgery or fibrosis in these pts. Further investigation into heartburn in CD pts and its management is warranted.

P193

Faecal calprotectin differentially predicts postoperative endoscopic recurrence in Crohn's disease according to therapy. A prospective multicenter study

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Background: Faecal calprotectin (FC) is a marker of gut inflammation that correlates with endoscopic activity in Crohn's disease (CD). However, its accuracy to predict endoscopic postoperative recurrence remains to be completely elucidated. We aim to prospectively analyze if FC levels associate with the presence and severity of postoperative endoscopic recurrence in patients with CD. The relationships between C-reactive protein (CRP) serum levels, clinical disease activity and postoperative endoscopic recurrence are also analyzed.

Methods: A prospective multicentre observational study of diagnostic accuracy was carried out in 5 hospitals at the Ciudad Real province (Spain) from March 2014 to November 2016. Blood and faecal samples were collected from all CD patients with ileocolonic resection, at the moment of undergoing to colonoscopy to assess endoscopy recurrence. Quantitative FC was determined by enzyme-linked immunoassay tests (FC-ELISA). Clinical disease activity was assessed by the Harvey-Bradshaw index and postoperative endoscopic recurrence was graded according to Rutgeerts score.

Results: Sixty patients (35 [58.3%] male) aged 36.3 to 53.1 years were recruited. An ileal disease (L1) was present in 26 (43.3%) of cases, having the remaining an ileocolonic (L3) location. At the moment of colonoscopy, anti-TNF α and immunosuppressant therapy had been used in 54.2% and 66.1%, respectively. Table 1 summarizes main characteristics of participants.

Table 1. Baseline characteristics of CD patients at the time of endoscopy

	Overall cohort (N=60)
Disease duration (years), mean (IQR)	8.1 (3.6–17.8)
Smoking habits, N (%):	
current/former/no smoker	9 (23.1)/10 (25.6)/20 (51.3)
Harvey-Bradshaw index, mean (IQR)	3 (0–7)
CD location, N (%): L1/L3/L4	26 (43.3)/27 (44)/7 (11.7)
Disease behavior, N (%): B1/B2/B3	8 (13.3)/31 (51.7)/21 (35.5)
Treatment, N (%):	
immunosuppressants/biologics	39 (66.1)/32 (54.2)
FC (μ g/g), median (IQR)	103 (63.3–257.5)
CRP (mg/l), median (IQR)	0.24 (0.1–0.76)
Rutgeerts Score, N(%): i0/ i1/i2/i3/i4	17 (18.3)/9 (15)/15 (25)/9 (15)/10 (16.7)

Overall, FC concentrations, serum CRP levels and clinical disease activity were significantly higher in patients with endoscopic recurrence (Rutgeerts $>i2$). Area under curve (AUC) of FC in endoscopic recurrence was 0.69, slightly better than that for serum CRP (0.65). FC cut-off of 50 and 250 mcg/g obtained respectively 91.2% and 44.1% sensitivity, and 30.8% and 92.3% specificity in detecting recurrence; PPV were 63% and 88.2%, while NPV were 69.2% 55.8% for 50 and 250 mcg/g, respectively (Table 2).

The ability of FC to predict disease recurrence significantly improved

Table 2. Sen, Spe, PPV and NPV for FC in predicting postoperative endoscopic recurrence in patients with CD

	Sen (%) (95% CI)	Spe (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
FC cutoff				
50	91.2 (77–97)	30.8 (16.5–50)	63.3 (49.3–75.3)	69.2 (50–83.5)
100	64.7 (47.9–78.5)	57.7 (38.9–74.5)	66.7 (49.6–80.2)	55.6 (37.3–72.4)
200	50 (34.1–65.9)	76.9 (57.9–89)	73.9 (53.5–87.5)	54.1 (38.4–69)
250	44.1 (28.9–60.5)	92.3 (75.9–97.9)	88.2 (65.7–96.1)	55.8 (41.1–69.6)

in patients under biologic compared to those receiving only immunosuppressant therapy (AUC 0.76 vs. 0.59; $p < 0.05$) AUC for serum CRP did not change according type of therapy.

Conclusions: The ability of FC to predictive endoscopic post-surgical recurrence in CD patients is moderate but improves in patients receiving treatment with anti-TNF α agents.

P194

Anti-TNF α treatment following surgical resection for Crohn's disease is effective despite previous pharmacodynamic failure

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Background: The outcome of crohn's disease (CD) patients who failed anti-TNF α therapy despite adequate serum drug levels (pharmacodynamic failure) is unclear. We aimed to assess such pediatric patients who underwent intestinal resection and were re-treated with the same anti-TNF α agent post operatively.

Methods: Pediatric CD patients who underwent intestinal resection and were treated with anti-TNF α agents post-operatively were assessed retrospectively. Patients were stratified to those with pre-operative anti-TNF α pharmacodynamic failure and those with no pre-operative anti-TNF α treatment.

Results: A total of 61 children were included, 21 with pharmacodynamic failure and 40 controls. Median age at intestinal resection was 15 years with 28 (46%) females. The median time from intestinal resection to anti-TNF α initiation was 7 months (IQR 4–13 months). At the time of post-operative anti-TNF α initiation there were no differences in clinical, laboratory and anthropometric measures between groups. Similar proportions of patients from both groups were in clinical remission on anti-TNF α treatment after 12 months and at the end of follow-up (1.7 years, IQR 1–2.9 years): 90.5% vs. 87.5% and 85.7% vs. 82.5% for pharmacodynamic failure patients and controls, respectively; $p=0.8$. No significant differences were observed at 14 weeks and 12 months of post-operative anti-TNF α treatment including endoscopic remission rate and fecal calprotectin. Both groups significantly improved all measures during post-operative anti-TNF α treatment.

Conclusions: Pediatric CD patients who failed anti-TNF α therapy despite adequate drug levels and underwent intestinal resection can

be re-treated with the same agent for post-operative recurrence with high success rate similar to anti-TNF α naïve patients.

P195

The utility of fecal microRNAs in the diagnosis of inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC), chronic disease that still present challenges for physicians treating it: diagnosis, prognosis, and assessment. The current biomarkers for it are still limited. We aim to detect fecal miRNAs in IBD patients compare to healthy controls (HC), in order to get a novel and ideal biomarker for IBD.

Methods: Differential expression of fecal microRNAs micro-array for UC, CD and HC is analyzed, and validated by real-time polymerase chain reaction (RT-PCR).

Results: Seven miRNAs are selected by micro-array and literatures. RT-PCR shows that mir-16-5p is up-regulated in both UC and CD ($p < 0.01$, $p < 0.01$; respectively), while mir-21-5p is up-regulated just in UC ($p=0.002$). The sensitivity and specificity of mir-16-5p in UC are 83.3% and 88.2% (cut-off 10.92); The sensitivity and specificity of mir-16-5p in CD are 76.2% and 88.2%; The sensitivity and specificity of mir-21-5p in UC are 66.7% and 88.2% (cut-off 6.53). However, the sensitivity and specificity of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for UC and CD are lower than biomarkers detected above. For UC patients, mir-16-5p is correlated with age, disease duration, occult blood and S100A12 ($p=0.02$, $r=0.56$; $p=0.02$, $r=0.53$; $p=0.02$, $r=0.54$; $p < 0.01$, $r=0.75$. respectively). For CD patients, mir-16-5p correlated none of the clinical factors.

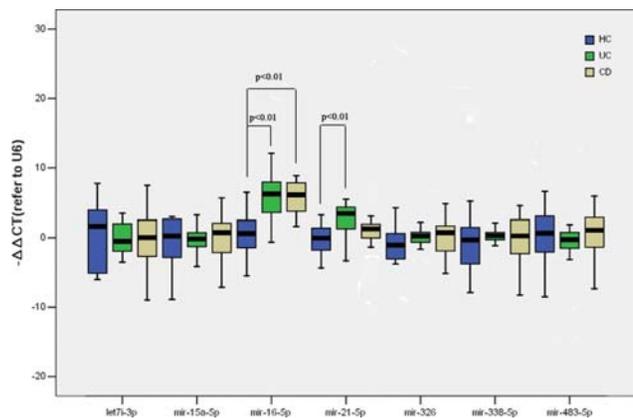


Figure 1

Conclusions: The value of mir-16-5p and mir-21-5p in diagnosis of IBD are higher than ESR and CRP, they are not correlated with ESR and CRP, but correlated with occult blood, disease duration, albumin and platelet.

P196

Patients with ulcerative colitis (UC) and concomitant primary sclerosing cholangitis (PSC) have more subclinical endoscopic and histologic disease activity in the right colon compared to UC patients without PSC

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Background: Primary sclerosing cholangitis (PSC) is an independent risk factor for colorectal cancer (CRC) in ulcerative colitis (UC) patients (pts), however the reason for this is not known. We hypothesized that patients with UC and concomitant PSC (UC-PSC) may have more active subclinical disease than patients with UC alone.

Methods: This is a retrospective case control study of pts with UC-PSC (cases) and UC without PSC (controls). Included pts had pancolitis and were in clinical remission (defined as Simple Clinical Colitis Activity Index score ≤ 2) within 3 months of a colonoscopy. Colonoscopy, pathology and clinical data from 2011–2016 were reviewed. Disease activity was scored using a modified Mayo score for 3 segments: right colon, left colon, and rectum. Histologic scores were translated from pathology reports as quiescent, mild, moderate or severe. We dichotomized results to quiescent and active disease, and compared degree of endoscopic and histologic activity by segment between cases and controls using univariate and multivariate generalized estimating equation (GEE) logistic regression models. We also assessed concordance between endoscopic and histologic scores.

Results: 143 patients (23 UC-PSC; 120 UC) with 205 exams (36 UC-PSC; 169 UC) were included. Cases and controls were similar except that cases were younger at first colonoscopy and more often males.

Table 1. Demographics of cases (PSC-UC) and controls (UC)

	PSC-UC n=23	UC n=120	p value
Age at first colonoscopy (Mean (SD))	38.1 (13.7)	46.4 (16.8)	0.01
Female gender	6 (26.1%)	52 (43.3%)	0.12
White	19 (82.6%)	93 (79.5%)	0.73
Ever used anti-TNF	8 (34.8%)	36 (30.0%)	0.65
Ever used IMM	13 (56.5%)	59 (49.2%)	0.52
Ever used steroids	5 (21.7%)	26 (21.7%)	0.99
Ever used 5-ASA	13 (56.5%)	70 (58.3%)	0.87
Ever used vedolizumab	3 (13.0%)	7 (5.8%)	0.21

Cases had significantly more endoscopic activity (OR=4.12, 95% CI 1.67–10.20, $p=0.002$) and more histologic activity (OR=5.13, 95% CI 2.25–11.68, $p<0.001$) in the right colon compared to controls, which remained significant after adjusting for gender, age at colonoscopy, steroid use and race. Cases also had significantly greater odds of worse histologic vs. endoscopic inflammation of the right colon compared to controls (OR =3.14, 95% CI 1.24–7.97, $p=0.02$). In contrast, cases had significantly less histologic activity than controls in the rectum on multivariate analysis (OR=0.24, 95% CI 0.08–0.72, $p=0.01$).

Table 2. Multivariate analysis of cases (PSC-UC) compared to controls (UC) adjusting for gender, steroid exposure, race and age at first colonoscopy

	OR (95% CI)	p value
Right colon		
Endoscopic activity	4.21 (1.67–10.63)	0.002
Histologic activity	4.87 (2.04–11.61)	<0.001
Left colon		
Endoscopic activity	1.54 (0.61–3.90)	0.36
Histologic activity	1.51 (0.62–3.68)	0.37
Rectum		
Endoscopic activity	0.80 (0.33–1.96)	0.63
Histologic activity	0.24 (0.08–0.72)	0.01

Conclusions: UC patients with PSC in clinical remission have more

frequent and severe histologic and endoscopic disease activity of the right colon compared to UC patients without PSC. We believe that these findings provide insight into the increased cancer risk of PSC patients, and warrant more careful right-sided disease activity monitoring in these at-risk patients.

P197

Improved maternal and neonatal outcomes in a clinic dedicated to pregnant patients with inflammatory bowel disease

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Background: IBD patients are at a high risk for cesarean section (CS), prematurity, low birth weight (LBW). A unique multidisciplinary clinic, “IBD MOM”, composed of a gastroenterologist and gynecologist was established to reduce these risks.

The objective of this study was to identify risk factors for poor maternal and neonatal outcomes and to reduce these outcomes for high risk IBD pregnant patients treated in the IBD MOM clinic.

Methods: A cohort study of all deliveries in a single tertiary center between 2005–2016 were included. A retrospective analysis between IBD patients and all others was performed for maternal and neonatal outcomes. Based on this analysis, an IBD pregnant severity score was composed. These included active disease at conception, perianal disease, two or more drugs given, use of biologics and exacerbations during pregnancy [1 for each, range 0–5]. A prospective analysis was then conducted on a high risk group followed up by IBD MOM clinic compared to a low risk IBD group.

Results: 61,705 healthy women were compared to 296 women with IBD. Out of them, 90 (30.4%) were treated in the IBD MOM clinic. Compared to healthy women, IBD patients had a significant higher rate of CS (20% vs. 12%, $p<0.001$), prematurity (12.5% vs 5.4%, $p<0.0001$) and LBW (mean of 3.061 vs 3.233 kg, $p<0.0001$), respectively. Women who attended the IBD MOM clinic vs. community care, had a higher IBD pregnancy severity score (median score 2 [1–3] vs. 0 [0–1], $p<0.0001$), more disease exacerbations (38% vs 19%, $p=0.001$) and hospitalizations (13% vs 3%, $p=0.001$) during pregnancy. However, when comparing IBD MOM clinic to community care patients, the primary outcomes including risk for surgery, prematurity and LBW were similar between the groups (20% vs. 19%, 24% vs. 19% and 17% vs. 13%, respectively, p N.S. for all comparisons).

Conclusions: Women with IBD are at increased risk for CS, prematurity and LBW. A novel IBD pregnant severity score can predict risk factors. High risk patients treated in a specialized IBD MOM clinic had similar maternal and neonatal outcomes to low risk patients.

P198

Dipeptidyl peptidase 4: a strong predictive marker of disease activity and treatment escalation in inflammatory bowel diseases

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Background: Blood-based biomarkers provide a non-invasive estimation of the inflammatory burden in patients with inflammatory bowel diseases (IBD). We aimed to investigate the diagnostic and prognostic value of plasma Dipeptidyl peptidase 4 (DPP-4) in IBD patients.

Methods: A total of 203 adult patients [n=149 IBD patients; n=42 healthy controls; n=12 immune controls - systemic lupus erythematosus (SLE) in remission] were prospectively recruited. Disease activity was assessed using the Harvey-Bradshaw Index (HBI) for Crohn's disease (CD), the partial Mayo Score (pMS) for Ulcerative colitis (UC) and the Systemic Lupus Erythematosus Disease Activity Index for SLE. A multi-biomarker model was derived using logistic regression to evaluate predictors of disease activity and Cox regression to evaluate predictors of treatment escalation (disease outcome). Treatment escalation was defined as the need for escalation to immunomodulatory/biologic therapies or intestinal resection surgery, as a consequence of a disease flare.

Results: Median DPP-4 values were lower in active CD vs CD in remission [1043ng/mL, interquartile range (IQR): 824–1345 vs 1685ng/mL, IQR: 1519–2237; $p<0.001$]; as well as in active UC vs UC in remission (1323ng/mL, IQR: 1064–1766 vs 2149ng/mL, IQR: 1616–2478; $p<0.001$). IBD patients in remission showed DPP-4 values significantly lower than healthy subjects; no differences were found between immune and healthy controls. In CD, DPP-4 correlated strongly with faecal calprotectin (FC) ($r=-0.61$, $p<0.001$), C-reactive protein (CRP) ($r=-0.60$, $p<0.001$) and HBI ($r=-0.56$, $p<0.001$). In UC, DPP-4 correlated moderately with FC ($r=-0.31$, $p<0.05$) and CRP ($r=-0.32$, $p<0.05$), and strongly with pMS ($r=-0.52$, $p<0.001$). The multivariable logistic regression model revealed that DPP-4 and CRP (in CD) and DPP-4, FC and CRP (in UC) are independent predictors of disease activity (Table 1).

Table 1. Multiple logistic regression model of predictors of disease activity

Variable	Odds ratio (95% CI)	p-value
Crohn's disease		
DPP-4 (≤ 1512 ng/mL)	26.95 (3.01–240.96)	0.003
Calprotectin (≥ 125 μ g/g)	1.86 (0.21–16.60)	0.579
CRP (≥ 4.2 mg/L)	38.02 (4.25–340.48)	0.001
Ulcerative colitis		
DPP-4 (≤ 2012 ng/mL)	62.10 (2.93–1315.62)	0.008
Calprotectin (≥ 135 μ g/g)	65.90 (4.96–875.53)	0.002
CRP (≥ 6.2 mg/L)	48.19 (3.35–692.76)	0.004

At follow-up (median 578 days, IQR: 426–688), DPP-4 and CRP showed to independently predict treatment escalation in both CD and UC (Table 2).

Table 2. Cox proportional hazards model for predictive factors of treatment escalation

Variable	Hazard ratio (95% CI)	p-value
Crohn's disease		
DPP-4 (≤ 1512 ng/mL)	9.09 (1.77–46.57)	0.008
Calprotectin (≥ 125 μ g/g)	0.44 (0.08–2.53)	0.357
PCR (≥ 4.2 mg/L)	5.90 (1.53–22.78)	0.010
Ulcerative colitis		
DPP-4 (≤ 1570 ng/mL)	7.80 (1.60–38.04)	0.011
PCR (≥ 6.2 mg/L)	12.23 (2.30–64.98)	0.003

At 1 year, the proportion of patients who needed treatment escalation was 66% in CD and 41% in UC, if ≥ 2 biomarkers criteria were met. **Conclusions:** An activity assessment model and a prognostic model

that combines DPP-4 and other biomarkers accurately predicts IBD activity and an aggressive disease course.

P199 PET/MR for evaluating subclinical inflammation of ulcerative colitis in remission

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Background: Colonoscopy is the gold standard for evaluating mucosal inflammation of ulcerative colitis (UC), but it is an invasive procedure with risks. Integrated positron emission tomography (PET)/magnetic resonance (MR) has the potential to be a non-invasive and sensitive tool for the evaluation of disease extent and activity in UC patients. The aim of this study was to explore the utility of PET/MR in patients with UC in clinical remission.

Methods: This prospective study was approved by the institutional review board of the hospital, and informed consent was obtained. Between November 2015 and September 2016, 19 patients with UC in clinical remission were enrolled. These patients received PET/MR and subsequent colonoscopy with biopsy. Laboratory biomarkers, including serum high sensitivity C-reactive protein (hs-CRP) and fecal calprotectin (FC), were also obtained. The findings of colonoscopy were graded using the Mayo score, and the PET activity grade were determined depending upon the maximum standardized uptake value (SUV_{max}) ratio of the colon segment to liver.

Results: Seventeen of 19 patients (89%) showed increased metabolism of colon on PET/MR.

On colonoscopy, nine of the patients had moderate to severe disease (Mayo score ≥ 2), six had mild disease (Mayo score =1), and four had inactive disease (Mayo score =0). The Mayo score showed significant correlation with the Nancy histological index (Spearman's $\rho=0.547$, $p=0.015$). There were significant higher PET scores in patients with moderate to severe disease (Mayo score ≥ 2) than patients with mild

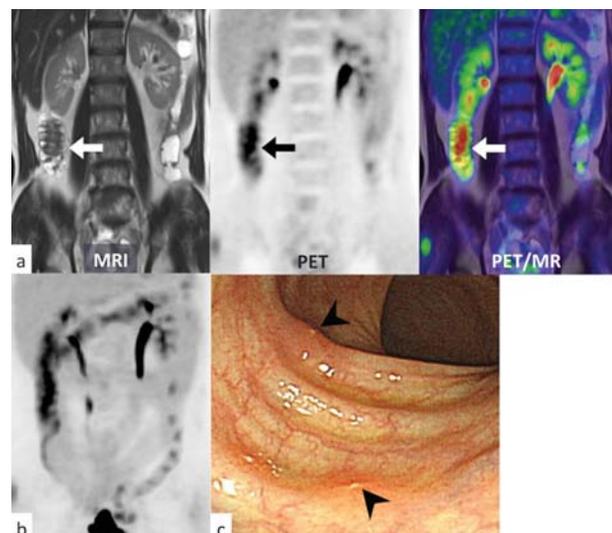


Figure 1. PET MR and colonoscopy image.

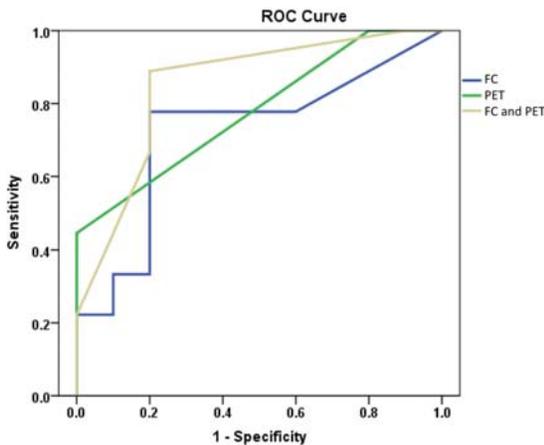


Figure 2. ROC analysis.

or inactive disease ($p=0.025$). In per-segment analysis, PET activity was seen in 38 of 95 (40%) colon segments, and the sensitivity and specificity for identifying moderate to severe disease were 0.67 and 0.64. In per-patient analysis, the area under the receiver operating characteristic curve (AUC) of hs-CRP, FC, and PET/MR were 0.589, 0.722, and 0.778, respectively. Using a combined index of FC and PET score, a higher AUC (0.850) can be achieved.

Conclusions: PET/MR is a promising non-invasive tool for evaluating subclinical inflammation in patients with UC in clinical remission.

P200

Faecal calprotectin as a marker of relapse in inflammatory bowel disease – its place in the management algorithm and cost effectiveness in Poland

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Background: Inflammatory Bowel Diseases (IBD) are characterized by alternating periods of flares and remission. Identifying patients at a significant risk of relapse during quiescent IBD could allow for early changes of treatment. Ileocolonoscopy is considered the gold standard in predicting IBD relapse, however it is invasive, expensive and not always well-accepted procedure. Measurement of calprotectin concentration in a stool sample is widely used as marker of gut inflammation and appears to be an alternative to endoscopy. Currently this test is not reimbursed by the National Health Fund in Poland. Aim: To evaluate the effectiveness of faecal calprotectin in predicting clinical and endoscopic recurrence of IBD and to decide whether its use in this indication would be cost-effective in Poland.

Methods: Medical databases (Medline, Embase, Cochrane) were searched. The predefined inclusion criteria comprised RCTs or cohort studies on adult patients with IBD in remission, calprotectin as index test and disease clinical activity assessment or colonoscopy as reference tests being performed and data on/enabling the calculation of diagnostic test accuracy parameters being present. The clinical and methodological heterogeneity of the included studies was judged and meta-analysis conducted. The decision tree opposing two strategies:

Test an Don't test was built. The assumption about clinical utility was deemed true only in case of endoscopic recurrence. CEA was done from the public payer's perspective.

Results: 701 studies were firstly identified and as a result of selection process 13 were further included into meta-analysis: 10 reporting clinical recurrence and 3 endoscopic one. The total number of patients was 1105. The sensitivity and specificity were estimated at 0.77 and 0.77 for clinical recurrence and 0.87 and 0.66 for endoscopic recurrence, respectively. In case of endoscopic recurrence the "test" strategy dominated over "don't test" strategy and in terms of one patient was about 1112 PLN cheaper allowing at the same time larger by 0.1 utility gain.

Conclusions: Faecal calprotectin concentration measurement can be used to predict clinical and endoscopic recurrence in IBD. The strategy assuming faecal calprotectin concentration measurement in all IBD patients in remission is more beneficial from the payer's perspective in Poland compared to the strategy that does not incorporate this test.

P201

A faecal bacterial markers correlates with Calprotectin for IBD activity monitoring?

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Background: Calprotectin (CP) faecal concentration is widely used as a non-invasive marker of inflammation of the intestinal mucosa, to assess the disease activity. In faecal samples, the abundance of *Faecalibacterium prausnitzii* (Fpra) and Fpra phylogroups (PGH-I and PHG-II), combined with *Escherichia coli* (Eco) seems to be an accurate biomarker to distinguish healthy (H) and diseased and also between disease locations according to a data also presented in this meeting by our group. The purpose of this study was to analyse the co-variation between these indicators and the disease activity in patients with CD and UC, and to determine its usefulness to discriminate between active and inactive disease.

Methods: A Spanish cohort consisting of 23 IBD (10 CD and 8 UC) and 12 H was enrolled. Sixty seven faecal samples (26 CD, 30 UC and 11 H) were obtained during treatment. Fpra, PHG-I, PHG-II and Eco abundances were determined by qPCR, and CP levels, using values above and below 250 μ g/g for active and inactive disease, respectively.

Results: The abundances of Fpra in CD and UC were lower in group CP >250 μ g/g compared to CP <250 μ g/g ($p=0.024$ and $p=0.019$, respectively). The abundance of PHG-II was lower in CD samples with CP >250 μ g/g ($p=0.008$), while PHG-I was less abundant in samples of active UC ($p=0.002$). No significant differences were found for Eco.

There was a significant inverse correlation between abundances of Fpra and the level of CP for both IBD ($p=0.038$ for CD and 0.035 for UC). CP was also inversely related to both, PHG-I and PHG-II in UC ($p=0.013$) and in CD ($p=0.050$), respectively.

Conclusions: The abundance of Fpra could be an accurate general discriminator of active disease, for IBD. In addition, PHG-I and PHG-II can be used as specific indicators of active disease in CD and UC, respectively.

P202**Diagnosis of inflammatory bowel disease in asymptomatic subjects: disease characteristics, natural history and treatment requirements**

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Background: The diagnosis of inflammatory bowel disease (IBD) is usually made in a symptomatic phase, when bowel damage has already started. Some early findings can be detected even years before the onset of first symptoms. Our study has focused on the new diagnosis of IBD in an asymptomatic population undergoing an endoscopic investigation.

Methods: We reviewed the database of our colorectal cancer screening programme. All patients were first assessed with faecal immunochemical test (FIT; OC-Sensor, Eiken Chemical Co., Tokyo, Japan) and, if this test was positive (cut-off 100 ng Hg/mL buffer), a colonoscopy was indicated. In this study we included all patients with a suspicion of IBD by endoscopy and further confirmed by means of histology. The study protocol was approved by the ethics committee of Euskadi. The primary aim of the study was to determine and characterize the incidental cases of new-onset IBD during routine screening colonoscopies.

Results: A total of 498.227 FIT were done in 11 hospitals (67% participation). In 31.005 of these cases a colonoscopy was performed (98% complete). We found 121 patients newly-diagnosed of IBD [58% male, age 57 years (SD 6.04), 62% ex or never smokers]: 87 ulcerative colitis (E1 in 30 cases, E2 in 28 and E3 in 29), 26 Crohn's disease (ileum in 12 patients, colon in 9 and ileocolonic in 5) and 8 IBD-U. FIT levels at diagnosis were comparable between all IBD subtypes. Only one patient associated perianal disease (anal fissure), and three patients had extraintestinal manifestations. Up to 24–38% of UC showed an atypical endoscopic appearance. UCEIS at diagnosis was 5 (4–6). We found no correlation between FIT value and UCEIS or histological activity at first presentation. At least one follow-up visit was available in 85% of the cohort. Median follow-up was 24 months (IQR 9–41). Between those subjects who were asymptomatic at diagnosis, thirty-four patients (37%) developed symptoms during this period (mainly rectal bleeding, diarrhoea and rectal syndrome). These symptoms appeared after 3 months (IQR 0–11). Those patients who developed symptoms were more likely to have higher levels of FIT at diagnosis [1096 pg Hb/g (230–2815) vs 429 pg Hb/g (215–1309)]. Treatment was prescribed in most cases

(83%): mesalazine in 77%, steroids in 18%, thiopurines in 6%, 1 with methotrexate and 1 with leukapheresis. Two patients required anti-TNF biologics. Two subjects underwent surgery.

Conclusions: We found a 0.39% of new diagnosis of IBD during the colorectal cancer screening programme. Most of the cases were diagnosed of ulcerative colitis. More than a third of patients developed symptomatic disease (37%). Higher levels of FIT at diagnosis showed a higher probability of developing symptoms during the follow-up.

P203**Factors associated with restless legs syndrome in patients with ulcerative colitis: a study in a tertiary care center in Romania**

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Background: Ulcerative colitis (UC) is a lifelong systemic multifactorial disease with a negative impact on health-related quality of life (HRQoL). Restless Legs Syndrome (RLS) as an extraintestinal manifestation of UC is not very common. This association has been investigated in a small number of studies but results remain controversial. The primary aim of the current study was to investigate the prevalence and association between RLS and UC.

Methods: 120 subjects (man/female: 67/53, age at diagnosis: 39.3 years, SD: 16.2) with biopsy confirmed UC and 120 age and gender matched controls were included in this prospective single-center study. All patients with diabetes, peripheral neuropathy, renal failure and those who underwent treatment with antipsychotic drugs and antidepressants that increase serotonin were excluded from the study. Basic demographic data, clinical information and laboratory findings were collected and comprehensively reviewed. All subjects were prospectively evaluated using the International Restless Legs Syndrome Study Group criteria (IRLSSG). The IRLSSG ten-item severity scale was also used. Gender, age at diagnosis, family history, occupation, smoking status, caffeine intake, BMI, iron, vitamin B12, folate and hemoglobin levels were analyzed as potential impact factors.

Results: Based on our findings, the prevalence of RLS in UC patients is 24.1% compared with 5% in the control group (p=0.001). Symptom severity in the RLS group (according to the IRLSSG rating scale) was mild in 4 patients (13.7%), moderate in 10 patients (34.4%), severe in 13 patients (44.8%) and very severe in 2 patients (5.8%). In a multivariate analysis performed by binary logistic regression, elderly onset UC (age at diagnosis >60 years), BMI ≥ 30 kg/m² and caffeine intake were the strongest predictors of RLS in patients with UC. There was no significant correlation between RLS and occupation, iron, folate, hemoglobin and vitamin B12 levels. RLS was significantly correlated with sleep disorders (86.2%), fatigue (60.9%) and anxiety (31.03%) in patients with UC (p<0.001).

Conclusions: Our study demonstrates that RLS is rather common in patients with UC. The results of our research are limited by the small number of patients enrolled in the study. Further investigations are needed to confirm RLS as an extraintestinal manifestation of UC.

P204 Lipid profile in inflammatory bowel disease under maintenance with anti-TNF: a prospective longitudinal cohort study

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Background: The role of tumor necrosis factor (TNF) inhibitor in patients with inflammatory bowel disease (IBD) in mediating cardiovascular risk and changing lipid profile is controversial. The aim of the study was to evaluate the effect of anti-TNF monoclonal antibodies on lipid profile in IBD patients

Methods: A prospective, observational cohort study was designed. Inclusion criteria were consecutive IBD patients in clinical remission for at least six months under a continuous standard dose of 40mg/eowadalimumab therapy or 5mg/kg infliximab therapy every 8 weeks. Relapse was defined as a Harvey-Bradshaw score >4 in Crohn's disease and a partial Mayo score >3 in ulcerative colitis. Hypercholesterolemia was defined as a cholesterol count above 200 and hypertriglyceridemia was defined as a triglyceridemia count above 150. They were quantified at 4-month intervals for one year. All patients completed a basal demographic and clinical questionnaire. Differences between laboratory results were evaluated with paired samples T test in cholesterol (normal distribution) and with nonparametric test with in triglycerides (not normal distribution).

Results: 95 consecutive patients were included. The median age was 44 years (18–78), 51% female and 75% with CD. 10.6% of patients presented arterial hypertension, 3.3% mellitus diabetes and 3.1% a previous cardiovascular event. 65 (68.4%) patients remained in clinical remission and 30 (31.6%) suffered from a relapse during the follow-up period. We compared lipid profile between month 0 and month 12, almost statically significant differences were noted in triglycerides ($p=0.05$) but not differences in cholesterol ($p>0.5$). There was not a statistically significant difference in lipid profile during the follow-up, the subgroup with relapse showed a not significant increase in both cholesterol and triglycerides.

Table 1. Triglycerides profile modification according to relapse (median, range)

	Month 0	Month 4	Month 8	Month 12
Remission	88 (33–407)	98 (38–483)	101 (32–801)	100 (29–442)
Relapse	103 (40–189)	71 (33–240)	110 (44–214)	121 (44–353)

Table 2. Cholesterol profile modification according to relapse (mean, standard deviation)

	Month 0	Month 4	Month 8	Month 12
Remission	178 (31.8)	178 (35.5)	181 (35.5)	180 (38.6)
Relapse	172 (34.5)	176 (38.0)	172 (32.1)	176 (38.1)

Conclusions: In IBD patients under maintenance therapy with anti-TNF, triglycerides increased almost significantly after one year of follow-up. Anti-TNF therapy can have a role in changes in the lipid profile, but without clinical relevance.

P205 A telemanagement system web in patients with complex inflammatory bowel disease: design and implementation of a randomized clinical trial

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Background: Inflammatory bowel disease (IBD) is a chronic and relapsing gastrointestinal disorder that requires continuous and personalized follow-up to achieve long remission and minimize short and long-term damage. Telemedicine has been successfully used to provide healthcare services remotely with the implementation of information and communication technologies in IBD patients. Aims: To develop a platform web, TECCU (Telemonitorización en Enfermedad de Crohn y Colitis Ulcerosa), for a remote control of complex IBD patients (moderate-severe activity) and compare disease activity over 24 weeks in a clinical trial of IBD patients who received standard care (Control_G) vs nursing care by telephone (NT_G) vs intervention based on distance monitoring TECCU_G). Secondly, to assess health-related quality of life, adverse events, therapeutic adherence and the impact on direct health care costs.

Methods: We describe the development of a remote monitoring system and the difficulties encountered in the platform design. Moreover, a three-arm randomized controlled trial was designed to evaluate the effectiveness of this web platform in decreasing disease activity compared to NT_G and Control_G.

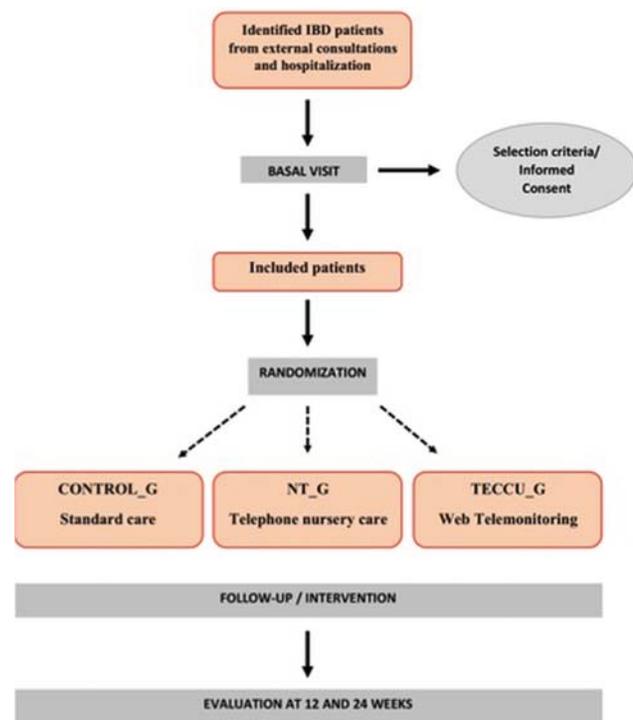


Figure 1. Flowchart of study participants.

Inclusion criteria: IBD patients diagnosed according to internationally criteria; ≥ 18 years; CD or UC patients with moderate or severe activity attending in the IBD unit during the inclusion period; Patients starting medical treatment with corticosteroids, immunosuppressive or biological agents.

Results: Patients from each group, according to schedules established in relation to the started treatment, answer periodic questionnaires regarding disease activity, quality of life, treatment adher-

ence, side effects, satisfaction, work productivity and social activities. Blood and stool (fecal calprotectin) analysis is performed periodically. Based on the results of these tests in G_TECCU, alerts are generated in a platform web, with adapted action plans including changes in medication and following-up frequency. Similarly, in the telephone and usual care groups these interventions are developed by telephone and clinical visits, respectively.

Conclusions: The development of a remote management program of IBD patients via web (TECCU) can be a challenge for achieving adequate and safe control of the disease from a distance. The results of this clinical trial could show the efficacy of a web-based telemonitoring system to improve disease activity, quality of life and to decrease health care using in complex IBD patients.

P206

Celiac disease and inflammatory bowel disease, a rare association

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Background: Celiac disease (CD) and inflammatory bowel disease (IBD) association is rarely described in the literature. In this study, we propose to determine the prevalence of IBD in a population of celiac patients monitored in our hospital structure. We will also specify the clinical, evolutionary and therapeutic characteristics of the IBD during this association.

Methods: This is an open prospective study, patient were recruited between January 2009 and January 2015. The diagnosis of CD is based on clinical, serological (anti-endomysium and/or anti-transglutaminase antibody), histological (villous atrophy) and evolutionary criteria. The diagnosis of IBD is based on the clinic, biology (CRP), endoscopy, histology and progression of the disease. Patients are treated with the gluten-free diet (GFD) and the specific treatment of IBD.

Results: Of the 357 celiac patients followed, there are 5 IBDs, a prevalence of 1.4% of which 4 women and 1 man (M/F: 0.25). Their mean age is 40.8 years (22–61 years). These are 4 Crohn's disease and 1 ulcerative colitis (UC). The diagnosis of Crohn's disease is concomitant with CD in 1 case, it precedes that of CD in 2 cases and it occurs after CD in 1 case. The diagnosis of UC precedes that of CD. The 4 Crohn's diseases are stenosing, fistulating and operated, including one in the emergency for perforation on megacolon after failure of Infliximab. The latter also had severe ano-perineal lesions. The other patients are in remission treated with Azathioprine for one patient and fail to immunosuppressants for both the two others (one of whom died as a result of an infectious complication). For UC, it is a corticoreistant form treated with Infliximab but it had to be stopped following a serious pulmonary complication. These 5 patients were also placed under GFD, of which 3 patients correctly follow the GFD.

Conclusions: IBD is rarely associated with CD (1.4%). In our study, it is most often Crohn's disease. It is also noted that whatever the nature of the IBD, this one is severe; in contrast, the CD is relegated to the second plane.

P207

Prevalence and characteristics of Romanian patients with upper GI tract involvement in Crohn's disease

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Background: Prevalence of upper GI involvement in CD has been reported to be low. This can be due to difficulties encountered in establishing a clear diagnosis. The aim of the study was to evaluate the rate of upper GI involvement in CD patients based on the data coming from a regional, population-based romanian registry, and to identify their characteristics on diagnosis and during follow-up.

Methods: In order to study the characteristics of patients with upper GI Crohn's disease, we used data from EPIROM- a regional, population-based registry. Data was collected between 2014–2016. Upper GI tract involvement was considered when endoscopy described erythema, edema, linear or aphtoid erosions or deep ulcers, combined with a histologic report describing nonspecific chronic inflammation, focally enhanced gastritis or granuloma.

Results: Out of 113 patients with CD, fourteen (12.38%) were considered to have upper GI tract involvement: 10 had gastroduodenal lesions, 3 had only gastric lesions and one patient had only duodenal lesions. None of the patients had esophageal CD. Aphthoid erosions and deep ulcers were the most common endoscopic findings (64.28%). Chronic active gastritis was the most common histologic finding (71.42%). Only one patient was found to have gastric granuloma.

Two thirds of patients with upper GI tract involvement were considered to have severe disease, based on the endoscopical and histological scores.

Upper GI tract disease was most commonly found in association with ileocolonic disease (50%), followed by ileal disease (28.57%) and colonic disease (21.42%) No cases with exclusive involvement of the upper GI tract were registered.

Intestinal stenosis was the most common complication of CD in these patients and it was found to be significantly associated with upper GI tract involvement (p=0.021). Intestinal stenosis was found in 9 patients with upper GI tract involvement (64.28%), 7 of these associated ileal disease, and 2 associated ileocolonic disease.

Conclusions: The rate of upper GI involvement in CD is low. Most of the patients had gastroduodenal lesions combined with ileocolonic involvement. The disease is more severe in these cases and the development of intestinal stenosis occurs more frequently.

These patients usually associate a poor prognosis, thus a prompt and highly efficient therapeutic method is needed early in the course of the disease.

P208

Long term follow up of lymphocytic colitis patients

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Background: Microscopic colitis has been increasingly diagnosed in recent years with improved awareness amongst endoscopists that biopsies must be taken from macroscopically normal colons, in pa-

tients presenting with diarrhoea. The two main variants are lymphocytic colitis (LC) and collagenous colitis (CC). Aim: To evaluate the long term natural history and follow-up of patients diagnosed with lymphocytic colitis in a University teaching hospital.

Methods: This is an ongoing retrospective study. Patients diagnosed with lymphocytic colitis were identified from the histopathology department database in our institution. Clinical details were obtained through a combination of chart review and follow up telephone interview.

Results: To date 60 cases of LC have been identified. The female to male ratio 2.1: 1. Median age at diagnosis 55 years. 92% of patients presented with diarrhoea. The median follow-up period was 5.9 years. 20/60 (33.3%) of patients had 1 colonoscopic and histologic follow-up at a median of 2.6 years from time of diagnosis. Of these, 8/20 (40%) had normal histology. Of these 20 patients 12 were on treatment. 8/60 (13.3%) of patients underwent a second colonoscopy at a median of 6.6 years from diagnosis and biopsy was normal in 7/8 cases. At diagnosis, CRP was raised in 8 patients (13.3%), normal in 16 patients (26.6%) and not available in 60% of the patients. 26 (43%) patients were smokers, 9 (15%) patients had coeliac disease and 38 (63%) patients had thyroid disease. 18 (30%) of patients were on NSAIDs, 16 (27%) on statins and 27 (45%) were on a PPI. 33 patients had regular follow (55%) with minimal symptoms. No follow up data is currently available for 27 (45%) of patients but is being sought.

Conclusions: LC colitis is commonly associated with other autoimmune conditions. In those patients in whom follow up histology was available, there was complete histologic remission in 40%. A significant proportion of patients had no follow-up/did not seek follow-up which raises the possibility that their symptoms were not problematic. Further follow-up of patients with microscopic colitis is necessary to gain better insight into the natural history of this condition.

P209

Long-term effectiveness and safety of vedolizumab in patients with ulcerative colitis: 5-year cumulative exposure of GEMINI 1 completers rolling into the GEMINI open-label extension study

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Background: Approval of vedolizumab (VDZ) for moderately to severely active ulcerative colitis (UC) was based on the phase 3 GEMINI 1 study. [1] The GEMINI open-label extension (OLE) trial is an ongoing study investigating the long-term safety of VDZ (NCT00790933). Here we report the 5-year exploratory analyses of effectiveness and safety in patients (pts) with UC who had completed GEMINI 1 and were enrolled in GEMINI OLE.

Methods: Analyses included pts who responded to VDZ induction at Week (Wk) 6 and had received VDZ maintenance (every 8 or 4 wks; data were combined) to Wk 52 of GEMINI 1, followed by VDZ every 4 wks in GEMINI OLE. Pts with 248 wks of cumulative VDZ treatment (data were collected from 22 May 2009 to 21 May 2015) were assessed for clinical response (decrease in partial Mayo Score

Abstract P209 – Table 1. Effectiveness outcomes in patients with UC and cumulative VDZ exposure for up to 248 wks

Cumulative VDZ exposure (wks)	GEMINI OLE study wk	Combined VDZ, observed cases*			Combined VDZ, non-responder imputation [†]		
		N	Clinical response, n (%)	Clinical remission, n (%)	N	Clinical response, n (%)	Clinical remission, n (%)
52	0	154	146 (95)	135 (88)	154	146 (95)	135 (88)
80	28	145	134 (92)	127 (88)	154	134 (87)	127 (82)
104	52	136	124 (91)	120 (88)	154	124 (81)	120 (78)
128	76	127	119 (94)	117 (92)	154	119 (77)	117 (76)
152	100	118	114 (97)	110 (93)	154	114 (74)	110 (71)
200	148	108	104 (96)	100 (93)	154	104 (68)	100 (65)
248	196	63	62 (98)	57 (90)	154	62 (40)	57 (37)

*Number of patients in clinical response or remission (n) over number of observed cases (N) at study visit

[†]Patients without available data (for reasons including discontinuation and patients ongoing in the study who have not yet reached specified assessment time points) were included as non-responders

Clinical response was defined as a decrease in PMS of ≥ 2 points and $\geq 25\%$ change from baseline, with either an accompanying decrease in rectal bleeding subscore of ≥ 1 point from baseline or an absolute rectal bleeding subscore of ≤ 1 point. Clinical remission was defined as a PMS of ≤ 2 with no individual subscore > 1

OLE, open-label extension; PMS, partial Mayo Score; UC, ulcerative colitis; VDZ, vedolizumab; wk, week

[PMS] of ≥ 2 points and $\geq 25\%$ change from baseline [BL], with an accompanying decrease in rectal bleeding subscore of ≥ 1 point from BL or absolute rectal bleeding subscore of ≤ 1 point), clinical remission (PMS of ≤ 2 with no individual subscore > 1) and health-related quality of life (HRQoL), including IBD Questionnaire (IBDQ) and Euro Quality of Life-5D visual analogue scale (EQ-5D VAS). Safety was also assessed.

Results: Of 247 pts in GEMINI 1 who responded to VDZ induction at Wk 6 and received VDZ in maintenance, 154 (62%) completed VDZ maintenance and were enrolled in GEMINI OLE (anti-TNF α -naïve n=107; anti-TNF α failure n=42). At the time of this analysis, 63 pts had completed 248 wks of cumulative VDZ treatment; 54 had discontinued (n=19 [35%] due to lack of continued benefit) and 37 are ongoing (have not yet reached 248 wks of treatment). Of pts with data at Wk 248 (n=63), 98% had clinical response and 90% were in remission (Table). HRQoL improvements were observed at Wk 248, with mean change from BL IBDQ and EQ-5D-VAS scores of 58.7 and 24.0, respectively. In the safety population, 137 pts had adverse (AEs); 17 discontinued due to AEs. Serious AEs were reported in 44 pts (in 7 pts these were drug-related; 8 pts discontinued as a consequence of serious AEs). No deaths were reported.

Conclusions: In UC patients who were responders at Wk 6 of GEMINI 1 (who continued to respond during the study), long-term VDZ therapy (~ 5 years) was associated with clinical benefits including clinical response, clinical remission and HRQoL improvements. The safety profile was consistent with that previously observed in a 3-year interim analysis of the OLE study.

References:

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P210

The associations of optimism, social support, and coping strategies with health-related quality of life in a cohort of patients after proctocolectomy with ileal Pouch-anal anastomosis

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Background: Inflammatory bowel diseases (IBD) are associated with reduced health-related quality of life (HRQoL). We aimed to identify factors that influence patients HRQoL by exploring the role of optimism, social support and coping strategies in contributing to patients' HRQoL. We focused on patients with ulcerative colitis (UC) after pouch surgery representing a distinct population which is followed up in a dedicated referral clinic.

Methods: Patients were recruited at the Comprehensive Pouch Clinic and completed six questionnaires: demographics, HRQoL (IBDQ), dispositional optimism (revised Life Orientation Test, LOT-R), social support inventory (ENRICHED), Coping strategies (brief COPE), and illness acceptance (DDAQ). Pouch behavior was determined clinically and defined as normal pouch (NP) or pouchitis.

Results: A total of 151 pouch patients were recruited: 75 (50%) females, average age 47.91 \pm 15.51 years, average age of UC diagnosis 27.11 \pm 13.53 years, mean time since pouch surgery 10.03 \pm 8.09

years. At the time of recruitment 48 (32%) had NP. Women had lower HRQoL than man (p=0.04), education level was correlated with HRQoL (r=0.27, p=0.001), age at diagnosis was negatively correlated to HRQoL (r=-0.19, p=0.02).

Optimism was associated with higher HRQoL (R=0.40, p<0.001). Pessimism was associated to older age at diagnosis (r=0.23, p=0.01) and to lower education level (r=-0.20, p=0.02). Optimists and pessimists differed in the manner they cope with disease – optimists used more positive reframing and tended to find alternative meaningful activities, while pessimists tended to use self-blame, behavioral and mental disengagement. Furthermore, optimists reported better social support (r=0.29, p=0.00).

Social support was also associated with higher HRQoL (R=0.40, p<0.001). Patients with pouchitis had lower HRQoL and social support (all p<0.01 compared to NP) but did not differ in the level of optimism.

Predictors of HRQoL in the multivariate Hierarchical Regression analysis were gender (β =-0.12; p<0.05), educational level (β =0.22; p<0.001), social support (β =0.12; p<0.05) and coping strategies: behavioral disengagement (β =-0.19; p=0.05), mental disengagement (β =-0.22; p<0.001), activities engagement (β =0.29; p<0.001), and symptom tolerance (β =0.19; p=0.05).

Conclusions: Factors affecting HRQoL levels in UC pouch patients are Gender, education level, age at disease diagnosis and pouch behavior. Dispositional optimism, social support and coping strategies play significant role in patients HRQoL.

P211

Differences in therapeutic approaches and outcomes in paediatric and adult onset Crohn's disease with perianal fistula: comparison of 2 multicentre fistula cohorts

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Background: While paediatric and adolescent onset Crohn's disease (CD) is more severe disease with adverse outcomes, there is no comparative data on outcomes in perianal fistulas in paediatric/adolescent versus adult onset CD. Management paradigms in perianal fistulas in Crohn's disease is not fully defined and approaches from paediatric and adult IBD clinicians and surgeons may be different. We aimed to study any differences in diagnostic and

treatment approaches in paediatric/adolescent onset CD with perianal fistula (CD-PAF) and adult onset disease and the outcomes of CD-PAF.

Methods: Data was collected on patients included in 2 retrospective multicentre multinational cohorts (11 adult and 7 pediatric centres) of perianal fistula with paediatric/adolescent onset and adult onset CD PAF. We evaluated fistula characteristics, surgical and medical treatments following onset of CD-PAF and fistula healing. We also compared the need for re-intervention defined as the need for re-insertion of seton or abscess drainage or diverting stoma or proctectomy.

Results: 253 adults and 116 paediatric/adolescent patients were included. Complex fistulas were identified in 53% of adult and 67% of paediatric/adolescent group. MRI was done at presentation in 77% and 73% respectively in adult and paediatric/adolescent group. Proctitis was recorded in 43% of adult onset and in 3% of paediatric/adolescent onset CD-PAF. Examination under anaesthesia (EUA) was done in similar proportion of patients (70% and 69%) but significantly higher proportion of adult CD-PAF patients had seton insertion (15% vs 54%, $p < 0.001$). Anti TNF use was more often in paediatric onset CD-PAF (83% vs 68%) when compared to adult onset CD-PAF with majority of patients maintained on combination therapy. Complete clinical fistula healing was more often noted in paediatric/adolescent onset CD-PAF (71% vs 49%, $p = 0.015$). Reintervention rates were higher in adult onset CD (40.3% vs 16.05%, $p = < 0.001$). Radical surgery (diverting stoma or proctectomy) was required in 3 patients (2.58%) with paediatric/adolescent onset and 26 patients (10.28%) with adult onset CD-PAF ($p = 0.04$).

Conclusions: Paediatric/adolescent onset CD-PAF appears to have better outcomes with less radical surgery or re-interventions when compared to adult onset disease despite less frequent use of seton. The impact of more frequent and prolonged therapy in paediatric/Adolescent onset CD-PAF with combined immunomodulation needs further evaluation.

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Location and Kudo pit pattern reflect neoplastic histology of lesions detected at surveillance colonoscopy in inflammatory bowel disease

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Background: Effective colonoscopic surveillance of IBD benefit from having reliable predictors of neoplasia, since targeted biopsies and endoscopic resection are increasingly used as standard of practice. It is not clear whether Kudo pit patterns may be applicable in characterizing IBD associated lesions.

We aimed to identify the specific clinical and endoscopic features of colonic lesions which predict dysplasia in IBD.

Methods: All lesions identified in a randomized study to determine the detection rates of neoplastic lesion (NL) in patients with long standing colitis in IBD (ClinicalTrials.gov NCT02098798) were included. Endoscopic NL were classified by the Paris classification and Kudo pit pattern, and by the Vienna classification histologically. Exploratory univariate analysis was performed, and age, duration of

disease, extra-intestinal manifestations family or personal history of polyps/cancer, smoking, size of lesion, Paris classification, Kudo pattern, localisation/extension of disease were considered in the patients with IBD-associated NL. Subsequently a multivariate logistic regression model analyses was created with candidate variables which had p values ≤ 0.05 based on univariate analysis

Results: A total of 270 patients (55% men; age 20–77y) were assessed by High Definition – white light ($n=90$), virtual chromoendoscopy ($n=90$) or dye chromoendoscopy ($n=90$). Ninety-one (33.7%) colonic dysplastic lesions and 1 adenocarcinoma were found. Sixty-two (68.8%) were polypoid and twenty-nine (31.8%) were non polypoid. Most of these lesions (92.3%) had Kudo pattern III–V (Table). By univariate analysis, age – Odds Ratio (OR) 1.05 (95% CI: 1.02–1.08), localization of the lesions in the right colon – OR 6.15 (95% CI: 3.12–12.12), Kudo pattern IIO, III-IV and V – OR 20.91 (95% CI: 9.34–46.7) and Paris Is/Ip classification OR – 3.29 (95% CI: 1.69–6.38) were associated with NL. Subsequently proportional multivariate logistic regression model for the prediction of colonic neoplasia confirmed that the endoscopic Kudo pit pattern – OR 21.50 (95% CI: 86.5–60.1) and localization of the lesions in the right colon – OR 6.52 (95% CI: 1.98–22.5) were predictors of colonic neoplasia at surveillance colonoscopy in IBD (Table). The overall accuracy of independent variables which predict neoplastic changes was 78% (95% CI 68–88%), sensitivity 82% (95% CI 68–97%), specificity 68% (95% CI 47–89%), PPV 85% (95% CI 76–95%) and NPV 64% (95% CI 42–86%) which were significant in the multivariate analysis.

Conclusions: We demonstrated that the endoscopic Kudo pattern and localisation of the lesions in the right colon were predictors of colonic neoplasia in IBD. This may guide management strategy of NL detected at IBD surveillance.

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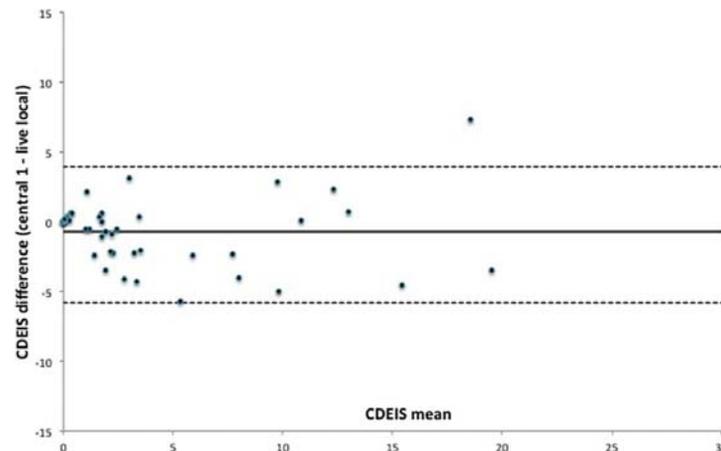
Agreement between Crohn's disease endoscopy severity scores derived from live local, delayed local video-recorded and central readings

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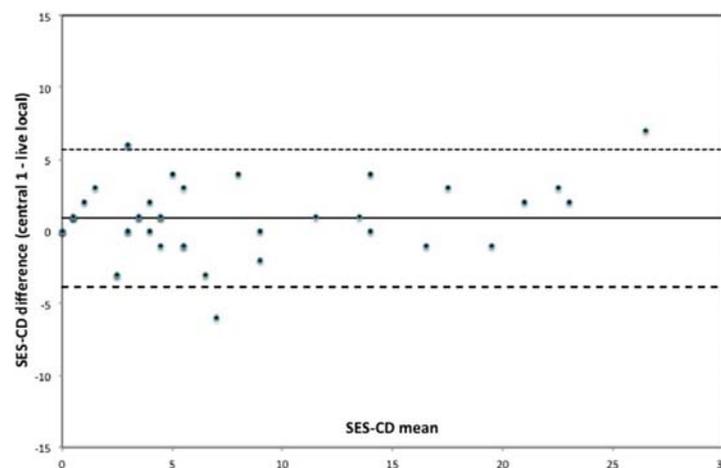
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Background: The Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn's Disease (SES-CD) are used to assess endoscopic disease severity in Crohn's disease (CD). Central reading has become the standard practice in clinical trials for inclusion and evaluation of endoscopic response to therapy. However, the agreement between severity scores (CDEIS or SES-CD) derived from live local, delayed local video-recorded and central readings has not been studied.

Methods: We conducted a monocentric prospective study between April 2015 and December 2015. Fifty-three CD patients were recruited by three endoscopists trained to endoscopic readings for score calculation (TU, JM and BC). All colonoscopies were recorded on-site and videos were labeled according to the segment of interest: ileum, right colon, transverse colon, left and sigmoid colon, and rec-



Abstract P213 – Figure 1. Bland and Altman plots of CDEIS derived from live local reading and central reading 1.



Abstract P213 – Figure 2. Bland and Altman plots of SES-CD derived from live local reading and central reading 1.

tum. Each endoscopist performed immediate readings of his patients and delayed local video-recorded readings of his patients' colonoscopies at least 3 months after the live local reading. Two central readers (JCD and FP) read all videos. CDEIS and SES-CD scores were then computed automatically based on all readings. Intra-class correlation coefficients (ICC) were estimated and Bland and Altman plots were used to assess the agreement between severity scores derived from various readings. In a first step, we studied the agreement between severity scores derived from live local (L) and central (C1 and C2) readings and L and delayed local video-recorded (D) readings.

Results: ICC estimates of CDEIS (n=44) and SES-CD (n=46) scores were respectively 0.89; 95% confidence interval (CI), 0.80–0.94 and 0.94; 95% CI, 0.87–0.97 between L and C1 and 0.80; 95% CI, 0.58–0.90 and 0.85; 95% CI, 0.74–0.91 between L and C2. ICC estimates between L and D were respectively 0.87; 95% CI, 0.78–0.93 and 0.88; 95% CI, 0.79–0.93. An example of Bland and Altman plots derived from L and C1 are shown in figure 1 for CDEIS and figure 2 for SES-CD scores.

Conclusions: Overall, the agreement between severity scores (CDEIS or SES-CD) derived from live local, delayed local video-recorded and central readings is excellent. This data suggests that both local readings by trained endoscopists and central reading could be used in clinical trials.

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What is the diagnostic accuracy of faecal calprotectin regarding endoscopic relapse in Crohn's disease patients following ileocecal resection? A tertiary single center experience

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Background: There is still some discrepancy about the accuracy of faecal calprotectin (FC) in Crohn's disease (CD) patients after ileocecal resection and data from real daily practise on this topic is still scarce.

Methods: For this purpose we prospectively gathered the simultaneous FC results of CD patients who were referred to the endoscopy unit in the postoperative (postop) setting. Patients with upper GI involvement were excluded. Demographic data like age, sex, disease duration, Rutgeerts score, FC, CRP results were all noted. All patients gave a stool sample 24 hours before colonoscopy and FC was determined via ELISA (Quantum Blue Calprotectin, Bühlmann Lab. AG, Switzerland).

Results: Seventy-four CD patients [38 female (51%)] with an ileocecal resection were enrolled into the study protocol. Their mean age was 38.56±12 yr. with a mean disease duration of 123.52±84.88 mo. Forty-four of 74 (60%) patients were in endoscopic remission whereas 30 (40%) had endoscopic relapse [i0- 31 patients (42%);

i1- 13 patients (18%), i2- 11 patients (15%), i3- 14 patients (19%), i4- 5 patients (6%]. Nonparametric Spearman correlation test only revealed that FC using a cut off of 30 µg/g weakly correlated with endoscopic relapse ($r=0.329$, $p=0.004$). Diagnostic accuracies of FC using different cut offs is shown in Table 1.

Table 1 Diagnostic performance of FC regarding endoscopic relapse using different cut offs

Cut-off values for FC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)
30 µg/g	97	30	48	93	57
50 µg/g	80	34	45	71	53
100 µg/g	67	50	48	69	57

Conclusions: According to our results from our daily routine practice, the very low specificity of FC for each cut off in CD patients with an ileocecal resection lets us question the diagnostic utility of this non-invasive marker as an alternative tool to colonoscopy in the postop setting. A speculative explanation for this could either be the presence of unidentified lesions proximal to the ileocolonic anastomosis or ischemic anastomotic ulcers which might have been the reason behind the confusion of the endoscopist and let us judge the value of Rutgeerts score.

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Clinical features of chronic enteropathy associated with *SLCO2A1* gene (CEAS)

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Background: Chronic enteropathy associated with *SLCO2A1* gene (CEAS) is a rare hereditary disease caused by mutations in *SLCO2A1* gene, encoding a prostaglandin transporter. CEAS resembles Crohn's disease (CD) in presenting multiple small intestinal ulcers. However, because immunosuppressive therapies such as corticosteroid and anti-tumor necrosis factor-alpha antibody therapies are ineffective for CEAS in contrast to CD, recognition and precise diagnosis of CEAS are critical to avoid unnecessary therapies.

Methods: Forty-one Japanese patients (10 male and 31 female) were diagnosed with CEAS by clinical findings and genetic analysis during a period of 2012 to 2016 and they were enrolled in this study. To identify the clinical features of CEAS, we reviewed the clinical information for the patients. In addition, because *SLCO2A1* gene has also been reported as a causative gene of primary hypertrophic osteoarthropathy (PHO; OMIM 614441), we investigated whether CEAS patients had clinical manifestations of PHO.

Results: We found recessive *SLCO2A1* mutations located at 11 sites. Among the identified *SLCO2A1* mutations, a splice-site mutation of intron 7 (c.940+1G>A) was the most frequent, and 17 of the 41 patients were homozygous for this mutation (41%). Median age at onset was 17 (1 to 69) and parental consanguinity was present in 12 patients (29%). Anemia and abdominal pain were present in 40 (98%) and 16 (39%) patients, respectively. On the other hand, there were

little inflammatory findings in blood tests (median CRP 0.16mg/dl). During the course of the disease, 27 patients (66%) had undergone one or more surgeries such as partial resection of the small intestine. The most frequently involved gastrointestinal site was ileum (98%), but there was no patient with ulcerations in the terminal ileum. The stomach and duodenum were affected in 11 (27%) and 18 (44%) patients, respectively. Although no patients had clinical manifestations of PHO that required treatment, mild digital clubbing or periostosis was present in 12 patients (29%). Moreover, 4 male patients fulfilled the major clinical criteria for PHO, having digital clubbing, periostosis, and pachydermia.

Conclusions: Although CEAS mimics CD, some clinical features of CEAS are different from those of CD, such as low inflammatory findings, terminal ileum-sparing ulcerations and extraintestinal manifestations. Genetic analysis should be considered if CEAS is clinically suspected.

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Mesenteric disease is directly related to mucosal disease in Crohn's disease

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Background: Crohn's disease (CD) displays mesenteric disease manifestations such as fat wrapping and mesenteric thickening. The frequency at which these occur in CD point to a pathobiological relevance. Fat wrapping in particular has been suggested to play a role in disease progression [1]. This study aimed to evaluate the relationship between mesenteric disease and other manifestations of CD and to examine the significance of advanced mesenteric disease.

Methods: Ethical approval and informed consent were obtained from the HSE Mid-Western Regional Hospital Research Ethics Committee. All patients undergoing resection for ileocolic CD in University Hospital Limerick since 2010 have undergone a resection which included the mesentery. Novel disease activity indices were generated to quantify mesenteric and mucosal disease. Mesenteric disease was graded based on the presence and extent of mesenteric thickening and fat wrapping (Table 1A). Mucosal disease was graded based on the presence of different intestinal features of CD (Table 1B). Pre-operative Crohn's disease activity index (CDAI) was recorded for all

Table 1A. Mesenteric disease activity index in Crohn's disease

Mesenteric disease score	Severity	Stage	Score
FW minimal, MT minimal	Mild	One	1
FW <25%, MT adipovascular pedicle only	Moderate I	Two A	2
FW <25%, pan-mesenteric MT	Moderate II	Two B	4
FW >25%, pan-mesenteric MT	Severe	Three	6

Key: FW = fat wrapping, MT = mesenteric thickening.

Table 1B. Mucosal disease activity index in Crohn's disease

Intestine	Scores
Oedema	1
Aphthous ulcer	2
Confluent ulcer	3
Stricture	4
Fistula	5

patients. The effect of smoking on all disease activity indices was investigated. The relationship between histologic fat wrapping and surgical recurrence was determined in all intestinal forms of CD (n=94). **Results:** Mucosal and mesenteric disease were topographically coupled in all resection specimens examined. There was a direct association between mesenteric and mucosal disease when investigated using the novel disease activity indices ($r=0.78$, $p<0.0001$). Higher CDAI scores were associated with higher mesenteric and mucosal disease scores ($r=0.72$; $r=0.70$, respectively, $p<0.0001$). Patients who smoked had more severe mesenteric disease ($p<0.05$) but there was no effect on mucosal disease or CDAI. Fat wrapping was observed histologically in 13 (41.9%) index resection specimens and 18 (72%) recurrence specimens. Fat wrapping was an independent predictor of increased risk of surgical recurrence (HR 4.7, 95% CI: 1.71–13.01, $p=0.003$) and was also associated with a shortened time to recurrence ($p<0.001$).

Conclusions: There was a direct association between mesenteric disease and mucosal disease manifestations. Fat wrapping independently predicted surgical recurrence and was associated with a shortened time to recurrence.

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The relationship between thiopurine use during pregnancy and anemia in the offspring during the first year of life

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Background: Thiopurines are given safely to patients with inflammatory bowel diseases (IBD). Repeated studies did not show a connection between thiopurine exposure in pregnancy to major teratogenic outcomes. Anemia has recently been shown to be found more commonly in children born to pregnant IBD patients exposed to thiopurines during pregnancy. The aim of this study was to assess the relationship between thiopurine exposure during pregnancy to development of anemia in their offsprings during the first year of life.

Methods: A prospective comparative observational study was performed at an IBD clinic dedicated for pregnant women. All IBD patients who gave birth between 2009–2015 were allocated. Only patients who were treated exclusively by thiopurines both at pregnancy onset and throughout pregnancy were included in the study arm. The control group consisted of IBD patients not medically treated during pregnancy. The hemoglobin level was performed during the first year of life. Both groups were also compared to the expected hemoglobin levels during the first year of life.

Results: Altogether 34 patients (21 study group and 13 controls) were analyzed. Median years of thiopurine use prior to pregnancy was 24 months (range 12–72 months) and average dosage was 98 mg (range 50–175 mg). Median age of the study group was 32 compared to 29 in the control group ($p=0.02$). Mean years of disease prior to birth was 9.5 ± 4.9 in the study group vs. 4.3 ± 5 in the controls ($p=0.008$). IBD activity, use of either oral iron or intravenous iron as well as the presence of iron deficiency during pregnancy were all similar between both groups. Mean Hemoglobin (G/dL) in the study

group compared to the control group was 11.8 ± 0.8 vs. 11.5 ± 0.6 ($p=0.81$). The white blood count (109/L), platelets (109/L), mean corpuscular volume (MCV) and red cell distribution width (RDW) were 12.2, 355, 75 and 15 in the study group compared to 12.4, 396, 75 and 15 in the control group, respectively ($p=0.89$, $p=0.26$, $p=0.3$, $p=0.46$ for each of the comparisons).

Conclusions: The use of thiopurines during pregnancy in IBD patients is not correlated with anemia in the newborn during the first year of life. Thiopurines continue to show high levels of safety during pregnancy.

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Venous thromboembolism in a Finnish IBD cohort

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Background: Venous thromboembolism (VTE) presents a common and life-threatening extra-intestinal complication of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC).

The aim of this study is to investigate the prevalence of thromboembolism in patients in a Finnish IBD cohort, and to analyze VTE risk factors.

Methods: A register of IBD patients was established in 1986 at Tampere University Hospital, Tampere, Finland, and it was maintained until the end of 2007. A total of 1915 patients (47% female) were included, of which 65.4% were diagnosed with UC and 28.8% with CD. The register included all IBD patients in the area regardless of the level of difficulty of the disease.

Index patients were identified from the IBD register on the diagnosis of either thrombophlebitis, deep venous thromboembolism, and/or pulmonary embolism.

VTEs that occurred 1986–2014 were collected retrospectively. A control group of non-VTE IBD patients was collected from the IBD register as well. Two controls for each case were matched regarding gender, year of birth, IBD diagnosis, and location of the disease

Results: Between 1986 and 2014, 85 IBD patients out of 1915 developed one or several venous thromboembolisms (range 1–5 VTE events). VTE index patients (49.4% female) included 57 UC (67%), 27 (32%) CD, and 1 (1%) IBD unclassified. The incidence was 2.20/1000 patient years. 39% of the first VTE events were deep venous thromboembolism (DVT) in lower extremity and 31% were pulmonary embolism (PE). VTE group and non-VTE group are compared in Table 1.

Table 1. Comparison of VTE and non-VTE groups

	VTE group	Non-VTE group
Total N	85	170
Gut operated ($p=0.118$)	38.8%	28.2%
Mean number of non-transient risk-factors*	1.20	1.04
Mean number of VTE risk-increasing conditions**	0.59	0.43
CD patients: kidney malfunction or other kidney disease ($p=0.031$)	14.8%	1.7%

*Smoking, oral contraceptives/hormone replacement treatment/pregnancy, obesity, VTE tendency in family, presence of one more VTE risk increasing conditions. **Non-exhaustive list: cancer; asthma, COPD; diabetes; atrial fibrillation or other arrhythmia; kidney failure; cardiac failure, rheumatoid arthritis.

43.8% of gut-operated and 18.2% of non-gut-operated VTE patients had more than one VTE event ($p=0.086$). In a sub-group of 1986–2007 data, the extent of the UC disease correlated with the number of VTE events ($rS=0.471$, $p=0.005$).

Conclusions: According to our study and in agreement of previous work, IBD patients have roughly a twofold risk of VTE to that of general population. In a sub-group, the extent of CU correlated with the number of VTE events.

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Inflammatory bowel disease in children is a challenging diagnosis when overlaps with coeliac disease

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Background: Inflammatory bowel disease (IBD) and coeliac disease (CD) are conditions associated with chronic inflammation of the gastrointestinal tract. Underlying aetiology includes genetic susceptibility, abnormal immune response and various environmental factors not fully understood to date. Both entities can overlap in paediatric patients although this is uncommon and difficult to confirm. We present our experience with patients who developed both conditions during early years of life.

Methods: We retrospectively reviewed all IBD patients seen in our centre who also had a diagnosis of coeliac disease over a 10-year-period. Data were collected from electronic notes and laboratory registries. Demographics, consultations, laboratory and endoscopic findings were extracted to a STATA database. Descriptive analysis was performed using absolute value, percentage and mean functions through STATA software version 14.

Results: Only 8/578 patients were found to have both diagnosis, this accounts for 1.4% of all paediatric IBD patients seen in our centre (mean 57 new patients per year, past 10 years). 5 of them were female, 1 male had Down syndrome, and 1 patient had incomplete records. Mean age of diagnosis was 7.1 and 8.9 years for CD and IBD respectively. In terms of the IBD subtype, 4 patients suffered of Crohn's disease, 3 of ulcerative colitis and 1 of IBD unclassified. 3 patients were diagnosed with both entities within 3 months, other 4 had a previous history of CD and developed IBD years later (mean in years 3.0), despite having a well-controlled disease. Positive anti-transglutaminase (TTG) serology was found in 4/7 patients. Endoscopic findings were difficult to interpret, complementary specific biopsy immunostaining, small bowel imaging (MRI, CT) and video capsule endoscopy were required in order to support both diagnoses. Endoscopic assessment when there was a previous diagnosis of CD obeyed to persistent gastrointestinal symptoms despite normal TTG values, these 4 known CD patients had significant IBD features including granulomata and cryptitis in small bowel (3/4) and pancolitis (1/4).

Conclusions: Inflammatory bowel disease can overlap with coeliac disease in paediatric IBD patients although this association is rare. IBD can follow the appearance of CD years later despite TTG normalization and can also present at the same time of CD. Proving the coexistence of IBD and CD in children is a challenge, and requires of a multidisciplinary team involving expert histopathologists,

gastroenterologists, dieticians and clinical laboratory scientists. IBD must be considered in CD patients with new onset of gastrointestinal symptoms or in CD patients whose gastrointestinal symptoms do not seem to respond to a gluten-free diet.

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Current practices in ileal pouch surveillance for ulcerative colitis patients in Three London IBD referral centres

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Background: There are no universally accepted guidelines regarding surveillance of IBD patients after ileal pouch-anal anastomosis (IPAA). The British Society of Gastroenterologists suggests "considering" pouchoscopy and biopsy but accepts "there is no clear evidence that surveillance is beneficial and thus it cannot be strongly recommended". Nonetheless, a recent study of the self-reported practice patterns of US clinicians showed a majority (79%) felt that surveillance was indeed necessary.

We aimed to assess how frequently pouch surveillance is being carried out at our centres. We also evaluated the approaches used for pouchoscopy and the use of endoscopic biopsies.

Methods: The records of 177 patients who underwent IPAA for IBD at three London IBD referral centres (Guy's & St Thomas', University College London and St Mark's Hospitals) were reviewed. Patients with Crohn's disease and those with less than 1 year post-surgical follow-up were excluded.

Data regarding the endoscopic follow-up of the remaining 126 patients was collected retrospectively. Fisher's exact (categorical data) and signed rank sum (continuous data) tests were used.

Results:

Table 1. Demographic and surgery related details

Characteristic	n=126
Gender, male:female	72:54 (58%:42%)
Median age at time of colectomy (range), years	35 (16–64)
Median duration since completion of pouch surgery (range), years	8.2 (1.3–13.4)
<i>Indication for colectomy</i>	
Acute severe UC	49 (39%)
Chronic active UC	49 (39%)
Colorectal cancer	7 (5%)
High-grade dysplasia	5 (4%)
Unknown	16 (13%)

15/126 (12%) had never undergone pouchoscopy for any indication. Of the 111 who had, the median interval between completion of pouch surgery and first pouchoscopy was 1.3 years (0.2–6.4). Median number of pouchoscopies was 3 (0–11), carried out at a median frequency of every 2.4 years (0.9–8.1). Two rectal cuff cancers were found.

59/126 (47%) had never undergone pouchoscopy solely for surveillance. Duration since completion of pouch surgery, speciality of sur-

Table 2. Comparison of surveillance vs non-surveillance groups

		Patients having undergone at least one pouchoscopy with surveillance as stated indication	Patients having undergone no pouchoscopy with surveillance as stated indication	p-value
Department supervising care	Gastroenterology	7	9	0.382
	Surgery	28	18	
	Joint care	32	32	
Duration elapsed since completion of pouch surgery, median (years)		7.1	8.4	0.193
Previous clinical history of pouchitis	Present	29	22	0.501
	Absent	36	37	

pervising clinician and a history of pouchitis did not significantly effect rates of surveillance.

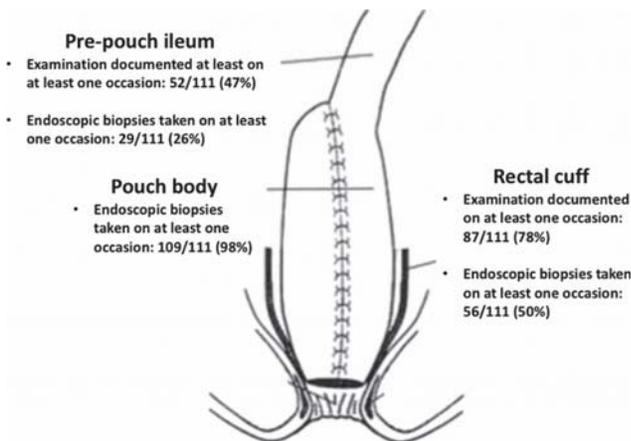


Figure 1. Documentation of pouch regions examined and biopsied at pouchoscopy.

Conclusions: Our results demonstrate a wide variation in endoscopic surveillance of UC-IPAA patients, even amongst experienced clinicians. Some patients underwent several pouchoscopies for surveillance, whereas others had none. Surveillance rates did not seem to be risk factors related. In addition, pouchoscopy could be considered incomplete in a significant proportion of patients with no description of the pre-pouch ileum or rectal cuff/anal transition zone.

P221

Natural history of perianal Crohn's disease in patients with elderly-onset disease: a population-based study

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Background: Population-based studies usually described a mild course of elderly-onset (>60 years) Crohn's disease (CD). However the natural history of perianal CD in this population is unknown. We aimed to describe the prevalence and the natural history of perianal CD in patients diagnosed with CD after 60 years.

Methods: All patients diagnosed with CD after the age of 60 years between 1988 and 2006 were included (n=372). Perianal CD was defined by a perianal abscess or fistula and was classified according to Cardiff classification. Logistic regression and Cox model were used to identify factors associated with perianal CD.

Results: Thirty-four patients (34/372, 9%) were diagnosed with perianal CD at diagnosis. After a median follow-up of 5.4 years [Interquartile range, 2.0–10.1], a total of 59 patients (59/372, 16%) were diagnosed with perianal CD. The 5-year cumulative probability of perianal CD was 17% [CI 95%, 13–21]. Thirty-nine percent of patients (23/59) had complex fistula. At the end of follow-up, incontinence was observed in 22% of patients with perianal CD as compared to 4% of patients without perianal CD (p=10–4). Perianal CD at diagnosis was significantly associated with 5-years immunosuppressants exposition (29.6% [9.8–45.1] vs 16.6% [12.0–21.0]; p=0.02) and with intestinal resection (54.2% vs 29.4%; p<10–3). Twenty-four percent of patients with perianal CD had definitive stoma as compared to 4.5% of patients without perianal CD (p<10–2). At diagnosis, rectal disease was significantly associated with perianal CD occurrence (Odds Ratio, 2.3 [95% CI, 1.1–4.8]). During follow-up, both isolated rectal disease (OR, 2.9 [95% CI, 1.6–5.0] and pure colonic location (L2) (OR, 8.7 [95% CI, 1.2–63.4] were significantly associated with perianal CD occurrence.

Conclusions: In a large elderly-onset population-based cohort, about 20% of patient had perianal CD. The occurrence of perianal CD was associated with pure colonic location and rectal involvement. Although these patients have received more frequently immunosuppressants, one-quarter had definitive stoma, emphasizing the value of early biologic therapy in these patients.

P222

Sequential MRI volume measurements of perianal fistulae in Crohn's disease

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Background: MRI scanning is an important tool in the diagnosis and assessment of perianal Crohn's disease. We aimed to explore whether measurements of the volume of fistulous tracts on MRI at diagnosis and follow-up correlated with clinical outcomes

Methods: This was a single centre pilot study. Patients with a new diagnosis of perianal Crohn's disease on MRI were identified (n=25). 12 patients had a follow-up MRI for following multimodality treatment were included. Measurements of the length of the tract, width (3 point average), as well as a grading of the severity of associated inflammation (T2 imaging) were made by a specialist radiologist. The volume of the tract was calculated based on an approximation to the volume of a cylinder (πr^2). Details of the patient's treatment with biologics, immunomodulators, antibiotics and surgical interventions were collated, as well as an assessment of the clinical response of the perianal disease to treatment (none, partial, or complete healing).

Results: All patients had initiated, or had already received, some treatment for perianal Crohn's disease (thiopurine n=11; antiTNFa n=11; antibiotics n=11; surgical drainage/EUA n=11). In all cases there was a decrease in the grading of inflammation around the tract suggesting some impact of medical therapy. 8 patients had a decrease in tract volume and this was greater than 50% in 7 cases. Of these patients, 1 had a complete clinical response with closure of the fistula, 5 had a partial clinical response with significant symptom improvement but no closure, and 1 patient had no response. In three cases the

volume of the tract increased (range 79–214%) despite treatment. Of these patients, 2 experienced no healing whilst the 3rd patient with the smallest increase in volume experienced a partial clinical response.

Conclusions: This pilot study, using simple and readily generalizable technique for MRI measurement of perianal fistula volume in Crohn’s disease, appears to suggest that changes in fistula volume on MRI correlate with clinical outcomes. Further prospective work in a larger patient cohort adjusting for additional clinical variables is needed to confirm this observation

P223
C-reactive protein improvement after vedolizumab induction phase is associated with remission after 6 months of treatment in ulcerative colitis patients

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Background: Vedolizumab, a gut-selective anti-integrin inhibitor is a biologic agent indicated for ulcerative colitis (UC) treatment. We retrospectively investigated whether improvement of serum C-reactive protein (CRP) levels, after the first 3 infusions of vedolizumab (induction phase) predicts responsiveness at 6 months of therapy.

Methods: Adult UC patients followed at a tertiary IBD center and treated with vedolizumab were included. Cumulative rates of clinical remission (CR, partial Mayo score ≤2 with a bleeding subscore 0) and steroid-free clinical remission (SFCR) were assessed at 3 and 6 months. Responses were calculated using nonresponder imputation. Mann-Whitney U-test was used for unpaired samples and Wilcoxon signed-rank test for paired samples to analyze for differences in CRP levels between patients in remission and in no remission at 6 months of continuous vedolizumab treatment.

Results: Fifty-seven UC patients (Table 1) were analyzed. Two thirds had prior anti-TNF treatment exposure and two thirds had pancolitis. All 57 patients completed 3 vedolizumab infusions by week 6 and 49 completed 5 infusions by week 22. Following 3 infusions, CR and SFCR were 37% (21/57) and 30% (17/57) and at 6 months

the cumulative rates of CR and SFCR were 49% (28/57) and 44% (25/57) respectively (Table 1). Patients in remission at 6 months had significantly lower baseline median CRP levels compared to those not in remission (3 versus 12 respectively, p=0.005). Low CRP levels at baseline were not associated with steroid use. Only patients in remission at 6 months had a significant reduction of median CRP levels after 3 vedolizumab infusions as compared to median baseline levels (z=3.225, p=0.001, Figure 1). Nine out of 36 patients who were non-responders after the induction phase achieved clinical remission at 6 months. Their (n=9) median CRP levels at baseline and after 3 infusions were significantly lower compared to the non-responders (n=27) (3 versus 13; z=2.028, exact p=0.043 and 2 versus 10, z=2.093, exact p=0.035, respectively).

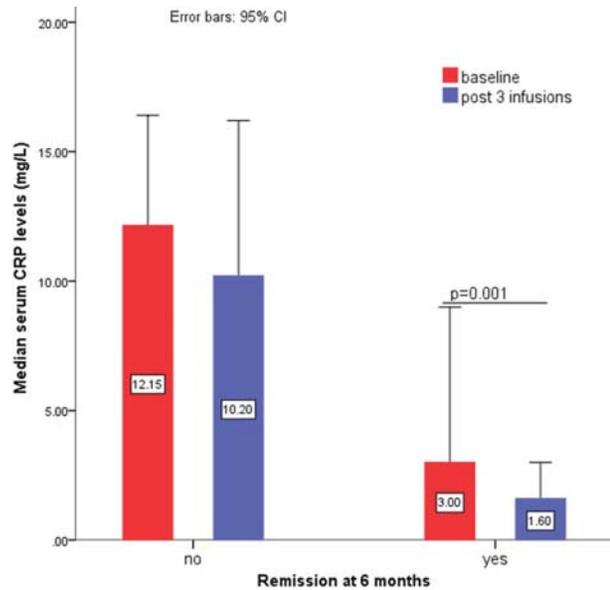


Figure 1. Changes in median CRP levels after vedolizumab induction in UC patients.

Conclusions: Low baseline CRP levels and further reduction of the levels after the induction phase of vedolizumab treatment are associated with clinical remission at 6 months. A decrease in CRP following vedolizumab induction may be used to predict those patients who will be in clinical remission at 6 months.

Abstract P223 – Table 1. Ulcerative colitis patients: baseline characteristics and vedolizumab treatment outcomes

Patient characteristics	N=57
Males	68%
Age at start of vedolizumab, median [IQR], years	33 [26-41]
Disease duration, median [IQR], years	6 [4-10]
Disease extent	
Ulcerative proctitis (E1)	2%
Left-sided colitis (E2)	26%
Extensive colitis/Pancolitis (E3)	72%
Extraintestinal manifestations	16%
Prior immunomodulators	53%
Prior anti-TNF exposures	0=32%, 1=47%, 2=18%, 3=3%
Vedolizumab monotherapy	47%
Concomitant corticosteroids (Cs)	46%
Concomitant immunomodulators (IMMs)	18%
Concomitant Cs & IMMs	11%
Treatment outcomes	
Clinical remission, months 2, 4, 6	37%, 37%, 49%
Steroid-free clinical remission, months 2, 4, 6	30%, 33%, 44%
Median clinical Mayo Score, baseline and months 2, 4, 6	7,4,3,5,2
Median CRP (mg/L), baseline and months 2, 4, 6	9.9, 5, 2.8, 4
Vedolizumab discontinuation	14%

2 months=post 3rd infusion at week 6, 4 months=post 4th infusion at week 14, 6 months=post 5th infusion at week 22. Over the 6-month period drop out patients (surgery or VDZ discontinuation) were included and considered treatment failures

P224
Virtual chromoendoscopy with i-Scan as alternative to dye-spray chromoendoscopy for dysplasia detection in long-standing colonic inflammatory bowel disease

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Background: Dye-spray chromoendoscopy (DCE) with targeted biopsies is the preferred technique for surveillance of dysplasia in long-standing colonic inflammatory bowel disease (cIBD). The aim of the study was to assess the effectiveness of virtual chromoendoscopy (VCE) with i-Scan and targeted biopsies in dysplasia detection in long-standing cIBD.

Methods: A prospective case-control study of long-standing (>7 years) cIBD patients referred for colorectal cancer (CRC) surveillance colonoscopy was performed from January 2013 to September 2016. Case group: VCE with i-Scan (mode 1 and mode 3 combined);



Figure 1. Left: IC-DCE high-grade dysplasia. Right: IC-DCE low-grade dysplasia.



Figure 2. Top: i-Scan-VCE high-grade dysplasia. Bottom: i-Scan-VCE low-grade dysplasia.

control group: 0.4% indigo carmine DCE. All suspicious areas were biopsied and/or resected. High definition endoscopies and video processors (Pentax, Tokyo, Japan) were used. Exploration time and histologic characteristics were analyzed.

Results: 66 patients were included (33 in each group): 51.5% female; mean (SD) age at inclusion, 48.2 (13.0) yr; and median (IQR) disease duration, 15 (13–21) yr. Ulcerative colitis, 54 (81.8%); pancolitis, 39 (59.1%); smoking history, 52 (78.8%); and high risk of CRC, 59 (89.4%) patients. 44 lesions were detected in 35 patients (Table 1). There were no statistical significance differences in the number of lesions detected (dysplastic or not) between DCE (Figure 1) and VCE (Figure 2) (Fisher exact test). Time to intubation and withdrawal of the endoscope in control group were higher than in case group (mean, 5’ vs. 3’, p<0.001; and 15’ vs. 11’, p=0.002, respectively; student’s t-test).

Conclusions: VCE with i-Scan present a similar diagnostic performance to conventional 0.4% indigo carmine DCE in the detection of colonic dysplasia in patients with long-standing cIBD. However, VCE with i-Scan appears to be a less time-consuming alternative to DCE.

P225
Clinical characteristics of patients who have inflammatory bowel disease associated with hyperamylasemia and pancreatitis

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Background: Inflammatory bowel disease (IBD) is often associated with hyperamylasemia. Recently, the concurrent development of type 2 autoimmune pancreatitis (AIP) has also received considerable attention.

Methods: We retrospectively studied 1) the incidence of hyperamylasemia, 2) the clinical characteristics of patients with hyperamylasemia, 3) the relation between hyperamylasemia and concurrent medication, and 4) the clinical characteristics of patients with pancreatitis.

Objective: To clarify the clinical characteristics of IBD associated with hyperamylasemia and pancreatitis.

Subjects: Among 959 patients with IBD whose serum amylase levels were measured at least once, we studied 147 patients (91 with ulcerative colitis and 56 with Crohn’s disease) whose serum amylase levels were higher than the upper limit of normal in our hospital (125 IU/L) on at least one occasion.

Results: 1) Elevated serum amylase levels were found in 147 (15.3%) of the 959 patients. The mean maximum serum amylase level was 215±186 IU/L (range, 126 to 1939). As for other enzymes, lipase levels were elevated in 10 (77%) of 13 patients, and elastase 1 levels were elevated in 7 (88%) of 8 patients. Imaging examinations such

Abstract P224 – Table 1. Histology of lesions detected in 66 patients

Variable	Total: n (%)	IC-DCE (Dye-spray chromoendoscopy with 0.4% indigo carmine)	i-Scan-VCE (virtual chromoendoscopy with i-Scan)	p (Fisher exact test)
Patients	35 (53.0%)	19	16	–
Dysplasia:	6 (13.6)	4	2	0.336
– Invasive cancer	1	–	1	–
– High-grade dysplasia	1	1	–	–
– Low-grade dysplasia	4	3	1	–
– Non-dysplasia:	38 (86.4)	21	17	0.311
– Postinflammatory polyp	31	17	14	–
– Hyperplastic polyp	7	4	3	–

as abdominal ultrasonography and computed tomography were performed in 78 patients (53%, some overlap) and showed gallstones in 12 patients (8.7%). No patient had primary sclerosing cholangitis. 2) Drug-induced hyperamylasemia was suspected in 19 patients (13%). The causative drugs were prednisolone in 10 patients, immunomodulators in 5 patients, and 5-aminosalicylic acid preparations in 4 patients. The mean time from the initiation of treatment to the development of hyperamylasemia was 54.4 ± 52.3 days (range, 7 to 202). Drugs that had already been continuously received for 1 year or longer at the time of elevation of the serum amylase level were excluded. 4) Acute pancreatitis was diagnosed in 9 (0.9%) of the 959 patients. Three patients had AIP, diagnosed on the basis of pancreatic duct findings on magnetic resonance cholangiopancreatography (MRCP), the concurrent presence of IBD, and the response to steroids. Three patients had immunomodulator-induced pancreatitis, and 3 patients had idiopathic pancreatitis. Among the 3 patients with severe pancreatitis, 1 patient received pancreatic regional arterial infusion. There were no deaths.

Conclusions: Hyperamylasemia can develop during follow-up in a considerable number of patients with IBD. Because drug-induced pancreatitis can occur in such patients, careful follow-up is essential after starting treatment. Our study showed that AIP can develop as a complication in Japanese patients with IBD. Therefore, AIP should be actively investigated.

P226

Comparison of four different immunoassays for measuring golimumab and anti-golimumab antibody concentration in patients with ulcerative colitis

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Background: Golimumab is an anti-TNF antibody with higher affinity for TNF compared to infliximab and adalimumab and higher stability compared to infliximab. The PURSUIT trials showed a significant exposure-response relationship with golimumab in ulcerative colitis (UC). Low drug exposure may be related to primary and secondary non-response as described for infliximab and adalimumab. To assess if assay results obtained with different methods can be considered comparable, we conducted a comparison of different immunoassays measuring levels of golimumab and anti-drug antibodies (ADA).

Methods: We included serum samples from 80 patients with UC recruited in an ongoing prospective observational study who started on golimumab treatment. Golimumab was quantified by either an anti-IgG detection antibody (Theradiag) or an antibody directed against the idiotype of golimumab (Sanquin and KU Leuven, Janssen R&D). Bridging drug-sensitive ELISA assays (Theradiag, Janssen R&D, KU Leuven), a bridging drug-tolerant ELISA assay (Janssen R&D), and a radioimmunoassay (Sanquin) were used to quantify ADA.

Results: Median (IQR) serum golimumab levels were 4.5 (2.2–6.6), 3.5 (1.7–4.8), 4.9 (2.6–7.0), and 2.4 (1.2–4.0) $\mu\text{g/mL}$ with Theradiag, Sanquin, KU Leuven and Janssen R&D assays, respectively. Median assay values are different between assays in head to head comparisons ($p=0.0001$), except for comparison of median levels between Theradiag and KU Leuven ($p=0.155$) and comparison of Sanquin and Janssen R&D assay values ($p=0.055$). With the Sanquin and Leuven assays, 84% of samples are in the same quartile of distribution of values; this overlap was 71% for Sanquin and Theradiag, 66% for Theradiag and Leuven assays, 68% for Theradiag and Janssen R&D, 81% for Leuven and Janssen R&D and 86% for Sanquin and Janssen R&D. All but not the Theradiag assays showed specificity for golimumab as these make use of an anti-idiotypic antibody to golimumab for detection. We were not able to compare ADA concentrations determined by the different assays. However, ADA were detected in the two same patients by Theradiag, Sanquin and KU Leuven assays and in one of those two with the drug-sensitive Janssen R&D assay. ADA were detected in 27.5% of samples (22/80) with the Janssen R&D drug-tolerant assay.

Table 1. Correlation between assays to measure Golimumab serum levels

	Theradiag	Sanquin	KU Leuven	Janssen R&D
Theradiag		0.73	0.78	0.97
Sanquin	0.73		0.96	0.72
KU Leuven	0.78	0.96		0.96
Janssen R&D	0.97	0.72	0.96	

Conclusions: There is an acceptable correlation between golimumab serum concentrations measured with Theradiag, Sanquin, KU Leuven and Janssen R&D assays. The low number of ADA positive samples precludes statistical concordance between ADA values measured with the different assays.

P227

Outcomes of anti-TNF versus Vedolizumab therapy for ulcerative colitis: the Leeds experience

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Background: Two groups of biological therapies are licensed and approved by NICE for the management of moderate to severe UC in the UK. These are the anti-TNF drugs, Infliximab, Adalimumab and Golimumab & the $\alpha 4\beta 7$ anti-integrin Vedolizumab. There are no published head-to-head RCTs comparing the efficacy and safety of these two groups of drugs for UC. We aim to compare the outcomes for all patients treated with biological therapy for UC in our unit of 3, 000 IBD patients.

Methods: Anti-TNF or VDZ has been used routinely for UC maintenance therapy in Leeds since Oct 2015. We use biosimilar infliximab as our first-line anti-TNF agent with VDZ reserved for anti-TNF failures or contraindications. Acute severe colitis cases were excluded. We prospectively collected data on demographics, CRP, calprotectin & clinical outcomes over a 9 month period. Response and remission at 3 months were defined according to Mayo scores or physician global assessment (PGA) and compared using the Chi-squared test.

Results: A total of 36 (20 female) patients received biological therapy for UC in this period (17 IFX, 6 ADA, 13 VDZ). Results for IFX:ADA:VDZ respectively are; Mean age 38 (18–68), 30 (25–46) & 41 (19–77), disease duration pre-treatment (months) 92.8, 23.4,

54. Mean weight 74kg, 80kg, 81kg. Mayo scores at baseline were 6.4, 7.3, 7 or with endoscopy sub-scores 8.5 (n=14), 9.5 (n=2) & 9 (n=8). Mean steroid dose at baseline: 10.5mg, 1.6mg & 15mg. Thiopurines at baseline 59%, 33% and 62%. 17/17 (100%) IFX patients were given the drug first line as opposed to 4/6 (67%) of ADA and 2/13 (15%) VDZ pts. VDZ was used first-line in one case of MS & one of possible latent TB. By 3 months of IFX therapy 1 dose escalated, 3 switched to ADA due to low drug levels with high antibodies and 1 rash and 1 infusion reaction necessitated IFX withdrawal. 50% of Humira patients dose escalated by 3 months. There were 4 colectomies in the VDZ group, all had previously failed one or more anti-TNF therapy. There was no significant difference in response (p=0.17) and remission (p=0.62) rates between infliximab and VDZ.

Table 1. Response (Resp) and remission (Rem) rates by Mayo score or PGA for biological therapies in UC

Drug	n	Resp Mayo	Resp PGA	Rem Mayo	Rem PGA	Colectomy
IFX	17	8/13 (62%)	12/17 (71%)	7/13 (54%)	9/17 (53%)	
Adalimumab	6	3/6 (50%)	3/6 (50%)	0/5 (0%)	1/6 (17%)	
Vedolizumab	13	9/13 (69%)	9/13 (69%)	5/13 (38%)	4/13 (31%)	4

Conclusions: Anti-TNF and VDZ therapies are safe & effective in the management of UC. Whilst the numbers of adalimumab treated patients is small 50% of patients dose escalated which should be noted when considering the overall relative costs of these therapies. VDZ response and remission rates of 69% and 38% are encouraging in this largely anti-TNF failure cohort but more data on cost-effectiveness of anti-TNF versus VDZ first-line are required.

P228
Prevalence and risk factor of CMV infection among hospitalized patients with ulcerative colitis

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Background: Cytomegalovirus (CMV) infection was seen frequently among hospitalized patients with ulcerative colitis (UC). Infected patients are more likely to become hospitalized, have longer lengths of stay, and higher mortality rates. However, the risk factor of CMV infection in UC is not well understood. The aim of this study was to determine the prevalence of CMV infection in UC patients and identify the risk factors for CMV infection among hospitalized patients with UC.

Methods: Between January 2010 and December 2014, 131 patients diagnosed with UC and 88 patients were hospitalized at Pusan National University Hospital. We were retrospectively reviewed their medical records including disease severity, treatment & CMV infection by histological examinations. The clinical disease activity of UC was assessed using Modified mayo-score. CMV disease was defined as CMV inclusion bodies in biopsy specimens, or positive specific immunohistochemical staining for CMV. Differences in risk factors were determined between patients with UC and CMV and those with UC without CMV.

Results: Eighty-eight patient with UC were hospitalized at Pusan National University Hospital during study period. Among those, 31 patients (31/88, 35.2%) were diagnosed CMV infection. Modified mayo-score was significantly higher in patients with UC and CMV infection than those with UC without CMV (p=0.02). Also, steroid was a risk factor of CMV infection (p=0.014). In contrast, no association was seen with sex, age, the extent of disease, immunomodulator or anti TNF-α inhibitor use. All of the CMV-positive patients received immunosuppressive treatments.

Table 1. Baseline characteristics (n=88)

Variables		
Age (years)		44
Sex	Male	50 (56.8%)
	Female	38 (43.2%)
Disease extent at colonoscopy	Proctocolitis	15 (17%)
	Lt. colon	31 (35.2%)
	Pancolitis	34 (38.6%)
	No data	8 (9.09%)
mayo score	1	17 (22%)
	2	24 (31.2%)
	3	36 (46.8%)
	Average	2.21
	No data	11 (14.3%)
Symptoms	Abdominal pain	31(35.2%)
	Hematochezia	55(62.5%)
	Fever	3(3.5%)
	Diarrhea	23(26.1%)
	General weakness	5(5.7%)
Drug	No drug	12(13%)
	ASA	60(68.1%)
	Steroid	52(59.1%)
	Azathioprine	15(17.4%)
	anti TNF α blocker	3(3.4%)
Steroid total dose (mg)		3002
Disease duration (days)		1731

Table2. comparison between CMV (+) and CMV (-)

Variables	CMV (+) (n=31)	CMV (-) (n=57)
Age (years)	47.6	42
Sex		
	Male	18
	Female	13
Disease extent at colonoscopy		
	Proctocolitis	3
	Lt. colon	16
	Pancolitis	12
Mayo-score		
	1	1
	2	9
	3	21
	average	2.645
	No data	11
Drug		
	No drug	0
	ASA	22
	Steroid	22
	Azathioprine	8
	Anti TNF α blocker	2
Steroid total dose (mg)	average	3729
Disease duration (days)	average	1521.5
		1943.7

lator or anti TNF-α inhibitor use. All of the CMV-positive patients received immunosuppressive treatments.

Table 3. Predictive factors associated with CMV infection

Variables	Odd ratio	P value
Steroid	6.482	0.014
AZA	1.116	0.862
TNF	7.371	0.223
Mayo score (>3)	35.739	0.02
Ds. Ext. (Pancolitis)	1.061	0.918
Gender (Male)	0.845	0.764
Age (>65)	2.19	0.381

Conclusions: CMV infection in hospitalized patients with UC is associated with steroid therapy and severe colonic inflammation. CMV

infection should be suspected in steroid dependent patients with active UC. More rapid diagnosis and timely initiation of antiviral therapy for CMV-associated colitis in patients with UC are needed.

P229
The modified postoperative endoscopic recurrence score for Crohn's disease: Does it really make a difference in predicting clinical recurrence?

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Background: The Rutgeerts' score (RS) is widely used to guide post-operative management of patients with Crohn's disease (CD). The modified RS differentiates lesions at the anastomosis with or without <5 isolated neo-terminal ileal erosions (i2a) from presence of ≥5 isolated neo-terminal ileal erosions with or without anastomotic lesions (i2b), but its predictive value and clinical relevance has not been validated. We investigated if clinical relapse (CR) and need for endoscopic/surgical intervention (ESI) differ between i2a and i2b endoscopic recurrence (ER).

Methods: This was a retrospective, single-center study including all patients operated between 2000 and 2013 with an i2 ER observed <12 months after right hemicolectomy with ileo-colonic anastomosis. The modified RS was attributed based on the available endoscopic report and images. CR was defined as the occurrence of CD related symptoms along with objective signs of disease activity. ESI was defined as the need for balloon dilatation at site of the anastomosis, or new ileocolonic resection. Kaplan-Meier curves were plotted for time from index endoscopy to CR and ESI.

Results: The study population consisted of 94 patients [43 males, median age 37 years]. At index endoscopy, 53 patients (56%) had an i2a ER, and 41 (44%) an i2b ER. Groups were not different regarding disease characteristics and post-operative prophylactic therapy. Medical treatment was optimized according to index colonoscopy in 8 (15%) patients with i2a and 20 (49%) with i2b ER (Odds ratio (OR) 5.2 (95% CI 2.0–14.6), p<0.001). During a median (IQR) follow-up of 78 (37–109) months, CR and ESI were observed in 47 (50%) and 21 (22%) patients, respectively. As shown in Figure 1, i2a and i2b scores were not predictive of CR or ESI (Log Rank p=0.37 and p=0.10, respectively). Also after exclusion of patients with immediate post-endoscopy treatment optimization, i2a and i2b scores were not predictive (Log Rank p=0.73 and p=0.34, respectively). A previous ileocolonic resection (OR 2.0 (1.1–3.9), p=0.04) was associated with CR; immediate post-operative prophylactic therapy by anti-TNF was protective against CR (p=0.03). Post-operative prophylactic therapy by thiopurine was protective against ESI (p=0.02). **Conclusions:** No difference was observed in terms of clinical relapse and need for endoscopic/surgical intervention between patients with i2a or i2b endoscopic recurrence after right hemicolectomy with ileocolonic anastomosis. Further study is needed to confirm these results and evaluate the outcome of Rutgeerts' score i2 patients.

P230
Methotrexate in the treatment of Crohn's disease: a Portuguese real-life single center experience

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Background: Methotrexate (MTX) is frequently used as a second-line immuno-modulator in patients with Crohn's disease (CD) when

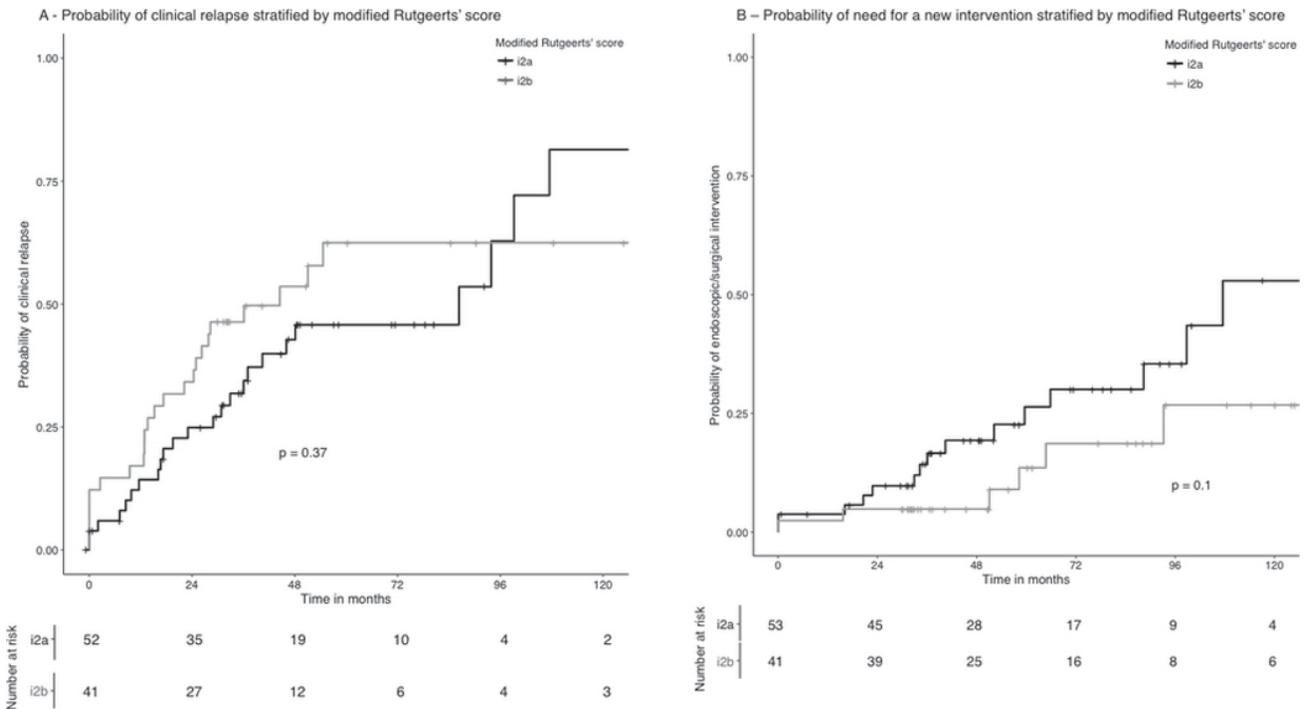


Figure 1 : Kaplan-Meier curves showing the cumulative probability for (A) clinical relapse and (B) need for endoscopic or surgical intervention after ileocolonic resection in Crohn's disease patients stratified by the modified Rutgeerts' score at index endoscopy after the surgery.

purine analogs are not tolerated or lack efficacy. However, evidence on indications for its use, efficacy, adverse effects and patient outcomes is still limited. Our objective was to evaluate the experience with the use of MTX in CD in a high-volume Portuguese tertiary center.

Methods: The records of all patients treated with MTX were evaluated with regard to the dose, duration, response, and tolerance to MTX. Remission was defined as improvement in symptoms with no corticosteroid requirement for 3 months or ability to wean off steroids.

Results: Sixty-two patients were included, 35 female (56.5%), with a mean age of 37.5 (\pm 11.3) years. According to the Montreal classification, the distribution of the disease was as follows: age - A1 12.9%, A2 46.8%, A3 38.7%; location - L1 27.4%, L2 12.9%, L3 51.6%, L1+4 1.6%; behavior - B1 33.9%, B2 25.8%, B3 40.4%. Twenty-one patients had perianal disease (33.9%) and half had previous surgery. MTX was the first-line immunosuppressant in 9 patients (14.5%). Indications for initiating MTX included: adjuvant to anti-TNF agent (43.5%), intolerance to azathioprine (27.4%), corticoid dependence (19.4%) and corticoid resistance (9.7%). Almost half of the patients were on steroids at the onset of MTX (n=28, 47.5%). Eighteen patients achieved clinical remission under MTX (29%), 22 clinical response (35.5%) and 22 were nonresponders (35.5%). Absence of response was associated with a lower cumulative dose (784 vs. 1365 mg, $p=0.004$), shorter duration of treatment (66 vs. 89 weeks, $p=0.003$), diagnosis at an earlier age (21 vs. 27 years, $p=0.028$), and colonic involvement (48% vs. 0%, $p=0.006$). During treatment with MTX 35.5% developed flare(s), 37.1% needed steroids, 9.7% started anti-TNF agent, and 12.9% had surgery. Forty-nine patients discontinued MTX after a mean period of 88 (\pm 86) weeks. Reasons for suspension included hepatitis (34%), absence/loss of response (31.2%), intolerance (17%), patient decision (14.9%) and pregnancy (2.1%). In total, 21 patients had adverse effects (36.8%) and 4 (6.9%) had opportunistic infections, all of them under anti-TNF. After MTX discontinuation, 43.6% of the patients had further flare(s), 20.4% started anti-TNF agent, and 12.7% underwent surgery.

Conclusions: Despite the moderate efficacy demonstrated in the management of Crohn's disease, mainly as an adjuvant to anti-TNF agents, the use of MTX is limited by the development of adverse effects by more than 30%. Longer treatment, especially in patients with localized ileal disease, is associated with higher response rates.

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Backgrounds and D-dimer on admission are useful factors for predicting venous thromboembolic complications in hospitalized patients with inflammatory bowel disease

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Background: Venous thromboembolism (VTE) is known as one of the complications of inflammatory bowel disease (IBD). VTE demonstrates serious extraintestinal manifestations complicating the clinical course of IBD and can lead to significant morbidity and mortality. Therefore, clinician's awareness of the risks of VTE in hospitalization will help the management of thromboembolic complications in IBD. The aim of the present study was to identify the predictive factors of VTE in hospitalized patients with IBD.

Methods: We evaluated patients with IBD who were hospitalized from February 2015 to March 2016. We defined the VTE onset within two months after the admission as the primary endpoint. VTE was diagnosed by enhanced computed tomography. We analyzed the relations between VTE onset and the patient factors including their clinical backgrounds, laboratory test data in hospitalization, and inserting the central venous catheter. Also we evaluated the utility of Caprini score and Padua score at the time of admission.

Results: Eighty-nine IBD cases (31 patients with ulcerative colitis and 58 patients with Crohn's disease; 60 men and 29 women) had been hospitalized and treated. Central venous catheter was placed in 43 patients. During the observation period, VTE had been occurred in seven cases (7.9%). Average age in IBD patients with VTE was 46.6 \pm 9.4 years old compared to 36.6 \pm 14.7 years old in patients without VTE. Median disease duration in IBD patients with VTE was 5.8 \pm 5.1 years compared to 7.4 \pm 9.0 years in patients without VTE. Univariate and stepwise multiple logistic regression analysis identified age at hospitalization (AGE; odds ratio (OR) 1.07, 95% confidence interval (CI) 0.99–1.17, $p<0.08$), gender (GEN; OR 8.89, 95% CI 0.93–183.3, $p<0.06$) and D-dimer value on admission (DD; OR 1.86, 95% CI 1.27–3.22, $p<0.0009$) as the risk factors highly associated with VTE onset. The calculation formula $\{-6.411 + 0.619DD + 0.065AGE - 1.092GEN \text{ (man: 0, woman: 1)}\} > 0$ significantly predicted the occurrence of VTE during hospitalization ($p<0.0007$, AUC=0.96). Meanwhile, the association between VTE onset and thrombosis risk score such as Caprini score and Padua score was not provided.

Conclusions: In hospitalized patients with IBD, gender, age, and D-dimer value on admission were highly related with VTE onset. The calculation formula using these factors significantly predicted the occurrence of VTE. The patient information and laboratory data on admission are critical for the management of thromboembolic complications in patients with IBD.

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Atherosclerosis in ulcerative colitis

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Background: To study the extent of early atherosclerosis in ulcerative colitis (UC) patients by measuring carotid intima-media thickness in UC. Our goal was to evaluate a possible connection between early atherosclerosis and ulcerative colitis (UC) evolution.

Methods: Our study included 120 patients (after excluding the patients with risk factors for atherosclerosis) divided in two groups: 60 with UC and 60 controls. Both groups had similar age distribution. For each patient included in the study we measured the carotid intima-media thickness, lipid profile (to exclude patients with risk factors), erythrocyte sedimentation rate (ESR), C reactive protein (CRP). We also collected clinical and anamnesis data.

Results: The carotid intima-media thickness was significantly higher in UC group compared with healthy subjects ($p=0.048$). In addition, we found significant correlations between some disease-related data (such as UC duration) and the values of carotid intima-media thickness ($p<0.01$). UC patients had significantly higher ESR and CRP ($p<0.05$).

Conclusions: In this study we showed that UC may have an influence

on early atherosclerosis formation, but further studies are needed to determine the pathophysiological mechanisms.

P233 Diagnostic delay in a large cohort of patients with inflammatory bowel disease – results of a multicenter study of the Austrian IBD Study Group (ATISG)

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Background: Long diagnostic delay is frequent in inflammatory bowel disease (IBD), especially in Crohn's disease (CD), and may lead to irreversible bowel damage.

We sought to investigate the diagnostic delay in a large cohort of Austrian IBD patients.

Methods: In a multicentre cohort study adult patients with IBD (Crohn's disease CD, ulcerative colitis UC, inflammatory bowel disease unclassified IBDU) attending 18 Austrian outpatient clinics were recruited between May 2014 and July 2015 to complete a multi-item questionnaire. Medical and socioeconomic characteristics including diagnostic delay were recorded by that questionnaire. Diagnostic delay was defined as the time period from the first symptom onset to diagnosis of IBD. The survey preparation, data capturing and exploratory data analysis were performed by using EvaSys software and SPSS.

Results: 1218 patients (792 with CD, 405 with UC, 21 with IBDU; 617 women) with a mean age at the time of investigation of 41.5 years (range 18–87 years) and a mean duration of disease of 12.4 years (range 0–49 years) were analyzed. Patients with IBDU were included in the UC group. The median diagnostic delay in patients with CD was 0.53 years (95% confidence interval (CI) 0.45–0.61 years) and in patients with UC/IBDU was 0.28 years (95% CI 0.28–

0.36 years) ($p < 0.001$). The probability to be diagnosed with IBD after first symptom onset is given in Figure 1.

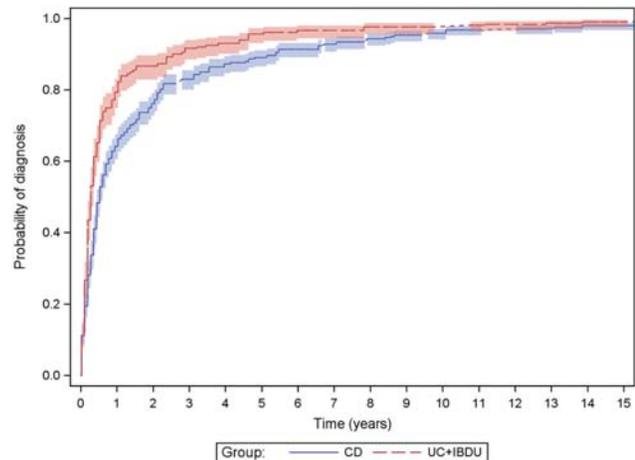


Figure 1. Time to diagnosis by type of disease.

Conclusions: In this large Austrian referral center based IBD cohort the diagnostic delay was significantly longer in CD than in UC/IBDU. The median diagnostic delay was 6 months in CD patients and 3 months in UC/IBDU patients.

P234 Recent trends in microscopic colitis: demographics, clinical features and outcomes in a Portuguese cohort

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Background: Microscopic colitis (MC) is a chronic inflammatory bowel disease characterized by chronic watery diarrhea and specific histopathological features. MC is still under-recognized in clinical practice. The authors intend to analyze the demographics, clinical, and therapeutic features and prognosis of patients diagnosed with MC.

Methods: Retrospective observational study of adult patients with histological diagnosis of MC, between 2008 and 2015, in a tertiary referral center. Data collection was performed from clinical records of the patients. Descriptive statistics, uni and multivariate analysis was performed using IBM SPSS Statistics 22 with $p < 0.05$ deemed to be statistically significant.

Results: During the period of the study there were 25 patients diagnosed with MC (54% women with a median age of 67 (IQR: 48–73) years, followed for a median of 16 (IQR: 4–29) months); lost follow-up in 4 cases. The younger patient had 22-year-old and the oldest had 83-year-old at the time of the diagnosis. There were 13 cases of collagenous and 12 of lymphocytic colitis. Diarrhea was almost invariably present (96%), while abdominal pain (44%), and weight loss (44%) were also frequently reported. The median time since the beginning of symptoms until a definitive diagnosis was 8 (IQR: 3–17) months. On endoscopic evaluation, two (8%) patients presented with abnormal findings, such as mucosal edema and erythema. In four (16%) patients the diagnosis of MC was made after admission due to acute kidney injury and electrolyte disorders (half of these cases were admitted in an intermediate care unit). One (4%) patient was re-admitted, despite treatment with aminosalicylates. Although only one (4%) case was considered to be drug-induced,

many patients were taking a variety of medications thought to be associated with MC, including proton pump inhibitors (48%), aspirin/clopidogrel (36%), and SSRIs (28%). The induction treatment of choice in most cases was budesonide (36%) and aminosalicylates (32%). During follow-up, recurrence of symptoms occurred in 36% patients after withdrawal of successful induction therapy. However, budesonide was associated with a lower recurrence rate comparing to aminosalicylates or oral corticosteroids (29% vs. 50%, $p=0.036$). **Conclusions:** Despite MC has a mild course in most cases, a considerable number of our cases were admitted due to severe dehydration with acute kidney injury and electrolyte disorders. Such situations carries a great burden on individual health and health-related costs. Polypharmacy should be a concern in at-risk cases and appropriate treatment (ie, budesonide) must be advocated, following international recommendations.

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Endoscopic, clinical, and surgical recurrence of Crohn's disease: In which direction are we going?

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Background: Crohn's Disease (CD) is a complex and heterogeneous disease, which requires the collegial effort of a multidisciplinary team which is motivated and constantly updated on the many facets of the disease. One of the unresolved issues is the recurrence of CD, which greatly affects the quality of life of those patients [1,2].

In an effort to understand where we are going and to improve ourselves we decided to retrospectively review our tertiary center experience, focusing on our data about endoscopic, clinical and surgical relapses after first major surgery.

Methods: We retrospectively reviewed our database dedicated on inflammatory bowel diseases from 2000 to October 2016, selecting patients affected by CD. We evaluated the mean duration of their follow up and we considered only the group of patients with at least 5 years follow up. We recorded the their demographic characteristics, the age at diagnosis of CD, the primary site of disease, the type of first surgery, the incidence of endoscopic, clinical and surgical recurrent disease after surgery.

We considered patients with Rutgeerts score ≥ 2 affected by endoscopic relapse; patients with CDAI > 150 affected by clinical relapse; patients who needed further surgery were considered affected by surgical relapse.

Results: 215 patients affected by CD have come to our attention since 2000. Among them, 92 patients underwent major surgery almost once and only 47 patients (51%) reached at least a 5 years follow up after operation. Male patients were 25 (53,2%). The mean age of CD onset was 34 years old. Smokers were 32 (48%).

The patterns of gastro-intestinal involvement of those patients at diagnosis were: ileum (L1) in 13 patients (27,7%), colon (L2) in 11 patients (23,4%), ileum plus colon (L3) in 23 patients (48,9%).

25 patients (53,2%) underwent major surgery in emergency setting. At follow up, cumulative endoscopic relapse rates were 38,3%, 59,6% and 74,5% at 1, 3 and 5 years after operation, respectively. Clinical recurrence affected 8,5% of patients at 1 year, 19,1% at 3 years, 44,7% at 5 years. Finally surgical recurrence accounted for 2,1%, 12,8% and 14,9% at 1, 3, 5 years of follow up, respectively. (Figure 1).

Conclusions: In line with what has long been known, CD ineluctably

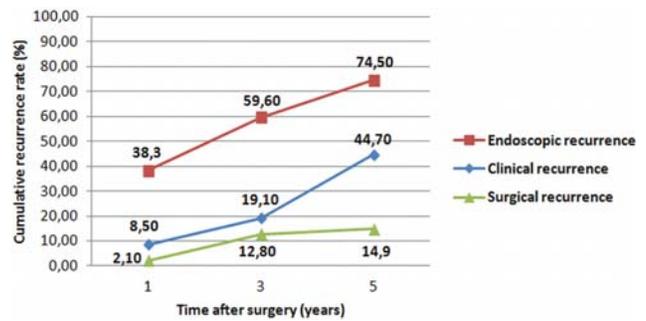


Figure 1. Cumulative recurrence rates in patients who underwent major surgery.

tends to recur. [3] The incidence of endoscopic recurrence remains consistently high over time. The clinical recurrence shows a gradual trend of increase. Surgical recurrence shows a low incidence for the entire follow-up.

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P236

Fecal calprotectin as suitable biomarker in evaluation of histological disease activity

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Background: Although acute and chronic microscopic inflammation has been associated with risk of relapse in patients with ulcerative colitis (UC), histological remission is still not recommended as a therapeutic endpoint. Sparse data exist about prediction of histological activity by Fecal Calprotectin (FCP). The aim of this study was explore the association of FCP with acute and chronic histological activity.

Methods: 82 patients with UC from a single tertiary IBD Centre were enrolled in this prospective observational study. Endoscopic activity was evaluated by Mayo endoscopic sub-scores. For the assessment of histological activity, Geboes score was used to evaluate active (structural changes, the presence of polymorphonuclear leucocytes with cryptitis and crypt abscessus, and erosions or mucosal ulcers) and chronic inflammation. Basal plasmocytosis, as a predictor of relapse, was described as well. Buhlmann rapid test was used to determine FCP using cut off level of 100 $\mu\text{g/g}3$. Statistical analysis was carried out using SPSS 20.0 (Chicago, IL).

Results: 38% (31/82) of patients were in endoscopic remission while 33% (27/82) achieved histological remission. Strong correlation was found between level of FCP and Geboes score ($p<0.001$ and $\rho=0.521$ – Spearman correlation). Statistically significant association was observed between FCP and histological indicators of active inflammation: a. structural changes $p=0.001$, $\text{CI} \pm 8.58$; b. presence of the pres-

ence of polymorphonuclear leucocytes with cryptitis and crypt abscess $p < 0.001$, CI ± 10.61 ; c. presence of erosion and mucosal ulcers $p < 0.001$, CI ± 6.72 , as well as with basal plasmacytosis ($p < 0.001$, CI ± 6.42). The relation with chronic inflammation was not observed ($p = 0.002$, CI ± 9.37)

Conclusions: Elevated value of FCP beyond 100 $\mu\text{g/g}$ among patient with clinical and endoscopic remission of UC should always be carefully interpreted. It may indicate a histological activity and predict a forthcoming relapse.

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Hair mineral and trace element contents as reliable markers of nutritional status compared to serum levels in children with inflammatory bowel disease

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Background: Patients with inflammatory bowel disease (IBD) are at high risk for mineral and trace element deficiencies because of long-term inflammation in the gut and decreased oral intake. Because serum levels of several micronutrients are influenced by systemic inflammatory responses, serum levels are limited in reflecting body nutrient status in IBD. The aim of this study was to investigate the influence of inflammation on serum micronutrient levels in children, and to evaluate the usefulness of hair mineral and trace element contents as reliable markers for nutritional status compared to serum micronutrient levels in children with IBD.

Methods: Between April 2012 and March 2016, a total 86 children (55 boys and 31 girls, aged 4.8–17.4 years) were included and divided into the 3 study groups; Crohn's disease ($n=43$), ulcerative colitis ($n=14$), and abdominal pain-related functional gastrointestinal disorder ($n=29$). Serum mineral and trace element levels, serum prealbumin and albumin levels, hemoglobin and hematocrits, inflammatory markers such as white blood cell counts, lymphocyte counts, C-reactive protein, and erythrocyte sedimentation rate (ESR), and hair mineral and trace element contents were measured in all subjects at initial diagnosis. Statistical analysis was performed among the 3 groups using one-way analysis of variance, and analysis of covariance was used to evaluate inflammation affecting serum micronutrient measurement.

Results: Serum calcium ($p < 0.001$), iron ($p < 0.001$), selenium ($p = 0.01$), prealbumin ($p < 0.001$), albumin ($p < 0.001$), hematocrit ($p < 0.001$), and lymphocyte ($p < 0.001$) were significantly different among the 3 groups. After adjusted for ESR, serum calcium ($p = 0.012$), iron ($p < 0.001$), prealbumin ($p < 0.001$), albumin ($p = 0.007$), hematocrit ($p = 0.002$), and lymphocyte ($p = 0.008$) were still significantly different, whereas serum selenium was not. Regarding hair mineral and trace element analysis, only hair calcium ($p = 0.04$) and selenium contents ($p = 0.035$) were significantly different among the 3 groups, whereas hair iron ($p = 0.067$), zinc ($p = 0.052$), magnesium ($p = 0.077$), copper ($p = 0.193$), manganese ($p = 0.213$), and chromium contents ($p = 0.687$) were not different.

Conclusions: Serum micronutrient levels should be cautiously interpreted in conjunction with inflammatory markers in patients with IBD. Furthermore, hair trace elements measurements may support understanding of body micronutrient status in children with IBD.

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Mental health issues and healthcare utilisation in outpatients with inflammatory bowel disease

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Background: In patients with Inflammatory Bowel Disease (IBD), anxiety and depression are known to be risk factors for increased hospitalisation and poor self-management practices such as low medication adherence and continued smoking. It is not yet known whether integrating psychological care in the outpatient IBD setting has a potential to yield economic or healthcare utilisation benefits. As part of a broader study investigating the need for and usefulness of integrated psychological support in IBD care (see abstract A-1765), we report here on initial data on the mental health and healthcare utilisation of patients in an established IBD service.

Methods: Potential participants were drawn from the IBD service at a large tertiary hospital, and were recruited via post and in-person at scheduled outpatient appointments. Screening data were gathered by questionnaire: mental health with the Hospital Anxiety and Depression Scale (HADS) and the Kessler 6 Scale (K6), medication adherence with the Morisky Medication Adherence Scale (MMAS-8) and quality of life by the Assessment of Quality of Life measure (AQoL-8D). Demographic and healthcare utilisation data for the twelve months prior to psychological screening were collected by electronic state-wide hospital records.

Results: 500 patients were approached; 67% participated in psychological screening and 37% scored within clinical ranges. An index of total healthcare utilisation was computed (comprising presentations to emergency, ward admissions, endoscopic and radiologic procedures, outpatient appointments and cancellations/no-shows). This index was significantly related to depression ($r = 0.131$, $p = 0.018$) and general distress ($r = 0.124$, $p = 0.026$). A further breakdown revealed small, positive correlations between general distress and emergency presentations ($r = 0.154$, $p = 0.005$), outpatient appointments ($r = 0.118$, $p = 0.033$), and appointment cancellations ($r = 0.168$, $p = 0.002$). There was also a small, positive correlation between depression and appointment cancellations ($r = 0.110$, $p = 0.045$). While anxiety was not related to the total healthcare utilisation index, there were small, positive correlations between anxiety and emergency presentations ($r = 0.124$, $p = 0.024$), outpatient appointments ($r = 0.119$, $p = 0.030$), and appointment cancellations ($r = 0.155$, $p = 0.005$).

Conclusions: Psychological distress was associated with increased healthcare utilisation in patients with IBD, in particular with emergency presentations, outpatient appointments and cancellation/no-show at scheduled appointments. These results provide support for psychological care being integrated into current IBD practice (where modifiable factors could be addressed more efficiently). Further data being gathered at present will determine any potential economic benefits of this approach.

P239**A novel user friendly model to identify key predictors of corticosteroid utilization in newly diagnosed patients with ulcerative colitis**D. Patel^{*1}, Y. Shah², N. Khan³¹Mercy Catholic, Philadelphia, United States; ²VA Medical Center Philadelphia, Philadelphia, United States; ³University of Pennsylvania, Philadelphia, United States

Background: Corticosteroid (CS) use in ulcerative colitis (UC) has been identified as a poor prognostic marker. However, key predictors for CS utilization at the time of UC diagnosis are poorly defined. We aimed to develop and internally validated a predictive model to approximate the risk of CS utilization over the course of disease in newly diagnosed UC patients.

Methods: Newly diagnosed UC patients from a US nationwide cohort treated in the VA health care system were followed over time to evaluate factors predictive of CS use. Multivariate logistic regression was performed. Model development was performed in a random 2/3 of the total cohort and then validated in the remaining 1/3 of the cohort. The primary outcome was to predict use of CS for the management of UC. Candidate predictors included routinely available data at the time of UC diagnosis, including demographics, laboratory results and index colonoscopy findings.

Results: 699 patients met the inclusion criteria and followed for median duration of 8 years. 118 sites from 48 states and Puerto Rico were represented. Of 699 patients, 288 patients (41.2%) required CS use for the management of UC. Key predictors for CS utilization selected for the model were: younger age, non-African American ethnicity, presence of hypoalbuminemia as well as IDA at the time of UC diagnosis, pan-colitis/right sided colitis and increased severity of endoscopy disease at index colonoscopy. The AUC for the model based on extent of disease at UC diagnosis was 0.71 (95% CI: 0.66–0.76). The AUC for the model based on severity of disease at UC diagnosis

was 0.71 [95% CI: 0.67–0.76]. Model calibration was consistently good in all models (Hosmer-Lemeshow goodness of fit $p > 0.05$). The models performed similarly in the internal validation cohort. The predicted probability of the outcome event is: $\text{Probability} = 1/[1 + \exp(-(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_k X_k))]$ where β_j is the regression coefficient for predictor X_j , and β_0 is the model intercept (Table 1).

Conclusions: We developed and internally validated a novel prognostic model to predict CS use among newly diagnosed patients with UC. This is the first model to incorporate individual risk factors and develop a cumulative risk for identifying CS use. Once externally validated, this prediction model can be used by clinician to identify high risk patients who may require escalation of therapy and closer follow-up with serial biomarkers to potentially avoid the CS use in future.

P240**Presentation and surgical interventions for Crohn's disease with perianal fistula in the biologics era: results from a multicentre study**C. Black¹, D. Pugliese², K. Sahnan³, A. Armuzzi², S.M. Elkady³, A.L. Hart³, K.H. Katsanos⁴, D.K. Christodoulou⁴, C. Selinger⁵, G. Maconi⁶, G. Fiorino⁷, Y. Davidov⁸, U. Kopylov⁸, S. Ben-Horin⁸, P. Navarro⁹, M.M. Bosca-Watts⁹, M. Muscar¹⁰, P. Ellul¹⁰, K. Karmiris¹¹, V. Allgar¹², S. Danese⁷, N.S. Fearnhead¹³, S. Sebastian^{*1,14}

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Background: Introduction of biologics particularly anti-TNF agents are thought to have resulted in changes in natural history of Crohn's disease (CD). The impact of these in presentation of CD with perianal fistula (CD-PAF) and subsequent surgical approaches is not known. We aimed to study this in a large cohort of CD-PAF patients diagnosed in the post biologics era.

Methods: 11 IBD centres across Europe and Israel were invited to collect data on CD-PAF patients diagnosed since January 2010 to Dec 2015. Data on demographics, mode and route of presentation, type of fistula, MRI, prior treatment for CD were collected. Patients who had at least one surgical therapy for CD-PAF fistula were analysed for reasons and the type of interventions.

Results: 253 patients with CD-PAF (161 M, 92 F) were included. The mean age at diagnosis of CD was 28 years (SD: 13.3), and at diagnosis of CD-PAF was 32 years (SD: 13.92). 65% of the patients with CD-PAF developed their fistulae in the period between 1 year before and 4 years after diagnosis of CD. 30% of patients were smokers at the onset of CD-PAF. 37.2% of the CD-PAF presented as emergency medical or surgical admission and 30% and 23.7% were identified in IBD clinics and colorectal clinics respectively. 77.1% has MRI pelvis done at diagnosis with 52.8% of patients having complex fistulae (38.7% trans-sphincteric, 10.3% extrasphincteric, 3.8% with suprasphincteric). Proctitis and anal stenosis at presentation were identified in 43.1% and 9.5% respectively. Examination under Anaesthesia (EUA) +/- abscess drainage was required in

Table 1. Full Prediction Models

Model including baseline UC extent			
	β Coefficient	SE	P value
Intercept	-0.4044684	0.7585868	0.105
Age at UC Diagnosis	-0.0220772	0.008369	0.008
Hypoalbuminemia at time of UC Diagnosis	0.8742616	0.2399702	0.000
African American race	-0.7859159	0.317456	0.013
IDA at baseline	0.8169098	0.2784588	0.003
Extent of UC at diagnosis E2	1.139555	0.3374509	0.001
Extent of UC at diagnosis E3	1.504308	0.350399	0.001
Model including baseline UC severity			
	β Coefficient	SE	P value
Intercept	0.1939544	0.7327147	0.016
Age at UC Diagnosis	-0.0213859	0.0083223	0.010
African American Ethnicity	-0.9250833	.3184885	0.004
IDA at UC diagnosis	0.7893546	0.2812354	0.005
Hypoalbuminemia at time of UC Diagnosis	0.9485255	0.2410636	0.001
Severity of UC at diagnosis level 2	0.9727209	0.2040347	0.001

69.6% of patients but only 53.8% had Seton inserted at first EUA (median number of Setons=1, range 1–6). 96 patients (68% of those needing Seton insertion) had them removed after medical treatment between 6 weeks to 7 months post insertion and only 33 of these needed Seton re-insertion. The reasons for non-removal of Setons included surgeons' preference (21); surgeon and physician preference (13) and patient preference (5). Overall repeat surgical intervention were required in 102 patients (40.3%) who included repeat abscess drainage (43), Reinsertion of Seton (33), Diverting stoma (20) and proctectomy (6).

Conclusions: A significant proportion of patients with CD-PAF present within 5 years of their diagnosis of CD with a third presenting as emergency. EUA with abscess drainage and Seton insertion is the main surgical intervention needed in this group with a significant proportion having attempt at Seton removal. Radical surgery appears to be less often requiring in comparison to previous studies.

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Defining patient-centered outcomes for IBD – an international, cross-disciplinary consensus

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Background: Value-based healthcare aims to achieve the best possible health outcomes for the lowest cost. Key to its success involves measuring outcomes that matter most to patients. Currently for in-

flammatory bowel disease (IBD), registries and clinical trials lack a unifying set of well-defined outcomes, making comparisons between populations difficult. Our goal was to develop a minimum Standard Set of patient-centered outcomes for IBD to provide a common language for outcomes that can be tracked systematically in a variety of healthcare settings.

Methods: An international, multidisciplinary working group (n=25) from 12 countries within Europe, North America, Asia, Australia, and South America representing patients, gastroenterologists, surgeons, specialist nurses, IBD registries, patient-reported outcome measure (PROM) methodologists, and patient organisations participated in a series of teleconferences incorporating a modified Delphi process. Systematic review of existing literature, registry data, patient focus groups and open review periods were used to reach consensus on a minimum set of standard outcome measures, the best validated tools for measurement and baseline risk-adjustment variables.

Results: A minimum Standard Set of outcomes (Figure 1), preferred tools and measurement frequency was defined by the Working Group for patients (aged ≥16) with IBD. Outcome domains included patient reported outcomes (including quality of life, symptom score, nutritional status and impact of fistulae); survival and disease control (survival, disease activity/remission, colorectal cancer, and anaemia); disutility of care (treatment-related complications); and healthcare utilisation (IBD-related admissions and emergency room visits), all measured at baseline and 6 or 12 month intervals. A single, accessible PROM (IBD-Control questionnaire) was recommended. A core set of patients' baseline characteristics including demographics, baseline clinical and condition factors, and treatment factors were further defined for collection at baseline and tracking annually to enable meaningful comparisons of outcomes between centres, regions, or countries.



Figure 1. ICHOM standard set for inflammatory bowel disease.

Conclusions: An international, multidisciplinary IBD Working Group that included patients has defined a minimum set of patient-centred outcomes, tools and PROMs for collection in patients with IBD based on evidence, patient input, and specialist consensus. The Standard Set provides a template for meaningful, comparable and easy-to-interpret measures as a step towards achieving value-based healthcare in IBD.

P242 Phenotypic characterisation of elderly – onset inflammatory bowel disease – IBD at the extremes

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Background: The incidence of Inflammatory bowel disease (IBD) is increasing globally at a rate outpacing what genetic influences alone could instigate. Data on elderly onset IBD (age 60 and over) are limited. The aim of our study was to study the phenotypic characteristics of elderly-onset IBD.

Methods: We conducted a retrospective analysis of 140 patients diagnosed with IBD at 60 years or above at our institution between 1995 and 2016. We collected data including demographics, disease characteristics (Montreal classification) and treatment using electronic case records.

Results: Of 140 patients, 70 were male. Median age was 71 years (range 62–91) and median age at diagnosis was 65 years (range 60–85). 49 patients had Crohn's disease (CD) (35.0%), 80 had Ulcerative colitis (UC) (57.1%) and 11 (7.9%) had IBD-unspecified (IBDU). Disease classification for UC was: E1 (27), E2 (30) and E3 (21) and 2 patients with UC proctosigmoiditis have not yet been classified. Montreal classification for CD was L1 B2 (18); L2 B1 (14) and L2 B2 disease in 4. L3 disease was found in 12 (7 B1 and 5 B2).

At diagnosis 88 patients were prescribed 5ASA's (18 topical and 6 in combination with oral preparations). Steroid induction at diagnosis occurred in 44 (31.4%) patients. Azathioprine was used in 3 (2 E3 and 1 L2B2) and 3 patients commenced Infliximab at diagnosis (L3B1 & L1B2 CD and E3 UC). Median CRP at diagnosis was 32.0mg/L.

At most recent follow up 26 patients were on corticosteroids, 35 were on immunomodulation (26 on Azathioprine, 5 on 6MP and 4 on Methotrexate) with a mean time to immunomodulation being 29.4 months (range 0–137). 14 were on biologic therapy (12 Infliximab and 2 Adalimumab) with a mean time to therapy of 37.1 months (range 0–189 months). 15 patients (10.7%) had surgery related to IBD: 2 UC vs 13 CD with median time to surgery 20 months (range 0–132). 2 patients were diagnosed with CD at emergency surgery. Colon cancer was diagnosed in 1 patient with L2B1 and curative resection undertaken. 4 deaths occurred: 1 from CLL (not on immunomodulation), 1 *Klebsiella pneumoniae* on Azathioprine, 1 from cryptococcal meningitis on Azathioprine and Infliximab and 1 from metastatic prostate cancer.

Conclusions: We noted a higher prevalence of UC with left sided and pancolonic disease and a colonic phenotype in CD corroborating with data from the EPIMAD registry [1]. A large proportion of patients received immunomodulation, which is an area of concern and needs careful consideration. There is an urgent need for more data on disease presentation, natural history and treatment paradigms for the considered and optimal management of elderly patients with IBD.

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P243 Complications of newly diagnosed Crohn's disease can be predicted by mathematical modeling of serologic responses

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Background: Crohn's disease (CD) is a heterogeneous progressive disorder. Predicting factors for complicated disease are scarce. We aimed to predict the natural history of a prospective inception cohort using biomarkers.

Methods: A longitudinal, prospective, observational inception cohort, in a tertiary referral center. Adults suspected of CD, or diagnosed with CD during the preceding six months prior to enrollment were recruited. Clinical and biological markers were obtained. Three common NOD2 gene variants, and the ATG16L1 variant were analyzed in blood DNA by TaqMan chemistry. Complicated outcome was defined as the first CD-related hospitalization or surgery. Data integration and analysis was performed using mathematical models.

Results: A total of 297 patients were enrolled. Of these, 154 attained a definite diagnosis of CD. Mean age at diagnosis 31.9±13.1 years. Males: 79 (51.2%). Average follow-up: 18±11.8 months. At enrollment median CRP was 10.5 (3–22) gr%, and median fecal calprotectin was 424 (181–913) µg/gr stool. Median time between first symptoms and diagnosis was 4 (2–10) months. Montreal classification: L1- 47.9%, L2- 19.9%, L3-32.2%, B1-83.5%, B2-6.3%, B3-10.2%, and perianal involvement in 17.6%. Sixty-two patients (40%) had a complication, almost half (28/62) already at diagnosis, and the rest in the first 10 months since diagnosis. Complications after 10 months from diagnosis were rare. The NOD2 variant carriage rates were 19.6%, and the ATG16L1 variant 47.4%, comparable in complicated and non-complicated patients. The complicated group had lower rates of B1 phenotype, higher rates of B3 phenotype (69.3% vs. 83.6%, p=0.002, and 21% vs 2.1%, p<0.001, respectively) and higher rates of absolute ASCA levels (51.6±46 vs. 26.08±29.1 IU, p=0.001). Complicated patients had expedited exposure to medications: antibiotics HR=2.07 (p=0.005), steroids HR=4.29 (p<0.001), immunomodulators HR=2.66 (p<0.001), and biologics HR=1.89 (p=0.01), compared with non-complicated patients. Multivariate logistic regression utilizing the most discriminatory variables complemented by a decision tree algorithm revealed that integrating the absolute serology levels (IU) at diagnosis impact the probability for an early complication: ALCA (OR 0.944, 95% CI 0.908–0.981), ASCA (OR 1.025, 95% CI 1.009–1.041), and ACCA (OR 1.020, 95% CI 0.999–1.042).

Conclusions: In a prospective inception cohort of CD patients early complications were noticed in 40% of patients within 10 months from diagnosis. Clinical data were not sufficient to stratify risk of complication. A decision tree based on serologic responses is reliable in detecting patients at risk for complication, enabling better decision making and patients' care.

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Diffusion-weighted MRI enables to accurately grade inflammatory activity in patients of ileocolonic Crohn's disease: results from an observational study

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Background: Diffusion-weighted imaging (DWI) is a novel technique to evaluate bowel inflammation in Crohn's disease (CD). It remains unclear whether DWI could differentiate grades of inflammation activity and add to the accuracy of conventional magnetic resonance enterography (MRE) in defining disease activity. We aimed to assess the accuracy of DWI for evaluating ileocolonic CD inflammation compared with conventional MRE, using ileocolonoscopy as reference standard.

Methods: This was an observational study of CD patients who underwent both ileocolonoscopy and MRE with DWI. The conventional MRE and DWI findings of the ileocolon were scored from 0 to 3. The respective segment endoscopic disease activity was scored by simplified endoscopic score for Crohn's disease (SES-CD) and was graded as inactive (0–2), mild (3–6) or moderate-severe (≥ 7).

Results: 185 bowel segments from 43 consecutive CD patients were evaluated and included inactive (n=86), mild (n=72), and moderate-severe (n=27) ileo-colonic segments. The area under the receiver operating characteristics curve (AUC) of 0.973 for apparent diffusion coefficient (ADC) to differentiate active from inactive CD was significantly higher than those of conventional MRE parameters (AUC between 0.840–0.940). Higher accuracy of ADC (AUC=0.919) for differentiating inactive-mild from moderate-severe CD was also shown compared with that of conventional MRE parameters (AUC between 0.868–0.915). ADC values demonstrated strongest correlation with SES-CD ($r=-0.880$) comparing to DWI SI and conventional MRE parameters (r between 0.787–0.867).

Conclusions: DWI enables to accurately grade inflammatory activity in patients of ileocolonic CD and may be better suited than conventional MRE for monitoring the activity of CD.

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A systematic review of outcomes reported in studies on fistulising perianal Crohn's disease

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Background: Treatment of fistulising perianal Crohn's disease (pCD) is challenging, and it can be difficult to ascertain gold standard interventions from the literature. One factor limiting development of a robust evidence-base is heterogeneity of reported outcomes, being prone to reporting bias and being difficult to meta-analyse.

Core outcome sets are used to reduce heterogeneity of outcome reporting. The aim of this systematic review was to make an objective assessment of outcome reporting heterogeneity in the literature, and through identifying outcomes currently reported, inform development of a fistulising pCD core outcome set.

Methods: A systematic review of studies assessing medical, surgical and combination treatment of pCD was performed. Search strategy was restricted to prospective studies from 2010-onwards. Studies of luminal Crohn's disease were included only if there was a defined perianal fistula subgroup.

Our primary aim was to list the type and frequency of outcome measures used in each study. The secondary aim was to assess the quality of reporting was assessed using Harman's criteria [1] and assess the methodical quality of the studies using the GRADE criteria.

Results: In total, 49 studies were included which reported a median of 6 (IQR 3–7) outcomes. The five most commonly investigated outcomes were: $\geq 50\%$ tracts not draining on clinical examination (22 studies; 45%); Perianal Disease Activity Index (20 studies; 41%); Crohn's Disease Activity Index (19 studies; 39%); closure of external opening (17 studies; 35%); and an absence of drainage either spontaneously or on gentle finger pressure (12 studies; 24%). No single outcome was reported in every study.

11 out of the 49 studies were classified as being of high quality, with GRADE scores ≥ 4 . The primary outcome was clearly stated in 73% (36 studies) and defined 76% (37 studies). Secondary outcomes were clearly stated 57% (28 studies) and defined 63% (31 studies). Authors only explained the rationale for using the outcome measures they selected in 33% (16 studies).

"Fistula healing" from the ACCENT II study was defined at more than one time-point. We found the definition of "fistula healing" to be particularly heterogeneous with only 9 of 49 studies (18%) reporting sustained healing on ≥ 2 clinical visits.

Conclusions: This review demonstrates the heterogeneity of outcomes used in fistulising pCD studies. Researchers should consider the views of all stakeholders, including patients, when determining which outcomes should be reported in clinical studies. This review represents the first step in informing a Delphi consensus with the aim of developing a Core Outcome Set for fistulising pCD.

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Risk factors associated with low ovarian reserve in young women of reproductive age with Crohn's disease

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Background: Crohn's disease (CD) mainly affects young adults of reproductive age. Few studies have been conducted on their ovarian reserve status, and factors associated with impaired ovarian reserve remains unknown. This study aimed to investigate potential risk factors associated with low ovarian reserve as reflected by serum anti-Mullerian hormone (AMH) in young women of reproductive age with CD.

Methods: This individual matched, case-control study was conducted in the First Affiliated Hospital of Sun Yat-sen University. Cases were 87 patients diagnosed with CD and controls were paired with no history of IBD, recruited in a 1:1 ratio, for age, height, weight and BMI index. Serum AMH levels were measured by ELISA.

Results: The serum AMH level was significantly lower in CD patients than health control group (2.47 ± 2.08 ng/ml vs 4.12 ± 2.31 ng/ml, $p < 0.001$), which remained comparable with the age younger than 25 years (4.41 ± 1.52 ng/ml vs 3.49 ± 2.10 ng/ml, $p = 0.06$), but decreased in CD patients after 25 years at any age stage ($p < 0.05$). Patients with active disease ($p < 0.05$), stricturing type (B2) ($p < 0.05$), perianal disease ($p < 0.05$), ileocolonic (L3) involved disease ($p < 0.05$) and receiving thalidomide therapy ($p < 0.05$) showed a significantly lower serum AMH level. Multivariable logistic regression analysis showed that age more than 25 years old (OR: 9.33, 95% CI 1.85–47.05, $p < 0.05$), active disease (OR: 24.2, 95% CI 5.56–104.75, $p < 0.05$) and thalidomide use (OR: 19.6, 95% CI 2.99–118.6, $p < 0.05$) were independent risk factors were associated with low ovarian reserve in CD patients.

Conclusions: Age more than 25 years old, active disease and thalidomide use were independently associated with low ovarian reserve in young women of reproductive age with CD.

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Fungal infections in children with inflammatory bowel disease

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Background: Paediatric inflammatory bowel disease is often considered the “purest” form of disease without many extraneous influences of adult behaviour, e.g. smoking or disease comorbidity. Although the exact relationship between fungi and Crohn disease has not been clearly established, some evidence points to the possible role of *Candida albicans* in the processes leading to, or maintaining, inflammation at this entity. The aim of our study is to compare the prevalence of *Candida* between IBD patients and control group

Methods: In cohort of 43 children with IBD (27 children with Crohn's disease and 16 with colitis ulcerosa, (mean age 16.44 (SD=2.92)) we considered fungal infection at the time of diagnosis and at least one time during the course of follow-up in and compared it with control group of 34 children with gastrointestinal symptomatology (mean age 9.16 (SD=5.16)). It was performed stool cultivation for isolation of fungi, blood analysis for antigen of *Candida* (mannan) and antibodies against *Candida* in class of IgM and IgG. Activity of bowel inflammation was evaluated by fecal calprotectin level in both of group. The obtained data were statistically analysed using chi-square test, spearman correlation and binary logistic regression.

Results: Patients with IBD showed significantly higher prevalence of positivity towards antigen of *Candida*, antigen of *Aspergillus*, antibodies against *Candida* class of IgM, fungi in stool and calprotectin (χ^2 range: 3.8–26.5, $p < 0.05$) compared to control group. There was no significant difference in antibodies against *Candida* class of IgG prevalence. The amount of fungi in stool moderately correlated with the amount of calprotectin ($\rho = 0.455$, $p < 0.001$) in all patients. Positive antigen *Candida* is associated with positive fungi in stool (OR=5.25, 95% CI: 1.32–20.92, $p < 0.05$) and positive calprotectin (OR=10.08, 95% CI: 2.35–43.31, $p < 0.01$).

Conclusions: Among the fungi colonizing the human gut, *Candida* species are the most prevalent in the digestive tract. *Candida albicans* is considered to be the most important commensal yeast in the human intestine. Bacterial composition in CD compared with healthy controls has been the subject of several investigations and several potentially disease-associated bacteria have been identified, but no study compared evidence of *Candida* in comparison with control group. Our study showed significant differences in evidence of *Candida* infection in IBD patients at time of diagnosis with comparison of control group of GI symptomatic patients.

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The new infliximab point-of-care quantitative test can equally be used for therapeutic drug monitoring of biosimilars of infliximab

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Background: CT-P13, a biosimilar of the originator infliximab, has been recently approved by the European Medicines Agency (EMA) for the treatment of inflammatory bowel disease (IBD). Therapeutic Drug Monitoring (TDM) is an effective strategy in the management of IBD patients and is widely used in the adjustment of the originator infliximab therapy. A validated point-of-care device for IFX (POC IFX) quantification is already available in the market. The aim of this study was to validate the first point-of-care IFX device for quantification of IFX biosimilar CT-P13 by comparing it with three validated ELISA assays.

Methods: Serum of 184 IBD patients treated with biosimilar infliximab, CT-P13, were analysed for infliximab concentration by POC IFX assay and three ELISA-based established assays. The results were statistically compared both in quantitative and qualitative terms. A statistical analysis of results was performed. Intraclass Correlation Coefficient (ICC) was assessed for quantitative comparison and both accuracy and kappa (95% CI) statistics were used for qualitative analyse. Spiking recovery was also assessed in donors' serum samples spiked with exogenous CT-P13.

Results: Quantitative comparison showed an excellent ICC between POC IFX assay and the three ELISA-based established methods.

ICC was 0.907 and 0.935 for POC IFX/in-house and POC IFX/r-biopharm, respectively. For qualitative comparison, accuracy and kappa (95% CI) statistics were determined after stratification of results by therapeutic interval (<3, 3–7 and >7). A good agreement was shown between pairs of assays: POC IFX/in-house showed accuracy and kappa (95% CI) of 80% and 0.776 [0.177–0.840], respectively. POC IFX/r-biopharm depicted an accuracy and kappa (95% CI) of 88% and 0.874 [0.824–0.922], respectively. POC IFX assay revealed an excellent average spiking recovery percentage (102% [80%–119%]).

Conclusions: POC IFX assay, a methodology already validated and available in the market to assess IFX originator concentration, showed good agreement with both ELISA-based established assays when used to assess IFX biosimilar. This new methodology, that delivers results in 15 min, should be used as a tool in TDM of CT-P13.

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Usefulness of abdominal ultrasonography for patency assessment using the patency capsule

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Background: The present study was undertaken to evaluate the usefulness of abdominal ultrasonography (US) in patency assessment using the patency capsule (PC).

Methods: This study involved 223 patients (139 men, mean age 39.9) for whom patency assessment using the PC was planned for capsule endoscopy (CE) at 2 domestic hospitals between August 2012 and August 2016. We excluded patients with ileus, those found to have small bowel stenosis on x-ray photography (XP) or US, and patients with apparently severe stenosis of the large bowel. Patency was judged on the basis of the morphology of the PC re-collected within 30–33 hours after oral PC intake. In cases in which PC re-collection was not possible, XP was performed approximately 33 hours later and, if localization of the PC by XP was difficult, abdominal computed tomography (CT) was additionally performed. In patients for whom patency was confirmed, CE was carried out within several days after confirmation of patency using PC. Complications, including CE retention, were analyzed.

Results: The 223 patients studied included 144 with Crohn's disease, 16 with unexplained enteritis and 63 with other reasons for undergoing this examination. PC tests were performed for 268 sessions in total for the 223 patients. Oral PC intake was not possible in 6 cases. Of these 6 cases, 2 received the PC test with endoscopy and 4 withdrew from the study. Of the 264 cases in whom patency was assessed using the PC, PC excretion was visually documented in 174. There were 12 cases in whom the PC was shown to be present in the large bowel by XP, 51 cases in whom PC localization by XP was difficult, and 27 cases in whom excretion of the PC was confirmed by XP. The latter 27 cases were excluded from analysis because morphological evaluation of the PC was not possible. US was performed on 51 cases for whom localization of the PC had been difficult. Among these 51 cases, US revealed PC within the small bowel in 16 and presence of the PC in the large bowel in 32 cases. In the remaining 3 cases, US assessment was difficult, and CT was additionally performed, allow-

ing confirmation of presence of the PC in the large bowel in all of these cases. CE was skipped in the 16 cases found by US to have PC within the small bowel, and CE was performed in the other 35 cases. Of the 221 cases in whom patency was confirmed with the PC, 220 underwent CE (1 case declined CE). No complications, such as CE retention, occurred in any of these patients.

Conclusions: Among the 268 cases receiving the PC test, localization of the PC by XP was difficult in 51, but localization by US was possible in 48 of these 51 cases, allowing avoidance of CT scanning. These results suggest US to be useful for patency assessment using the PC.

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DUBLIN (Degree of Ulcerative Colitis Burden of Luminal Inflammation) score, a simple method to quantify inflammatory burden in ulcerative colitis

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Background: Endoscopic scores, e.g. Mayo Endoscopic Subscore (MES), are validated scoring systems used to grade endoscopic severity in ulcerative colitis (UC). However these scores don't incorporate any measure of disease extent. The aim of this study was to determine the feasibility of using a composite score to quantify UC inflammatory burden.

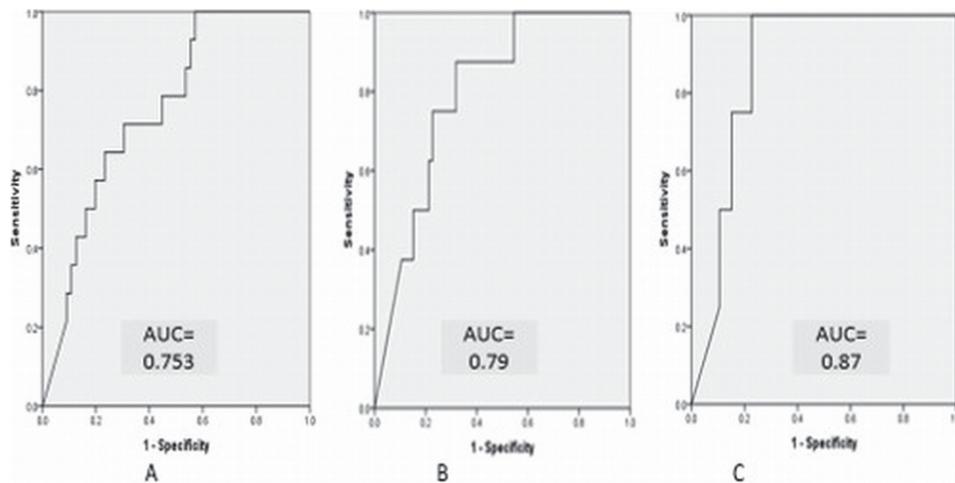
Methods: A retrospective analysis of faecal calprotectin (FC) results was performed (Jan 2015–June 2016). UC patients with contemporaneous endoscopic evaluations and FC measurements were included. The DUBLIN score was calculated as a product of the MES and disease extent, i.e. E1 = limited to sigmoid/rectum E2 = limited to left colon (distal to splenic flexure) E3 = proximal to splenic flexure. Analysis of correlation between DUBLIN score and its individual components with FC, an objective marker of inflammation was performed. ROC curves were compared.

Results: 279 FC results (n=181 patients, confirmed UC) were included. n=74 had contemporaneous endoscopy; it was possible to calculate the DUBLIN score in 70 cases. Patient characteristics and endoscopic activity as per Table 1.

Table 1. Patient demographics, disease characteristics and endoscopic activity

CHARACTERISTICS	MEDIAN	IQR			
AGE	36.5 YEARS	26-47.25			
GENDER	M=37 F=33				
EXTENT :					
E0 (No active disease)	16				
E1	29				
E2	11				
E3	14				
MAYO ENDOSCOPIC SUBSCORE		DUBLIN SCORE (N=70)			
MAYO 0	16	0	16	4	3
MAYO 1	25	1	16	6	9
MAYO 2	21	2	17	9	4
MAYO 3	8	3	5		

The median FC result was 186 ug/L (IQR 23–1108ug/L), 77.5ug/L (IQR15–833 ug/L) and 32ug/L (IQR 15–432ug/L) in those with pancolitis, left sided colitis and proctosigmoiditis respectively. There was a significant correlation between the MES and FC (r=0.359; p<0.01). A significant correlation was also identified be-



Abstract P250 – Figure 1. (A) Extent vs FC; (B) Mayo Endoscopic Score vs FC; (C) DUBLIN score vs FC (ROC).

tween C-reactive protein ($r=0.270$, $p<0.01$) and Albumin ($r=-0.129$, $p=0.04$) and endoscopic activity. Extent of disease also correlated significantly with FC ($r=0.286$; $p=0.016$). However, a stronger correlation was observed between DUBLIN score and FC ($r=0.394$; $p<0.01$). ROC curves demonstrated an AUC =0.79 for the MES in predicting FC; AUC=0.75 when calculated for disease extent. A greater area under the curve was observed when ROC was constructed for the Dublin score. (AUC=0.87) (Figure 1)

Conclusions: The DUBLIN score is a simple composite score that can be calculated at the time of endoscopy or retrospectively. These results show that it has potential as a measure of inflammatory burden in UC. A user-friendly scoring system that better reflects overall luminal inflammation may be particularly useful in personalising therapy.

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The contribution of clinical and psychosocial factors to fatigue in 182 patients with inflammatory bowel disease: a cross-sectional study

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Background: Fatigue is a frequently reported and predominant symptom experienced by patients with inflammatory bowel disease (IBD) and its impact has been associated with poorer quality of life (QoL). The complex interplay between disease-related variables and potentially modifiable psychosocial factors in IBD-fatigue has yet to be unravelled. Aim to evaluate the contribution of clinical, sociodemographic and psychosocial factors to the severity and impact of IBD-fatigue and QoL.

Methods: In a cross-sectional study, 182 patients with IBD were recruited from three tertiary referral hospitals’ outpatient clinics in London. Fatigue was assessed utilising the Inflammatory Bowel Disease-Fatigue Scale (IBD-F), the Multidimensional Fatigue Inventory (MFI); and QoL by the Inflammatory Bowel Disease Questionnaire (IBDQ). Patients completed self-report questionnaires evaluating emotional, cognitive and behavioural factors potentially correlated with fatigue. Sociodemographic data were collected. Disease-related and laboratory data were retrieved from patients’ hospital electronic medical records.

Results: In hierarchical regression models, disease activity was the

only disease-related factor consistently associated with severity and impact of fatigue and QoL ($p=0.01$). More negative fatigue perceptions were significantly associated with greater IBD-F1 scores ($p=0.01$). When controlling for clinical factors (disease activity and anti-TNF therapy), negative perceptions of fatigue, and all-or-nothing and avoidance behaviours explained an additional 41% of the variance in fatigue impact (Table 1). Disease activity ($p<0.001$) and currently taking steroids ($p=0.01$) were significantly associated with worse QoL. The addition of emotional, cognitive and behavioural variables significantly increased the validity of the model, with the fully adjusted model explaining 64% of the variance in QoL. Higher levels of IBD-related distress ($p=0.01$) was significantly associated with diminished QoL (Table 2).

Table 1. Hierarchical regression of sociodemographic, clinical and psychosocial predictors of fatigue

	IBD-F1			IBD-F2			MFI*		
	B(95% CI)	P-value	ΔR ²	B(95% CI)	P-value	ΔR ²	B(95% CI)	P-value	ΔR ²
STEP 1			.21			.32			.34
Sociodemographic									
Education to 16	0.62 (-1.90, 3.13)	0.63		-3.95 (-17.64, 9.74)	0.57		-1.34 (-3.47, 0.80)	0.22	
Education to 18	1.67 (-0.45, 3.80)	0.12		2.36 (-4.73, 13.44)	0.67		-0.45 (-2.20, 1.20)	0.61	
Employment retired	-1.83 (-4.48, 0.82)	0.17		-4.33 (-17.57, 8.90)	0.53		-0.52 (-2.61, 1.57)	0.63	
Employment not work	1.22 (-0.72, 3.15)	0.22		11.96 (2.88, 21.01)	0.01		1.22 (-0.40, 2.84)	0.14	
Female gender	1.61 (0.15, 3.07)	0.03		5.32 (-2.25, 12.88)	0.17		1.60 (0.40, 2.80)	0.01	
Single/5 parent	-0.44 (-2.00, 1.12)	0.58		-	-		-	-	
Divorced/Widowed	0.75 (-3.57, 5.07)	0.73		-	-		-	-	
Clinical									
5-ASA	-	-		-2.29 (-10.55, 5.97)	0.58		-	-	
Anti-TNF	-	-		11.30 (3.83, 19.07)	0.01		1.86 (0.87, 3.14)	0.01	
Diagnosis CD	-	-		-	-		0.78 (-0.62, 2.18)	0.27	
Diagnosis IBD-U	-	-		-	-		1.81 (-1.42, 5.05)	0.27	
Disease activity	0.27 (0.07, 0.46)	0.01		2.17 (1.21, 3.13)	< 0.001		0.21 (0.06, 0.36)	0.01	
Exercise <30 minutes	0.66 (-0.84, 2.16)	0.38		1.98 (-0.01, 9.96)	0.62		1.99 (0.72, 3.26)	0.01	
Methotrexate	-	-		-	-		1.74 (-1.77, 5.25)	0.33	
Smoking current	0.36 (-2.86, 3.58)	0.82		-	-		-	-	
Smoking ex	0.21 (-1.50, 1.91)	0.81		-	-		-	-	
Steroids	-	-		12.72 (-1.32, 26.76)	0.75		-	-	
Thiopurines	-1.17 (-2.60, 0.27)	0.11		-	-		-	-	
STEP 2			.54			.73			.54
Emotional									
Anxiety	0.04 (-0.17, 2.56)	0.68		-0.45 (-1.35, 0.45)	0.32		0.23 (-0.16, 0.21)	0.81	
Depression	-0.09 (-0.32, 0.14)	0.44		0.75 (-0.24, 1.74)	0.13		0.13 (-0.78, 0.34)	0.22	
Distress	0.01 (-0.01, 0.01)	0.67		0.06 (0.01, 0.11)	0.02		0.01 (-0.01, 0.01)	0.44	
Stress	-0.06 (-0.7, 0.19)	0.39		0.65 (0.09, 1.21)	0.03		0.10 (-0.02, 0.21)	0.10	
Cognitive									
Negative fatigue perceptions	0.28 (0.20, 0.36)	< 0.001		0.55 (0.12, 0.78)	0.01		0.18 (0.12, 0.25)	< 0.001	
Catastrophizing	0.01 (-0.19, 0.21)	0.92		0.49 (-0.36, 1.34)	0.26		-0.01 (-0.19, 0.16)	0.88	
Damage beliefs	0.08 (-0.11, 0.26)	0.40		-0.17 (-0.93, 0.59)	0.65		-0.01 (-0.15, 0.10)	0.93	
Embarrassment	-0.08 (-0.22, 0.05)	0.20		0.06 (-0.49, 0.62)	0.82		0.07 (-0.05, 0.18)	0.25	
Fear avoidance	-0.07 (-0.21, 0.08)	0.37		0.13 (-0.49, 0.75)	0.68		0.09 (-0.03, 0.22)	0.15	
Symptom focus	0.08 (-0.08, 0.25)	0.34		-0.16 (-0.88, 0.55)	0.65		0.01 (-0.14, 0.15)	0.92	
Behavioural									
All-or-nothing behaviour	0.07 (-0.07, 0.22)	0.31		0.86 (0.25, 1.48)	0.01		-0.02 (-0.15, 0.11)	0.71	
Avoidance behaviour	0.11 (-0.05, 0.26)	0.17		1.31 (0.65, 1.98)	< 0.001		0.01 (-0.13, 0.14)	0.98	
Daytime sleepiness	0.14 (0.01, 0.28)	0.04		0.27 (-0.30, 0.84)	0.35		0.12 (0.01, 0.24)	0.04	

Figures in bold are statistically significant at $p < 0.01$; IBD-F1 Fatigue severity; IBD-F2 Fatigue impact on daily activities; * MFI General Fatigue subscale
 Key: ΔR² - Adjusted R Square; Anti-TNF- anti-tumour necrosis factor; ASA- aminosalicylates; CI - confidence interval; CD - Crohn’s Disease; IBD-F - Inflammatory Bowel Disease-Fatigue Scale; IBD-U - Inflammatory Bowel Disease Unclassified; MFI- Multidimensional Fatigue Inventory; SEB - Standard Error Beta.

Table 2. Hierarchical regression of sociodemographic, clinical and psychosocial predictors of QoL.

	IBDQ#		ΔR^2
	B (95% CI)	P-value	
STEP 1			.42
Sociodemographic			
Education up to 16	1.28 (-5.46, 8.05)	0.71	
Education up to 18	0.74 (-4.42, 5.91)	0.78	
Employment retired	-1.47 (-8.88, 5.94)	0.69	
Employment not working/housekeeping	-2.86 (-7.72, 2.01)	0.25	
Female gender	-2.10 (-5.77, 1.56)	0.26	
Living alone	6.28 (-0.27, 12.83)	0.06	
Living single parent	-4.85 (-19.01, 9.31)	0.50	
Single/Single parent/Other	-2.57 (-7.38, 2.24)	0.29	
Widowed/Divorced	-1.20 (-11.77, 9.36)	0.82	
Clinical			
Disease activity	-1.86 (-2.35, -1.36)	< 0.001	
Exercise <30 minutes	-0.07 (-3.85, 3.70)	0.97	
Methotrexate	-5.99 (-17.67, 5.69)	0.31	
Platelets	-0.02 (-0.04, 0.01)	0.11	
Smoking current	2.20 (-5.24, 9.64)	0.56	
Smoking ex	1.96 (-2.21, 6.14)	0.36	
Steroids	-10.16 (-16.98, -3.35)	0.01	
Thiopurines	1.50 (-2.10, 5.11)	0.41	
STEP 2			.64
Emotional			
Anxiety	-0.40 (-0.94, 0.15)	0.15	
Depression	0.05 (-0.51, 0.61)	0.85	
Distress	-0.05 (-0.09, -0.02)	0.01	
Stress	-0.08 (-0.42, 0.26)	0.64	
Cognitive			
Negative fatigue perceptions	-0.01 (-0.21, 0.19)	0.89	
Catastrophising	-0.55 (-1.10, 0.01)	0.05	
Damage beliefs	-0.17 (-0.71, 0.38)	0.54	
Embarrassment	-0.03 (-0.39, 0.32)	0.85	
Fear avoidance	-0.18 (-0.58, 0.23)	0.40	
Symptom focus	0.32 (-0.14, 0.79)	0.17	
Behavioural			
All-or-nothing behaviour	-0.30 (-0.67, 0.06)	0.11	
Avoidance behaviour	-0.05 (-0.51, 0.61)	0.83	
Daytime sleepiness	0.07 (-0.29, 0.43)	0.70	

Figures in bold are statistically significant at $p < 0.01$; # The IBDQ total score is made up from the individual subscales.

Key: ΔR^2 - Adjusted R Square; ASA - aminosalicylates; CI - confidence interval; CD - Crohn's Disease; IBDQ - Inflammatory Bowel Disease Questionnaire; SEB - Standard Error Beta.

Conclusions: Apart from disease activity, emotional and behavioural factors and patients' negative fatigue perceptions may be key factors to be addressed. Further exploration of these factors in longitudinal and intervention studies may help to develop effective models of fatigue management.

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Elevated C-reactive protein level during clinical remission can predict poor outcomes in patients Crohn's disease

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Background: Intestinal mucosal damage in Crohn's disease (CD) is believed to progress even in patients showing clinical remission. We aimed to investigate the difference in the long-term prognosis of CD patients in clinical remission depending on serum C-reactive protein (CRP) levels during clinical remission.

Methods: A total of 339 CD patients in clinical remission (defined by Crohn's disease activity index less than 150) for more than 6 months between January 2008 and December 2010 were enrolled in

this study. Clinical outcomes represented by CD-related hospitalization, intestinal resection, perianal surgery, intestinal complications, and step-up of medical therapy were compared between normal CRP group and elevated CRP group during clinical remission.

Results: There were 150 patients with normal CRP through 6 months of clinical remission and 189 patients who showed elevated CRP at least once during 6 months of clinical remission. During follow-up (median, 7.9 years [interquartile range, 6.8–8.0]), the Kaplan-Meier analysis with the log-rank test showed the superiority of the normal CRP group compared with the elevated CRP group in terms of CD-related hospitalization-free survival (Figure 1A, $p=0.007$) and intestinal resection-free survival (Figure 1B, $p=0.046$).

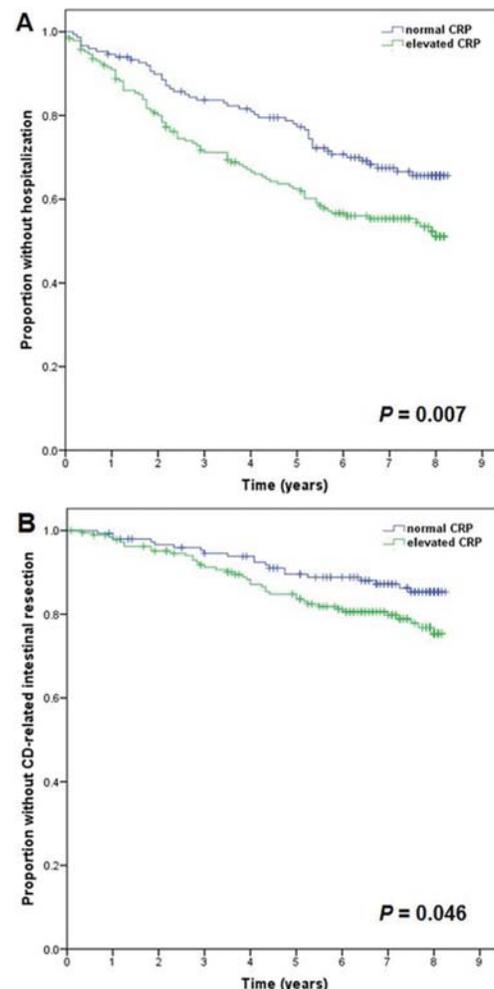


Figure 1. Kaplan-Meier hospitalization-free survival curves (A) and intestinal resection-free survival curves (B).

In multivariate analysis, elevated CRP and Montreal penetrating behavior were associated with increased risk of CD-related hospitalization (adjusted hazard ratio [aHR] 1.787; 95% confidence interval [CI] 1.245–2.565, $p=0.002$, and aHR 2.175; 95% CI 1.489–3.177, $p<0.001$, respectively). In addition, elevated CRP, Montreal structuring behavior, Montreal penetrating behavior, and use of immunomodulators were associated with increased risk of intestinal resection (aHR 1.726; 95% CI 1.003–2.969, $p=0.049$, aHR 2.722; 95% CI 1.223–6.058, $p=0.014$, aHR 4.149; 95% CI 2.117–7.907, $p<0.001$, and aHR 2.147; 95% CI 1.076–4.284, $p=0.030$, respectively).

Conclusions: Even if patients with CD are in clinical remission, elevated CRP showed a significant association with poor prognosis

represented by a higher risk of subsequent CD-related hospitalization and intestinal resection. More vigilant monitoring and therapeutic strategy are required for CD patients in remission, but with high CRP to improve long-term prognosis.

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Effects of time on urinary metabolic signatures in inflammatory bowel disease

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Background: Metabolic profiling (metabonomics) has been proposed as a novel clinical tool in IBD to predict development of complex disease, or for longitudinal non-invasive monitoring of activity and/or response to drug treatment. Urinary metabonomics can distinguish IBD from healthy controls [1] but no studies to date have assessed the stability of these discriminatory profiles over time. Studies in healthy adults show metabolic signatures are largely unchanged over periods of up to 3 years [2], but signals are influenced by multiple external factors including medication and surgery, so how these change in IBD is unknown. The aim of this study was to compare baseline urinary metabolic profiles of IBD patients with a repeated sample several years later to assess similarity, and also to test if any clinical outcomes could be retrospectively predicted from the baseline sample.

Methods: Two urine samples from 39 IBD patients (22 Crohn's disease (CD) and 17 ulcerative colitis (UC)) were collected - one at baseline and one several years later (range 7–9 yrs). These were analysed by ¹H NMR spectroscopy. Disease progression was defined as initiation of immunosuppression or biologics, progression of disease location or phenotype, or surgery. Principal components analysis was used to visualise the variance between the two time-points within the cohort. Orthogonal partial least squares discriminant analysis (OPLSDA) was used to establish if the metabolic signatures could be used to predict adverse clinical outcomes in the patients studied.

Results: There was a diverse clinical outcome across the groups; 57% of CD patients and 17% of UC patients had clinical progression at follow up sampling. PCA showed clustering of sample pairs from the baseline and several years later in most individuals, suggesting intra-individual similarity across time. OPLSDA showed no statistical models could be built to predict combined poor outcome based on the initial urinary metabolic profile (p=0.26). However, the small subgroup who went on to require surgical intervention could be separated from the cohort in a model (Q2=0.015; p=0.03) constructed on their baseline profiles.

Conclusions: The metabolic profile of IBD in an individual appears relatively stable over a significant time period despite a variety of clinical outcomes and interventions. Variations in longitudinal measurements appear to be subtle, and therefore application of this technique for disease monitoring and risk stratification could prove difficult. These results may suggest that metabolic profiling could be exploited to predict a higher risk of requiring future surgery. Large prospective studies are required to further investigate this.

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P254
Relationship between severe endoscopic lesions and plasmatic and fecal infliximab levels in acute severe ulcerative colitis: a case control study

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Background: Recent data suggest that early fecal excretion of infliximab (IFX) in acute severe ulcerative colitis (ASUC) is associated with poor treatment response [1]. Severe endoscopic lesions (SEL), such as deep ulcerations eroding the muscle layer, deep ulcerations not eroding the muscle layer but involving more than one third of the mucosal area, and mucosal detachment on the edge of ulcerations, could favor infliximab fecal leakage.

The aim of this study was to search for an association between SEL and IFX levels in blood and stools in ASUC.

Methods: This was a case-control, observational (with collection of biological samples), prospective, two-center study that recruited between February 2015 and July 2016 consecutive patients admitted for an ASUC treated with IFX who had a flexible sigmoidoscopy before starting the drug. Patients who received any anti-TNF within the previous 8 weeks were excluded. Cases were patients with SEL and controls those without. IFX serum levels were measured at D0, D1, D2 and fecal levels at D0, D1, D2 and D14. The objectives of the study were to compare the detection of IFX in the stool at D1 and/or D2 and, IFX serum levels at D1 and D2 between cases and controls.

Results: Sixteen patients were recruited (10 men, median age: 49 years). After exclusion of one patient for insufficient pharmacological data, 6 had SEL at baseline. IFX was detected in the stool at D1 and/or D2 in 2/6 (33%) of cases and 4/9 (44%) of controls (OR =0.6, 95% CI [0.03–7.9], p=1) and no difference was observed between the two groups regarding the plasma levels of IFX on D1 or D2. At D98, 3/6 (50%) cases and 1/9 (11%) controls had been colectomized.

Conclusions: In a group of patients admitted for an ASUC treated with IFX, SEL were not associated with more detection of the drug in the stools or less plasmatic levels. In this pilot study, primary IFX failure in ASUC does not seem related SEL and drug fecal leakage. The place of these early dosages remains to be studied in larger populations.

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P255
Predictors of negative C-reactive protein in active Crohn's disease

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Background: Due to its wide accessibility, fast availability and proven correlation with disease activity, C-reactive protein (CRP) remains an essential tool in the management of Crohn's disease (CD), namely when it comes to decide the appropriate treatment in a given situation. However, the correlation of CRP with CD activity is not perfect. It is therefore of great importance to identify the group of patients with active disease and negative CRP.

Methods: We performed a retrospective case-control study, with inclusion of CD patients with proven active disease as demonstrated by endoscopic and/or radiologic examinations. The CRP's cut-off value used to separate patients in two groups (cases and controls) was 1 mg/dL. Demographic, phenotypic and clinical characteristics were collected. Statistical analysis was performed with SPSS 20.0.

Results: We included 88 patients (42 men, 46 women) with a mean age of 34 ± 10.8 years and median of disease duration of 1.23 years (interquartile range 0.07–6.16). Twelve (13.6%) of these patients had negative CRP. There weren't statistically significant differences in CD activity between cases and controls, as evaluated by Harvey-Bradshaw index. Upon exploratory analysis, there were statistically significant differences regarding gender as 21.4% of men vs 6.5% of women had a negative CRP ($p=0.04$). Even though location was not a significant predictor, all patients with a negative CRP had ileal involvement. On multivariate analysis, gender remained a significant predictor, with an Odds ratios (OR) of 5.64 [Confidence Interval (CI) 95% 1.30–24.39; $p=0.02$]. There was also a tendency to a higher probability of negative CRP in isolated ileal disease (OR 3.87; CI95% 0.97–15.34; $p=0.055$). There were no differences in age, behaviour, disease duration, previous abdominal surgery or smoking status.

Conclusions: Despite being a useful tool CRP has some limitations and it can be negative in cases of active disease. In patients with the identified characteristics (ie men with ileal disease) other methods should be used to exclude with confidence the presence of inflammatory activity.

P256 Correlation of fecal calprotectin levels with endoscopic severity evaluated with balloon-assisted endoscopy in patients with Crohn's disease

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Background: Calprotectin is a calcium-binding protein that is abundantly contained in the cytoplasm of neutrophils and monocytes. It is secreted at the site of inflammation. Fecal calprotectin is a fecal biomarker used for the assessment of intestinal inflammation in patients with inflammatory bowel disease; however, the accuracy of fecal calprotectin in the evaluation of small bowel inflammation in patients with Crohn's disease (CD) is unclear. This study aimed to assess the diagnostic accuracy of fecal calprotectin to detect intestinal inflammation evaluated with small bowel balloon-assisted endoscopy (BAE) in patients with CD.

Methods: This was a cross-sectional observational study involving a total of 54 patients who underwent BAE between June 2015 and October 2016 at our institution. Endoscopic severity was evaluated with modified simple endoscopic score for CD (mSES-CD), which evaluated the ileum and jejunum in addition to the terminal ileum,

colon, and rectum. The severity of inflammation in each segment was evaluated with the same endoscopic parameters (0–3 for ulcer size, ulcerated/affected surface, and stenosis) as the original SES-CD. The total score of each segment was taken as the final score. Mucosal healing was defined as an mSES-CD score of 3 or less. Fecal calprotectin level was determined with EliA Calprotectin 2.

Results: Among the 54 patients, 44 patients (83.0%) were male, 13 patients (24.1%) had past history of bowel resection, and 22 patients (41.5%) were treated with anti-TNF α reagents. Fecal calprotectin levels were significantly correlated with mSES-CD scores ($r=0.589$). In the receiver-operator curve analysis, the cut-off value of fecal calprotectin level was determined as 250 $\mu\text{g/g}$ for mucosal healing. The sensitivity and specificity at this cut-off value to detect mucosal healing were 92.3% and 83.3% respectively. This cut-off value was also evaluated in 31 patients who had no large-bowel disease. The sensitivity and specificity to detect mucosal healing were 90.9% and 75.0% respectively in this subgroup.

Conclusions: The levels of fecal calprotectin were correlated with the endoscopic activity assessed with BAE.

P257 Evaluation of serum ICAM-1 and VCAM-1 as biomarkers for disease progression in Crohn's disease

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Background: Determining the severity and progression of bowel damage is crucial when evaluating different treatment strategies for inflammatory bowel disease (IBD). The identification of biomarkers that could predict disease progression would be of significant clinical value. Cell adhesion molecules (VCAM-1, ICAM-1) have been shown to be increased in IBD patients, recently found to signify an upcoming flare. Our study investigated whether they could serve as biomarkers and used as predictors of early complicated disease or requirement for surgery.

Methods: The GROWTH CD study (Growth, Relapses and Outcomes With Therapy) is geared to predict early outcomes such as complications and surgery by 24 months in children with treatment naïve new onset CD. Patients with early onset of complications or need for surgery would be considered the highest risk patients. Newly diagnosed children underwent colonoscopy, gastroscopy and imaging, and were phenotyped by the Paris classification and followed at baseline, 8, 12, 26, 52, 78 and 104 weeks. We used the GROWTH CD registry to elucidate the significance of serum VCAM-1 and ICAM-1 at baseline or after therapy (week 12) in predicting complications rate (fibrostricturing disease, penetrating disease or perianal abscess) or need for surgery by 2 years.

Results: 201 children were followed prospectively for 2 years in the GROWTH CD study, of whom serum ICAM-1 and VCAM-1 levels

were obtained at day 1. For ICAM-1 18/56 (32%) with an elevated serum level had a complication along the follow-up period, compared with 41/145 (28%; $p=0.607$) who had normal levels and also had a complications. In the case of VCAM-1 the rate was slightly higher with 10/27 (37%) with high levels having a complication, as compared to 49/174 (28%; $p=0.368$) with normal levels having a complication later in the course of disease.

Conclusions: Baseline and post treatment serum levels of ICAM-1 and VCAM-1 in patients with IBD were not effective as biomarkers for early complications and a need for surgery.

P258

Disease course and operative risk after diagnosis of ileal penetrating Crohn's disease: a cohort study

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Background: Although penetrating complications are common in Crohn's disease (CD), little is known about the disease course and operative risk after diagnosis of small bowel penetrating CD complications.

The aim is to study the disease course and need for surgery in patients presenting with penetrating ileal CD.

Methods: In this cohort study, all cross-sectional imaging exams (CT and/or MRI) performed between 2006 and 2014 in patients with CD in a tertiary referral centre were reviewed for the presence of ileal penetrating complications (defined as abscesses, phlegmons or fistula). Demographic, clinical, biochemical, radiological and endoscopic factors were retrospectively assessed in these patients as well as the need for surgery (intestinal resections and/or stricturoplasties) and postoperative complications.

Results: In total, we identified 1803 cross-sectional imaging exams in 957 CD patients. In 113 patients penetrating ileal CD complications were identified. The vast majority of these patients were sent to surgery (86%) over time. The median time to surgery was 1 month. Based on univariate analysis, the presence of abscesses ($p=0.003$) and increased C-reactive protein $>22\text{mg/L}$ (based on ROC curve analysis with AUC of 0.723) at documentation of the penetrating complication ($p=0.015$), were significantly associated with subsequent surgery. The post-operative course was complicated in 14% of patients. Surgery within one month after first documentation of penetrating disease ($p=0.004$) and previous CD related surgery ($p=0.01$) were significantly associated with postoperative complications. The presence of prestenotic dilation on imaging resulted in less postoperative complications ($p=0.02$). Previous therapy (corticosteroids, immunomodulators, anti-TNF alpha therapy) had no impact on the complication rate.

Conclusions: The vast majority of patients with penetrating ileal CD were sent to surgery over time. Abscesses and high inflammatory burden are the most important factors driving the multidisciplinary decision for surgery. Early surgery within one month after documentation of the penetrating CD manifestation was more likely to be associated with a complicated post-operative course, especially anastomotic leakage.

P259

The clinical course of ulcerative colitis after orthotopic liver transplantation in context of HLA-DR mismatch

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Background: Primary sclerosing cholangitis (PSC) is a chronic liver disorder of unknown etiology, characterized by inflammation, fibrosis and stenoses of both extra- and intrahepatic bile ducts. For those who develop end – stage liver disease, orthotopic liver transplantation (OLT) remains the only effective treatment currently available. PSC is accompanied with concomitant ulcerative colitis (UC) in a significant proportion of patients. Benefits of routine HLA (human leukocyte antigen) typing in donor and recipient prior to OLT were proved in the past. The aim of this study was to assess the impact of HLA-DR mismatch on *de novo* colitis (after OLT) development and on the course of pre-existing (prior to OLT) UC.

Methods: We retrospectively evaluated records of 57 patients transplanted at Institute for Clinical and Experimental Medicine (Prague, Czech Republic) between July 1994 and November 2011. Only patients with proper records (including regular colonoscopy) ± 5 years from OLT were included. We evaluated likelihood for each variable (course pre-OLT UC, *de novo* UC development) in patients with either single, or double mismatch in HLA-DR. Input data were analysed with χ^2 and Fisher's exact test using MedCalc statistical software. A p -value <0.05 was considered as statistically significant.

Results: Out of 57 patients, 27 (47.4%) had single mismatch and 30 (53.6%) had double mismatch in HLA-DR. No patient had full match. 12/57 (21.1%) had *de-novo* UC after OLT: 7/27 (25.9%) of single mismatch group and 5/30 (16.7%) of double mismatch group ($p=0.60$). In 37 (68.5%) patients, UC was diagnosed prior to OLT. 9/16 (56.3%) patients with single mismatch and 6/21 (28.6%) patients with double mismatch had more severe course of UC as compared to course prior to OLT ($p=0.17$).

Conclusions: Patients with single mismatch in HLA-DR have slight tendency towards worsening of pre-existing UC after OLT as compared to patients with double mismatch. Analysis of combined mismatch in HLA-DR and HLA-DQ could demonstrate more substantial linkages in respective clinical variables. Therefore, these data have to be considered as preliminary as typing for HLA-DQ from frozen blood samples is currently underway.

P260

Endoscopic surveillance in ulcerative colitis: an Algerian prospective study

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Background: Patients with longstanding extensive ulcerative colitis have an increased risk of colorectal cancer.

The aims of this study were: To determine the incidence of dysplasia and colorectal cancer, in patients with longstanding ulcerative colitis. We also evaluated prospectively, the proportion of dysplastic lesions

detected by chromoendoscopy from targeted biopsies of macroscopically visible abnormalities, as opposed to random biopsies of colonic mucosa.

Methods: In this prospective study, consecutive patients with clinically inactive, longstanding UC (8 years) were recruited from 4 centers; colonoscopy with chromoendoscopy using 0.1% methylene blue was performed for each patient. Four mucosal biopsy specimens were taken every 10 cm between the cecum and the rectum, with additional biopsies or removal of any abnormality mucosal. All the endoscopies were performed by a single endoscopist, all the biopsies have been reviewed by a pathologist experienced in gastroenterology.

Results: 224 chromoendoscopy were performed in 106 patients. We diagnosed 49 neoplastic lesions in 31 patients; there were 6 adenocarcinomas, 8 high grade dysplasia, 24 low grade dysplasia, and 11 lesions indefinite for dysplasia. We did 8035 random biopsies with found 7 dysplastic lesions in 6 patients: 1 high grade dysplasia, 2 low grade dysplasia and 4 lesions indefinite for dysplasia. Random biopsies alone diagnosed dysplasia in 2 patients (1.8%), and had clinical impact only in one patient (0.9%).

Conclusions: The risk of colorectal cancer in Algerian ulcerative colitis patients is high. Colonoscopic surveillance is actually the only way to detect colorectal cancer at an early stage in ulcerative colitis. Random biopsies don't have clinical impact and should be abandoned.

P261 Grading post-operative recurrence in Crohn's disease: a comparison between MRE and ileocolonoscopy

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Background: The Rutgeerts' score is the standard measure used for endoscopic quantification of post-operative recurrence in Crohn's disease, providing valuable prognostic information used to guide prophylactic treatment decisions. Magnetic resonance imaging of the small intestine or enterography (MRE) is increasingly used to assess disease burden, phenotype and activity in small bowel Crohn's disease. There are limited data on whether MRE to assess the presence/degree of recurrent Crohn's in the pre-anastomotic ileum correlates well enough with the Rutgeerts' score to offer a non-invasive alternative. The aim of this study is to compare Rutgeerts' scores from ileocolonoscopy with measures of inflammatory activity in the pre-anastomotic ileum on MRE performed at a single high volume centre.

Methods: Patients who had a diagnosis of Crohn's disease and history of ileal resection who underwent colonoscopy with prospective Rutgeerts' score evaluation were identified from an endoscopy electronic reporting system and cross-referenced with the hospital radiology system to identify those who had an MRE study within 6 months of ileocolonoscopy.

Results: 64 patients were identified who met the criteria. Mean age was 38.7 years (SD 13) with 52% female. 31 patients (48%) were classified as having active inflammatory disease in the pre-anastomotic ileum by MRI standards. 18 (28%), 13 (20%), 11 (17%), 15 (23%) and 7 (11%) of patients had a Rutgeerts' score of 0, 1, 2, 3 and 4, respectively. The median time between MRE and colonoscopy was 1.2 months (3.2 IQR).

There was no significant association between inflammatory activity

as measured by the Rutgeerts' score and MRE evidence of activity. The median Rutgeerts' score for patients classed as active by MRE was 2 (IQR 2.5), while for inactive disease was 2 (IQR 3) (P 0.34). A subset of 17 patients had colonoscopy and MRE on the same day and again there was no association between Rutgeerts' score and inflammatory activity on MRE (active 1 (IQR 1.25) versus inactive 2 (IQR 1), P 0.2).

Conclusions: Our data suggest that endoscopic evaluation remains important for accurate grading of inflammatory activity in this group.

P262 Evaluation of zinc as a biomarker of a complicated course in paediatric Crohn's disease

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Background: Zinc plays a critical role in innate immunity. It is associated physiologically with defensin release, autophagy, and TNF alpha regulation, while supplementation of zinc in animal models decreases intestinal permeability, and bacterial biofilm formation. The goal of the present study was to evaluate the possible role of zinc levels as a biomarker for adverse outcomes such as early complications or surgery.

Methods: The GROWTH CD study (Growth, Relapses and Outcomes With Therapy) followed newly diagnosed children with CD for 24 months and was geared to predict early outcomes such as complications and surgery. Children underwent colonoscopy, gastroscopy and imaging, were phenotyped by the Paris classification and followed at baseline, 8, 12, 26, 52, 78, 104 weeks. Serum for zinc levels was obtained at baseline, and analyzed in a central laboratory. We evaluated sustained remission and complications through follow up using dichotomous and quartile analysis.

Results: 125 children were followed prospectively for 2 years, of whom 34 (27.4%) developed complications and 8 (6.6%) required surgery. At baseline median zinc levels were 86.6 mcg/dl and low levels (below 70 mcg/dl) were found in 33 (26.4%) children.

There was no correlation between serum zinc and CRP (p=0.24) or PCDAI (p=0.69).

For those with low Zinc levels at baseline compared to those with normal zinc levels, no difference was observed in rates of sustained remission by 78 weeks (59% vs. 58%, p-value=0.9); or in rates of complications or surgery by week 104 (33.3% vs. 25.3% for complications p-value=0.37, 9.7% vs. 5.6% for surgery, p-value=0.43). The rate of complications by week 104 at the lowest quartile of baseline zinc levels was 32% and at the highest quartile 23% (p=0.5).

Conclusions: Zinc levels were not useful as a biomarker of adverse outcomes in children with newly diagnosed Crohn's disease.

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P263**De-novo inflammatory bowel disease after bariatric surgery: a novel association**

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Background: A reduced alpha diversity in the fecal microbiome of patients with Crohn's disease (CD) has been reported, similar to changes described after bariatric surgery. There have been only 5 case reports of IBD diagnosed in patients with a history of bariatric surgery. Our aim was to identify and characterize patients who were diagnosed with inflammatory bowel disease (IBD), either CD or ulcerative colitis (UC), after having undergone bariatric surgery.

Methods: Electronic medical records from January 1996 to January 2016 were reviewed using a bioinformatics search tool at a single institution to identify patients with co-occurrence of an ICD-9/10 code for CD or UC and clinical notes terms associated with bariatric surgery (Roux-en-Y, bariatric surgery, gastroplasty, gastric bypass, gastric sleeve, duodenal switch, gastric banding) were identified and reviewed. Data on demographics, type of bariatric surgical procedure, CD/UC disease phenotype, and medication usage were obtained.

Results: A total of 644 patients with co-occurrence of IBD and bariatric surgery were identified with the initial search tool. After record review, 36 patients met inclusion criteria (26 CD and 10 UC). Most patients were female (86.1%). At the time of bariatric surgery, median body mass index (BMI) was 47.2 (Interquartile range (IQR), 42.0–54.2) and age was 38 years (IQR, 30.5–46.7). Median time to IBD diagnosis after bariatric surgery was 6.5 years (IQR, 3.2–8.7); specifically, 6 years for UC and 7 years for CD. Median age at onset of IBD was 44 years (IQR, 38.0–53.7). Family history of IBD and current smoking was present in 5.5% and 30.5% of cases, respectively. Regarding type of bariatric surgery, 75% underwent Roux-en-Y (5 UC and 21 CD), 5.5% gastric banding (1 UC and 1 CD) and 2.7% stapling (1 CD). In the CD group, the most common disease location was ileal (50%) followed by ileocolonic (34.6%). Most CD patients had inflammatory disease behavior (73.1%) followed by penetrating (15.3%) and stricturing disease (11.6%). In patients with UC, 50% had extensive colitis, followed by left-sided colitis (30%) and proctitis (20%). Tumor necrosis factor-alpha inhibitors were used in 42.3% of CD and 10% of UC patients. Overall, 47.2% of IBD patients required hospitalization (50% in UC and 46.1% in CD) and 25% required surgical intervention for treatment of their disease (20% in UC and 26.9% in CD).

Conclusions: We have described a case series of patients developing *de-novo* IBD after bariatric surgery. This potential association requires confirmation in larger patient cohorts.

P264**Relation of inflamed resection margins to postoperative complications in Crohn's disease**

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Background: Our study evaluated if the presence of inflamed resection margins increased postoperative anastomotic complications in Crohn's disease patients.

Methods: Resection margins of 70 patients operated on due to

Crohn's disease were analysed and classified by a single pathologist according to the degree of inflammation. Anastomotic complications defined as anastomosis failure or postoperative perianastomotic abscess were recorded with a 1-month follow-up. The Fisher's exact test was used to analyse if the degree of inflammation in the resection margin increased anastomotic complications.

Results: Altogether 46 patients (65.6%) had inflammation in their bowel resection margins. 12 patients (17.1%) had mild, 5 patients (7.1%) intensive and 29 patients (41.4%) very intensive inflammation in their resection margins. The presence of inflamed resection margin did not significantly influence the appearance of postoperative anastomotic complications ($p > 0.05$). Only 3 patients (4.6%) had anastomotic complications including two anastomotic failures and one abscess.

Conclusions: Our study did not show correlation between the degree of inflammation in the bowel resection margin and the presence of postoperative anastomotic complications in Crohn's disease. Bowel conservative surgery with resection of only the most affected bowel segments should be chosen for Crohn's disease patients.

P265**Comparison of two faecal calprotectin assays in monitoring children with inflammatory bowel disease**

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Background: Faecal calprotectin (FC) is a good marker in monitoring mucosal healing in adults and children with inflammatory bowel disease (IBD). Its concentrations in faeces is closely related to state of mucosa observed in endoscopy. Due to increasing need in rapid, cheap testing for FC, especially in children, new point-of-care tests (POCT) are being developed. The aim of the study was to compare rapid immunochromatographic test (POCT) with standard enzyme-linked immunoassay (ELISA).

Methods: 20 paediatric patients with IBD (Crohn's disease [CD] 10, ulcerative colitis [UC] 10) were involved in the study and had elective colonoscopy performed. Each patient had FC level measured within a week before endoscopy by two assay (ELISA and POCT). Mucosa status during endoscopy was assessed with Baron score for UC and simple endoscopic score for CD (SES-CD). Full mucosal healing was defined as Baron score or SES-CD of 0. Results of FC were correlated with each other and with endoscopic findings by Spearman's rank correlation coefficient. We have identified two subgroups: those with full mucosal healing, and patients with inflamed gut mucosa. The receiver operating characteristic curves (ROC) were used as a statistical method to establish cut-off points. The area under the curve (AUC) assesses the differentiation quality of the study groups. The Deming regression was used to determine systematic differences between two measurement methods.

Results: Although both FC methods correlated significantly with $r = 0.66$, slope and intercept differed extensively, with up to 3-fold quantitative differences between assays ($y = 2.8x - 432$). The AUC for the ELISA and POCT was 0.89 and 0.82 respectively. The selected cut-off level of discrimination between subgroup with full mucosal healing vs. subgroup with mucosal inflammation present was 686 $\mu\text{g/g}$ with sensitivity 0.75 and specificity 0.88 for ELISA and 260

$\mu\text{g/g}$ with sensitivity 0.83 and specificity 0.88 for POCT. The ELISA method had stronger, clinically significant correlation with presence of inflammation than POCT with $r=0.66$ and $r=0.55$ respectively.

Conclusions: FC is a good marker of mucosal healing in monitoring of children with IBD. Both the POCT and ELISA method showed comparable clinical performance in finding inflammation lesions. However the cut of points for detection of inflammation differed extensively between methods. Further efforts are needed to standardize those two assays.

P266

Risk factors for colorectal neoplasia in ulcerative colitis

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Background: There is a higher risk of neoplasia in ulcerative colitis than in general population; the aim of this study was to identify risk factors for dysplasia and colorectal cancer in Algerian patients with ulcerative colitis.

Methods: In this prospective study, patients with longstanding ulcerative colitis in clinical remission, had an endoscopic surveillance between January 2009 and January 2015, then patients with neoplastic lesions were compared to patients without colorectal neoplasia, to identify risk factors for neoplasia in ulcerative colitis.

Results: 106 patients were enrolled in a surveillance program by chromoendoscopy. We diagnosed 49 neoplastic lesions in 31 patients; 6 patients with adenocarcinomas, and 27 patients with dysplasia. These patients were compared to the 75 patients without neoplastic lesions.

In univariate analysis, risk factors for colorectal cancer were: longstanding colitis, time between first symptoms and the diagnostic of colitis longer than 6 months, spondylarthritis, colonic stricture, tubular colon, and inflammatory polyps.

Risk factors for dysplasia were: high age at inclusion in the study, and time between first symptoms and the diagnostic of colitis longer than 6 months; after exclusion of the sporadic adenomas (adenomas outside colitic mucosa) risk factors for dysplasia were: longstanding colitis, time between first symptoms and the diagnostic of colitis longer than 6 months, inflammatory polyps, pancolitis, and corticoddependency.

After multivariate analysis, Risk factors for CCR or high grade neoplasia were longstanding colitis, time between first symptoms and the diagnostic of colitis longer than 6 months and inflammatory polyps. Risk factors for dysplasia were long standing disease and corticoddependency.

Regular maintenance treatment was a protector factor of colorectal cancer.

Conclusions: in our study, risk factors for CCR or high grade neoplasia are longstanding colitis, time between first symptoms and the diagnostic of colitis longer than 6 months and inflammatory polyps. Risk factors for dysplasia are long standing disease and corticoddependency. Regular maintenance treatment is a protective factor.

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Candidate serum markers in newly diagnosed Crohn's disease patients

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Background: More than half of patients with Crohn's disease (CD) develop disease complications requiring aggressive medical therapy or surgery over time. However, predicting disease course and treatment response remains difficult. We therefore identified distinctive serum analytes associated with disease activity and course in newly diagnosed, untreated CD patients at presentation and during their follow-up.

Methods: In a pilot study, a multiplex immunoassay analysis on 35 markers was performed on serum from 20 untreated CD patients at the time of primary diagnosis following endoscopic evaluation. The 11 most potent markers (IL-37, CCL-5, CCL-19, CXCL-13, sIL-2R, sIL-6R, sTNF-R1, sTNF-R2, S100A8, VCAM, MMP-1), associated with disease activity, phenotype or course, were measured in a consecutive cohort of 66 CD patients at primary diagnosis and during follow-up (n=39). A healthy control group was included (n=20).

Results: Almost all pro-inflammatory cytokines were undetectable at baseline in most of the CD patients in the pilot cohort.

In the consecutive cohort, CD patients had higher baseline levels of sTNF-R2 ($p=0.001$), sIL-2R ($p=0.0001$) and MMP-1 ($p=0.001$) compared to healthy controls. Serial measurements revealed that sTNF-R2, sIL-2R and MMP-1 levels dropped statistically significant from

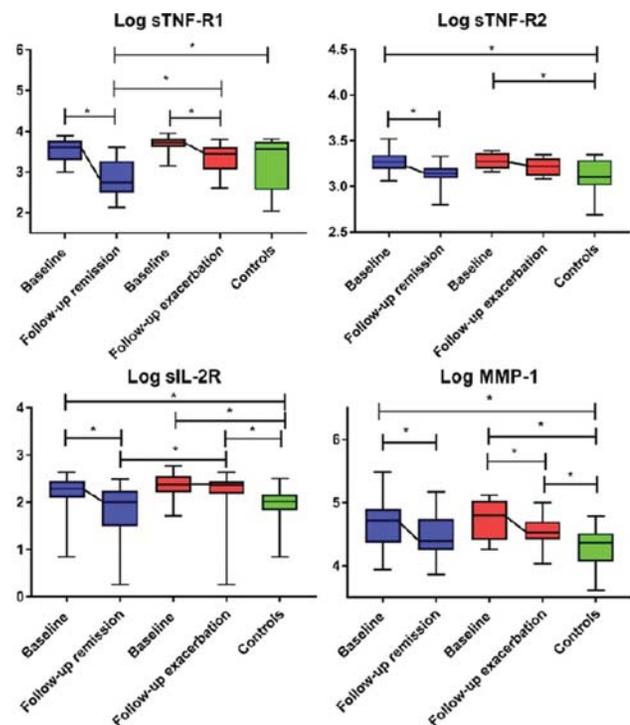


Figure 1. Serum analyte levels at baseline and follow-up, followed by log transformation. Levels of the group in remission (blue, n=29) and during exacerbation at follow-up blood collection (red, n=10). Healthy controls in green. *p-value <0.05.

baseline level when there was remission at follow-up, while they remained high during an exacerbation at follow-up (Fig. 1).

Great decline of sTNF-R1 levels was found during remission with 6.7 fold lower levels than in healthy controls ($p=0.015$, Fig. 1).

Patients that did not respond to initial prednisone treatment had higher baseline levels of sTNF-R2 ($p=0.001$).

Patients with relapsing disease (≥ 1 disease exacerbation during follow-up) had lower baseline sTNF-R2 and VCAM levels compared to patients with long-lasting remission.

Conclusions: There is a very small window of opportunity for the analysis of early inflammatory processes in CD patients, as therapy that influences the immune system is usually initiated soon after diagnosis. Serial measurements in patients at diagnosis and during follow-up identified sTNF-R1, sTNF-R2, sIL-2R and MMP-1 as potential markers of disease activity. Furthermore, baselinesTNF-R2 was associated with prednisone response and disease course. These candidate markers are easily accessible and implementable in daily practice and therefore warrant further investigation.

P268

Fecal calprotectin correlates more highly with endoscopic disease activity than symptom-based disease activity markers in paediatric PSC-IBD

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Background: Inflammatory bowel disease (IBD) with primary sclerosing cholangitis (PSC) has a distinct phenotype, with mild symptoms despite pancolitis and frequent backwash ileitis. The well-known greater risk of colonic neoplasia (where chronic inflammatory activity is a risk factor) led us to hypothesize that symptoms might be an inaccurate reflection of endoscopic disease activity in children with PSC-IBD.

Methods: In this single-centre prospective study, Paediatric UC Activity Index (PUCAI), physician global assessment (PGA) and fecal calprotectin (FC) were measured in all PSC-IBD patients undergoing colonoscopy. Patients with colonic IBD without PSC served as controls. Colonoscopies were scored by two blinded IBD physicians using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and endoscopic PGA. Spearman correlations were calculated between

variables. PUCAI and FC were compared between patients in and not in endoscopic remission (UCEIS 0–2), in both groups.

Results: 24 PSC-IBD and 32 colonic IBD patients were enrolled (Table 1). Median PUCAI and FC at colonoscopy were 2.5 (range 0–70) and 348 (37–8252) $\mu\text{g/g}$ in PSC-IBD patients, and 15 (range 0–75) and 1435 (range 29–16782) $\mu\text{g/g}$ in colonic IBD patients, respectively. As hypothesized, the correlations between symptom-based assessments of disease activity and endoscopy were poor in PSC-IBD patients ($r=0.421$ for PUCAI, $r=0.196$ for clinical PGA vs. UCEIS) (Table 2). The correlation between FC and UCEIS was significantly better ($r=0.782$). FC correlated poorly with both PUCAI and clinical PGA. In contrast, PUCAI correlated well with UCEIS in controls ($r=0.824$); this correlation was superior to that of FC vs. UCEIS ($r=0.696$). The correlation between PUCAI and FC was better in controls than in PSC-IBD patients ($r=0.525$ vs. 0.367). FC and PUCAI differed significantly based on endoscopic remission status in controls, but only FC differed in PSC-IBD patients (Table 1).

Conclusions: Absence of symptoms cannot be relied on to reflect endoscopic activity in paediatric PSC-IBD. FC appears to be more accurate in this setting. Given the emerging importance of the gut-liver axis in PSC, increasing attention must be paid to achieving mucosal healing, particularly in children in early phases of PSC, where the possibility of altering biliary disease progression may be greatest.

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Phenotypic predictors of endoscopic recurrence after ileal resection for Crohn's disease: an NIDDK IBD Genetics Consortium prospective study

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Abstract P268 – Table 1. Patient and disease characteristics

% or median (IQR)	PSC-IBD (n=24)	Colonic IBD
Male	67%	53%
Age at IBD diagnosis (years)	12.1 (4.0–13.6)	12.7 (7.8–14.7)
Pancolitis	79%	71%
Relative rectal sparing	35%	12.5%
Backwash ileitis	35%	12.5%
Age at PSC diagnosis (years)	12.6 (IQR 9.2–14.4)	–
Autoimmune hepatitis overlap	43%	–
FC by endoscopic remission status (in remission vs. not)	92 (IQR 42–32) vs. 2539 (IQR 2205–7606), $p=0.002$	282 (IQR 75–760) vs. 2795 (IQR 1896–13585), $p=0.002$
PUCAI by endoscopic remission status (in remission vs. not)	0 (IQR 0–10) vs. 17.5 (IQR 0–30), $p=0.15$	0 (IQR 0–0) vs. 35 (IQR 24–42.5), $p\leq 0.001$

Abstract P268 – Table 2. Spearman correlations between symptom-, biomarker- and endoscopy-based markers of disease activity in paediatric PSC-IBD

	PUCAI	Clinical PGA	FC	CRP	UCEIS	Endoscopic PGA
PUCAI	1.0	0.73 ($p=0.0018$)	0.37 ($p=0.27$)	0.64 ($p=0.008$)	0.42 ($p=0.07$)	0.40 ($p=0.08$)
Clinical PGA	0.73 ($p=0.002$)	1.0	-0.03 ($p=0.95$)	0.32 ($p=0.31$)	0.20 ($p=0.50$)	0.25 ($p=0.36$)
FC	0.37 ($p=0.27$)	-0.03 ($p=0.95$)	1.0	0.76 ($p=0.02$)	0.78 ($p=0.004$)	0.82 ($p=0.002$)
CRP	0.64 ($p=0.008$)	0.32 ($p=0.31$)	0.76 ($p=0.02$)	1.0	0.85 ($p<0.001$)	0.80 ($p<0.001$)
UCEIS	0.42 ($p=0.07$)	0.20 ($p=0.50$)	0.78 ($p=0.004$)	0.85 ($p<0.001$)	1.0	0.98 ($p<0.001$)
Endoscopic PGA	0.40 ($p=0.08$)	0.25 ($p=0.36$)	0.82 ($p=0.002$)	0.80 ($p<0.001$)	0.98 ($p<0.001$)	1.0

Background: Disease recurrence in patients after ileal resection of Crohn's Disease (CD) is predictable and represents an excellent model to study the mechanisms of intestinal inflammation in an at-risk population. Our aim is to investigate genomic and microbial factors associated with post-operative endoscopic recurrence (ER). Here we present preliminary phenotypic analysis of recruited subjects to a prospective NIDDK Inflammatory Bowel Disease Genetics Consortium longitudinal study.

Methods: Patients with CD scheduled to undergo ileocolic resection with primary anastomosis were recruited at 6 North American research centres using a standardised protocol. Clinical data and bio specimen collection for microbiome and histological assessment was performed pre-operatively and at follow up. A Rutgeert's score of at least i2 determined endoscopic recurrence. Bivariate analysis (χ^2 test) was performed using Graphpad.

Results: 294 patients were enrolled up to August 2016 and 122 had at least 1 post-operative endoscopy. The overall recurrence rate in the neo-terminal ileum up to 18 months was 33.6% (n=41/122). Early ER was present in 23.7% (n=29/122) at a median 6 months. CD recurrence was not significantly associated with Montreal classification, age, gender, smoking, or previous hospitalisations. Patients with a prior history of ileal resection had a higher risk of post-operative ER (p=0.004, RR 2.6 95% CI [1.5–3.8], n=9/41 vs n=3/81). Peri operative steroids (p=0.002, RR 3.4 95% CI [1.46–8.9]), combined immune suppressants and anti-TNF agents (p=0.028) and anti-TNF monotherapy use (p=0.056, RR 1.03 95% CI [1.002–4.04]) were associated reduced likelihood of ER. Use of anti-TNF therapy post-operatively was also associated with reduced recurrence (p=0.03, RR 2.81 95% CI [1.18–7.3], 15.7%, n=6/38 vs 41.6%, n=35/84). Patients recruited in the USA were more likely to receive anti-TNF therapy prior to first post-operative endoscopy (p=0.02, RR 2 95% CI [1.4–3.6]). Early recurrence rates were higher in Canadian centres although this was not statistically significant (p=0.45 [20% vs 40%]).

Conclusions: Preliminary phenotypic results showed that previous surgery predicted endoscopic post-operative recurrence, potentially indicating a more aggressive phenotype. Steroid exposure perioperatively and use of anti-TNF biologic therapy peri- and post-operatively before colonoscopy were associated with lower risk of endoscopic recurrence, validating studies which show benefit of anti-TNF in prevention of post-operative recurrence. Future studies in this population will investigate microbial and transcriptomic profiles related to disease recurrence and ongoing recruitment will further expand our cohort

P270

Correlation between endoscopic and histological activity in ulcerative colitis using validated indices

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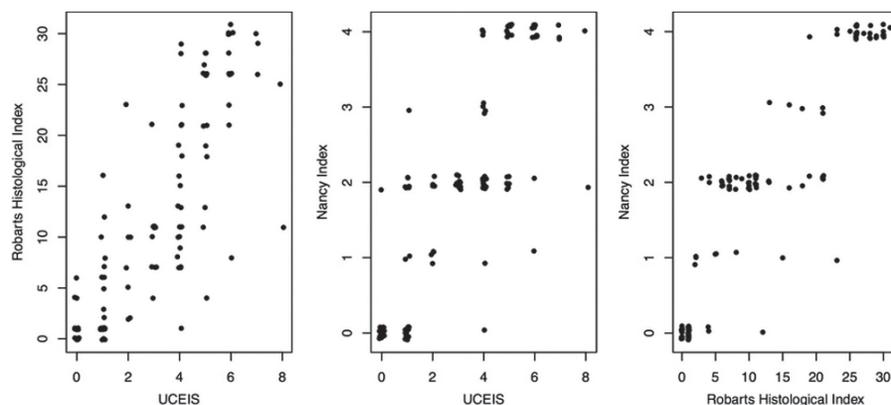
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Background: Endoscopy and histopathology are pivotal techniques for evaluating disease activity in ulcerative colitis (UC). Validated endoscopic [1] [2] and histological indices [3] [4] have only recently been published and their correlation has not yet been examined. We aimed to correlate the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) with the Nancy and Robarts' histological indices in patients with established UC.

Methods: Retrospective cohort study at a single centre on patients with an established diagnosis of UC who underwent flexible sigmoidoscopy or colonoscopy by a single clinician (ST) between March 2013 and August 2015. The UCEIS was recorded at the worst affected area in the left colon and mucosal biopsies taken from this and other areas. Histological disease activity using the Nancy (NI) and Robarts' (RHI) histological indices was scored by a specialist pathologist (LMW) blinded to the endoscopy report. Spearman correlation and area under the curve (AUC) between the UCEIS, NI and RHI, and between NI and RHI was performed.

Results: 125 patients were included in the study with a median age of 37 years (range 16–81 years), 64/125 (51%) male, and a wide distribution of UCEIS (scale 0–8): 0=21; 1–3=48; 4–6=51; 7–8=5. The correlation coefficient (r) between the UCEIS and NI (scale 0–4) was 0.84 (95% CI 0.76–0.89, p<0.001) and between UCEIS and RHI (scale 0–33) was 0.86 (95% CI 0.80–0.90, p<0.001), as shown in figure 1. The difference in correlation was not significant (p=0.57). When UCEIS=0, there was no microscopic activity in 20/21 (95%, NI 0–1) and 18/21 (86%, RHI 0–3). When UCEIS=1, microscopic inflammation was absent in 20/28 (71%) and 18/28 (64%) respectively (p<0.05). Quiescent disease activity defined as the absence of neutrophils (NI 0–1, RHI 0–3) was more closely correlated with UCEIS=0/8 than with UCEIS=1/8. AUC=0.71 for RHI and AUC=0.65 for NI. There was excellent correlation between the two histological indices (r=0.92, 95% CI 0.87–0.95, p<0.001), but the NI was considered (by LMW) easier to score.

Conclusions: The UCEIS shows strong correlation with both Nancy and Robarts' histological indices. Complete mucosal healing is best



Abstract P270 – Figure 1. Distribution scatterplot between UCEIS & RHI (r=0.86, 95% CI: 0.80–0.90, p<0.001), UCEIS & NI (r=0.84, 95% CI: 0.76–0.89, p<0.001) and NI & RHI (r=0.92, 95% CI: 0.87–0.95, p<0.001).

defined as a UCEIS 0/8, since this correlates most closely with the absence of microscopic disease activity.

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Complications of primary sclerosing cholangitis in patients with ulcerative colitis and normal liver function tests: a prospective magnetic resonance cholangiographic study with long-term follow-up

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Background: The prevalence of PSC in patients with UC and normal liver function tests is unknown. This prospective study sought to clarify the prevalence and characteristics of biliary abnormalities consistent with PSC on magnetic resonance cholangiography (MRC) in UC patients with normal liver function, and to evaluate evidence of disease progression and complications during long-term follow-up.

Methods: In phase one, 51 patients with extensive UC and normal liver function tests underwent MRC and blood evaluation. 28 age and sex-matched healthy volunteers and 28 patients with an established diagnosis of PSC and cholestatic liver function had MRC evaluation as negative and positive controls, respectively. In phase two, 19 patients with extensive UC and colorectal dysplasia (CRD) identified from colonoscopic surveillance, and 24 negative and positive matched controls underwent MRC evaluation. Two independent specialist radiologists blinded to clinical details interpreted MRC scans. Clinical outcome was assessed prospectively at outpatient clinic with liver biochemistry, endoscopic surveillance and abdominal imaging as indicated.

Results: 7/51 UC patients (14%) and 4/19 UC patients with CRD (21%) and normal liver function had biliary abnormalities on MRC consistent with PSC. Over half (7/11; 55%) had intrahepatic duct involvement only. The presence of biliary abnormalities was associated with quiescent disease ($p=0.03$) and negative smoking history ($p=0.03$) on multivariate analysis. Inter-observer ($\kappa=0.88$) and intra-observer ($\kappa=0.96$) agreement by radiologists for MRC interpretation was good, with 100% of positive PSC controls identified correctly. During a median follow-up of 8.8 years (range 30–116m), 4/11 pa-

tients (36%) with biliary abnormalities on MRC developed persistently abnormal liver function and 2/11 patients (18%) had radiological evidence of progression of PSC. 1/7 patients (14%) with extensive UC and biliary abnormalities developed a low-grade adenoma on colonoscopic surveillance that was endoscopically resected, and 1/4 patients (25%) with UC and CRD developed a cholangiocarcinoma (CCA) after 7.2 years. 2/11 patients died.

Conclusions: Unsuspected biliary abnormalities consistent with PSC were present in 14% of extensive UC patients, and 21% UC patients with CRD, and normal liver function. During 9 year follow up, a third developed abnormal liver function, a fifth developed progressive ductal disease, and one developed CCA. MRC may be appropriate in patients with extensive UC regardless of liver function, to identify subclinical PSC and stratify surveillance strategies. This is especially important in those with UC and CRD, with an increased risk of PSC and development of CCA.

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Faecal calprotectin and magnetic resonance imaging are highly accurate to detect endoscopic postoperative recurrence in Crohn's disease

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Background: The POCER trial [1] has recently confirmed that the therapeutic management has to be adapted according to endoscopic findings within the first year following surgery to prevent postoperative recurrence (POR) in Crohn's disease (CD). However, as colonoscopy is burdensome, alternative tools have been developed. We aimed to compare the performances of MRI and faecal calprotectin to detect endoscopic POR ($\geq i2$ according to Rutgeerts' score) or severe endoscopic POR ($\geq i3$) in CD patients.

Methods: Adult CD patients from two tertiary centers who underwent ileal or ileocolonic resection were consecutively included in this prospective study. All the patients underwent magnetic resonance enterography including diffusion-weighted sequences with apparent diffusion coefficient (ADC) calculation and evaluation of Clermont score [2], MaRIA [3] and MR score [4], 6 months IQR [5.0–9.3] after surgery or restoration of intestinal continuity. Colonoscopy was performed within a median time of 14 days with stools collection the day before.

Results: Overall, 28 CD patients were enrolled in the study (Table 1). Eight and 6 patients were respectively $i0$ or $i1$ according to Rutgeerts' score at 6 months after surgery. Endoscopic POR was observed in 14 patients including 7 patients classified as $i2$ (3 as $i2a$ and 4 as $i2b$) and 7 patients with severe endoscopic POR (5 with $i3$ and 2 with $i4$). While the mean ADC value was lower in patients with endoscopic POR (2.08 vs 2.38, $p=0.02$), Clermont score (7.4 vs 10.2, $p=0.04$) and related contrast enhancement (RCE) (77% vs 129%, 0.05) were higher in patients experiencing endoscopic POR. MaRIA value was not significantly higher in patients with endo-

Table 1: Characteristics of the 28 Crohn's disease patients included in the study.

Age at diagnosis, (years), mean \pm SD	34.9 \pm 14.1
Disease duration at inclusion, (years), mean \pm SD	9.0 \pm 9.5
Male gender, n (%)	14 (50.0%)
Active smokers, n (%)	7 (25.0%)
Montreal Classification	
Disease location	
L1, n (%)	14 (50.0%)
L2, n (%)	1 (3.6%)
L3, n (%)	13 (46.4%)
L4, n (%)	0 (0.0%)
Behaviour	
B1, n (%)	0 (0.0%)
B2, n (%)	15 (53.6%)
B3, n (%)	13 (46.4%)
Perianal lesions, n (%)	6 (21.4%)
Therapy in prevention of endoscopic postoperative recurrence	
None, n (%)	6 (21.4%)
5-ASA, n (%)	2 (7.2%)
Thiopurines, n (%)	14 (50.0%)
Anti-TNF agent	6 (21.4%)
Infliximab, n (%)	1 (3.6%)
Adalimumab, n (%)	5 (17.8%)
CDAI, mean \pm SD	68 \pm 51
CRP, mean \pm SD	4.5 \pm 5.7
Faecal Calprotectin (μ g/g), mean \pm SD	225 \pm 334

scopic POR (5.1 vs 8.1, $p=0.18$). Using ROC curves, we showed that ADC $<2.3\text{mm}^2/\text{s}$ (Se=0.82, Spe=0.71, NPV=0.83, PPV=0.69), Clermont score >8.4 (Se=1.0, Spe=0.55, NPV=0.74, PPV=1.0) and MaRIA >7 (Se=0.50, Spe=0.82, NPV=0.60, PPV=0.75) demonstrated substantial performances to detect endoscopic POR. Besides, ADC $<2.3\text{mm}^2/\text{s}$ (Se=0.67, Spe=0.86, NPV=0.5, PPV=0.92), Clermont score >12.5 (Se=0.57, Spe=0.78, NPV=0.82, PPV=0.50) and MaRIA >11 (Se=0.57, Spe=0.75, NPV=0.80, PPV=0.50) were highly effective to detect severe endoscopic POR.

Using a cut-off value of $100\mu\text{g/g}$, faecal calprotectin was very accurate to detect endoscopic POR (Se=0.62, Spe=1.0, NPV=0.68, PPV=1.0) or severe endoscopic POR (Se=1.0, Spe=0.94, NPV=1.0, PPV=0.88).

Conclusions: Faecal calprotectin and MRI are reliable tools to detect endoscopic POR in CD patients and could be used as non-invasive alternative options to colonoscopy.

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Prediction of treatment response in Crohn's disease patients using contrast enhanced ultrasound: a pilot study

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Background: Increased vascularity of the bowel wall is an early pathologic change that occurs in patients with active Crohn's disease (CD) and is used in imaging methods with intravenous contrast. We investigated whether a baseline contrast-enhanced ultrasound (CEUS) can differentiate responders from non-responders treated medically over a period of 6 to 12 months.

Methods: Unselected adult CD patients from a tertiary care IBD center were recruited. Baseline demographic and clinical data was gathered and CEUS was performed at baseline in patients using a second-generation US microbubble contrast agent (Definity[®]) using 0.2 ml as bolus followed by drip infusion at a fixed rate. Following placement of an ROI (region of interest) over the bowel wall, perfusion analysis software modeled time-intensity curves (TIC) and relative kinetic perfusion parameters were measured. In each patient, clinical activity, treatment and therapeutic outcome were assessed at 3, 6 and 12 months after the CEUS. Treatment changes after baseline, systemic steroid dependency, ongoing clinical activity, new disease complications and need for surgery during the observation period were considered treatment failures. CEUS parameters were compared in patients with active (aCD) versus inactive CD (iCD) at baseline

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Table 1. Crohn's disease patients baseline demographic and clinical characteristics

	Total (n=21)	inactive CD (iCD) (n=6)	active CD (aCD) (n=15)	P
Males, n [%]	9 [43]	2 [33]	7 [47]	
Age, yrs, median [IQR]	32 [25-51]	46 [31-63]	27 [24-47]	0.045
Disease duration, yrs, median [IQR]	13 [8-24]	19.5 [14-24]	9 [7-30]	
Montreal Classification				
Age at diagnosis: A1, A2, A3	5, 14, 2	1, 3, 2	4, 11, -	
Location: L1, L3	11, 10	4, 2	7, 8	
Behavior: B1, B2	4, 17	0, 6	4, 11	
Perianal disease	5	0	5	
Smoking, n [%]	3	1	2	
Previous surgery, n [%]	12 [57]	5 [83]	7 [47]	
Ileocolic anastomosis	11	5	6	
Small bowel resection	1	-	1	
Active disease at baseline, n [%]	15 [71]			
Clinically	6	3	3	
Clinically + Endoscopically	8	2	6	
Clinically + Imaging	3	1	2	
Clinically + Endoscopically + Imaging	4	-	4	
Median HBI score, median [IQR]	6 [3-12]	2 [2-3]	11 [5.5-12]	<0.001
Median CRP (mg/L), median [IQR]	10.4 [3-28]	7.8 [1.5-16]	11.3 [4.4-31]	0.353

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Table 2. CEUS kinetic parameters in CD patients

Baseline CEUS kinetic parameters median, [IQR]	inactive CD (iCD)		active CD (aCD)		P
	at baseline (n=6)		at baseline (n=15)		
PSV during bolus injection	8.9	[5.5-11.9]	25.9	[9.8-53.5]	0.023
WiWoAUC during bolus injection	248.8	[157.6-297.4]	769	[224.3-1718.9]	0.036
PSV during drip infusion	3.2	[2.3-4.4]	7.6	[4.1-10.1]	0.009
WiWoAUC during drip infusion	73.9	[33.8-154.4]	188.9	[89.2-230.7]	0.012

Baseline CEUS kinetics parameters median, [IQR]	Poor outcome at 6 months N=5		Favorable outcome at 6 months N=3		P
	PSV during bolus injection	18.8	[5.7-39.7]	41.53	
WiWoAUC during bolus injection	314.5	[175.3-1014.2]	1718.86	[1100.4-2019.4]	0.143
PSV during drip infusion	3.9	[2.9-10.5]	9.74	[7.6-13.5]	0.143
WiWoAUC during drip infusion	84.4	[75.1-212]	187.13	[154.7-246.3]	0.250
CRP (mg/L)	14.6	[5.9-31]	16.75	[1.5-32]	1

PSV: peak systolic velocity (wash in rate), WiWoAUC: wash in/wash out area under curve

and in patients with favorable versus poor outcome at 3, 6 and 12 months post CEUS.

Results: Twenty-one patients (9 men, median age 32 years, median disease duration 13 years; 15 aCD and 12 with previous surgery) were recruited. Baseline kinetic CEUS parameters peak systolic velocity (PSV-wash in rate) & wash in/wash out area under curve (WiWoAUC) in bolus and drip infusion differed significantly in aCD (n=15) versus iCD patients (n=6), while there was no difference in bowel wall US features including peristalsis, vascularity, layers loss, submucosa echogenicity nor in CRP levels between the two groups (Table 2). At baseline, 8 patients were started on a new treatment or were escalated and 5 of them were non-responders at 6 months. There was a trend towards higher median values in baseline CEUS kinetic parameters (PSV and WiWoAUC) in responders versus non-responders (Table 2).

Conclusions: CEUS is a potentially useful, non-invasive tool to identify patients with active CD and who are more likely to respond to therapy.

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Assessing the individual risk of acute severe colitis at diagnosis in a South Asian population

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Background: A new index has been shown to predict acute severe colitis (ASC) in patients diagnosed with ulcerative colitis (UC) [1]. When applied to patients at the time of diagnosis, this index can predict the 3 year risk of ASC. This 3 point scoring system is the sum of the following indices – 1 point for extensive disease, 1 point for a C-reactive protein [CRP] >10 mg/l, and 1 point for a haemoglobin [Hb] <12 g/dl F or <14 g/dl M. A score of 3/3 gives a 70% predicted risk of developing ACS within 3 years. This index was developed in an Oxford UC cohort, and externally validated in cohorts in Cambridge (UK) and Uppsala (Sweden). It is not clear whether this index would apply accurately to a South Asian (SA) cohort who have a higher rate of extensive disease at diagnosis, but a less aggressive disease course [2] We aim to assess whether this index can be applied to a South Asian population.

Methods: South Asian UC patients diagnosed between January 2006 and December 2013 were identified from the hospital's IBD research

database. Patients were included if the extent of disease, CRP and Hb data were accessible at the time of diagnosis. Electronic notes were accessed to provide follow up data regarding admissions and treatment in the 3 years following diagnosis. Patients lost to follow up were excluded.

Results: 48 UC SA patients were identified over the study period who had the requisite clinical data available to enable a predictive score to be calculated. 6/48 of these patients developed ASC within 3 years of diagnosis. In all index score categories, South Asians patients had a lower percentage of ASC compared to the Oxford median predictive risk.

Table 1. South Asian cohort stratified by index score and number with ASC – Side to side comparison with Oxford Development cohort

Index Score	0/3	1/3	2/3	3/3
Number of patients (n=48)	17	11	17	3
Mean Hb (g/dL)	14.2	13.1	11.8	10.8
Mean CRP (mg/L)	< 5	7.3	12.3	14.3
% with extensive disease	6% (1/17)	27% (3/11)	65% (11/17)	100% (3/3)
% requiring steroid	12% (2/17)	18% (2/11)	18% (3/17)	67% (2/3)
% developed ASC by 3 years	0% (0/17)	18% (2/11)	18% (3/17)	33% (1/3)
Oxford median predictive risk [1]	12%	25%	48%	69%

Conclusions: This study suggests that this index over estimated the risk of developing ASC in a South Asian population, which would affect the utility of this index in SA patients where more extensive but less aggressive disease has been demonstrated. Larger studies are needed to confirm these findings.

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Development and reliability of the new endoscopic virtual chromoendoscopy score: the PICaSSO score (the Paddington International Virtual ChromoendoScopy ScOre) in ulcerative colitis

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Background: Endoscopic inflammation and healing are important therapeutic endpoints in ulcerative colitis (UC). We developed and validated a new electronic virtual chromoendoscopy (EVC) score which could reflect the full spectrum of mucosal and vascular changes including mucosal healing in UC.

Methods: Eight participants reviewed a 60-minute training module outlining the three different i-scan modes demonstrating the entire spectrum of inflammatory mucosal and vascular changes in UC. Performance characteristics in endoscopic scoring and predicting the histologic inflammation with EVC (iscan) by using 20 video clips before (pre-test) and after (post-test) were evaluated. Exploratory univariate factor analysis was performed on "PICaSSO" score covariates for mucosal and vascular score separately. Subsequently a proportional odds logistic regression model for the prediction of histological scores were analysed

Results: The inter-observer agreement for Mayo endoscopic score in the pre-test (k=0.85, 95% CI: 0.78–0.90) and the post test (k=0.85, 95% CI: 0.77–0.90) evaluation were very good. This was also true for UCEIS in the pre and post-test score inter-observer agreement (k=0.86, 95% CI: 0.77–0.92 and k=0.84, 95% CI: 0.75–0.91). The inter-observer agreement of the PICaSSO endoscopic score was very good in the pre and post-test evaluations (k=0.92, 95% CI: 0.87–0.96; k=0.89, 95% CI: 0.84–0.94). The accuracy of the overall PICaSSO score in assessing histological abnormalities and in-

Figure 1 : The Paddington international virtual chromoendoscopy score (PICaSSO) in UC

PICaSSO MUCOSAL ARCHITECTURAL	
•	0 - No mucosal defect
-	A: Continuous/regular crypts
-	B: Crypts not visible (scar)
-	C: Discontinuous and/or dilated/elongated crypts
•	I - Micro erosion or cryptal abscess
•	1: discrete
•	2: patchy
•	3: diffuse
•	II - Erosions size <5 mm
•	1: discrete
•	2: patchy
•	3: diffuse
•	III - Ulcerations size >5 mm
•	1: discrete
•	2: patchy
•	3: diffuse
PICASSO VASCULAR ARCHITECTURE	
•	Vessels without dilatation
-	A: Roundish following crypt architecture
-	B: Vessels not visible (scar)
-	C: Sparse (deep) vessels without dilatation
•	I Vessels with dilatation
-	A roundish with dilatation
-	B crowded or tortuous superficial vessels with dilatation
•	II Intramucosal bleeding
-	A roundish with dilatation
-	B crowded or tortuous superficial vessels with dilatation
•	III - Luminal bleeding
•	A roundish with dilatation
•	B crowded or tortuous superficial vessels with dilatation

flammation by Harpaz score was 57% (95% CI: 48–65%), by RHI 72% (95% CI: 64–79%) and by ECAP (full spectrum of histologic changes) 83% (95% CI: 76–88%).

Conclusions: The EVC score "PICaSSO" showed very good inter-observer agreement. The new EVC score may be used to define the endoscopic findings of the mucosal and vascular healing in UC and reflected the full spectrum of histological changes.

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A snap-shot review of small bowel capsule endoscopy in the setting of inflammatory bowel disease

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Background: Evaluating small bowel involvement in the diagnosis of Crohn's Disease, CD, is part of the standard work up for all new diagnosis. While this previously took the form of radiological imaging by CTE, MRE or small bowel follow through, small bowel capsule endoscopy, SBCE, now offers an additional means to diagnose and evaluate small bowel Crohn's Disease.

The aim of the study was to review the diagnostic yield of SBCE in the setting of IBD.

Methods: As part of a small bowel capsule endoscopy service review in Tallaght hospital, to date, 286 SBCE for diagnosis/assessment of small bowel CD have been included. Patients were categorised as known CD or suspected CD. Small bowel pathology was recorded. Rates of capsule retention and subsequent 30 day retention rates were analysed.

Results: The total cohort comprised of 286 SBCEs. Demographics included; median age – 41 years, female – 174 (60.8%). 48 and 238 patients had CD and suspected CD, respectively. 108/286 SBCEs were reported as normal which comprised of 14.5% of CD cohort compared to 42.4% of suspected CD patients. Positive findings included – ileitis 94/286 (32.8%), strictures 17/286 (6%), fistulas 3/286 (1%), gastritis 43/286 (15%), non-specific enteritis 41/286 (14%), polyps 6/286 (2%), submucosal lesion 4/286 (1%) and fresh blood 4/286 (1%). 16 (2%) capsules in total were retained at time of reporting – 9 were retained in the small bowel and 7 were retained in the stomach. 8/16 (50%) had a previous successful patency capsule. Subsequent follow up available of 12/16 patients confirmed subsequent spontaneous passage of capsule.

Conclusions: The diagnostic yield for SBCE is higher in patients with known CD than suspected CD patients. However, over 50% of patients with suspected CD had pathology on SBCE. The rate of capsule retention was relatively low with no retrieval of capsule required by either double balloon endoscopy or laparotomy to our knowledge. SBCE is a useful and safe tool for the assessment of small bowel pathology in addition to radiological imaging.

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Comparative accuracy of US versus MRI and colonoscopy in assessing disease activity and complications and influencing the decision-making process in Crohn's disease

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Background: Bowel ultrasound (US) and MRI are accurate in assessing disease activity and complications in Crohn's disease (CD) patients. The comparative accuracy of US versus MRI + endoscopy in assessing disease activity and complications and influencing the decision-making process in Crohn's disease is unknown.

Methods: Ileo-colonic CD consecutive patients seen in a tertiary referral Center (Humanitas Research Hospital, Milan, Italy) were prospectively assessed by magnetic resonance imaging (MRI), colonoscopy (CS), and US, within 1 week. Sensitivity, specificity, accuracy, positive and negative predictive values (PPV and NPV) of US in assessing localization and extension, bowel wall enhancement (increase of vascularization at color Doppler), bowel wall thickening (>3 mm), strictures (narrowing of the lumen), fistulas and abscesses, and active disease (presence of ulcers at colonoscopy) were calculated using CS in combination with MRI findings as a reference standard. Two independent blinded IBD specialists reviewed separately MRI and US findings, and were asked to decide the therapeutic strategy (continue therapy vs. optimize/change therapy). Kappa agreement between MRI and US was also investigated.

Results: Forty-one consecutive CD patients, irrespectively of disease activity and current therapy, were enrolled. Twenty-five patients had active disease as assessed by MRI and colonoscopy (60.9%), 16/41 (39.1%) had CD-related complications. Sensitivity, specificity, accuracy, PPV and NPV of US are showed in Table 1. Based on US findings alone when compared to MRI and CS, the management of IBD patients (continuing or changing/optimizing therapy) was judged accurate in 85% of patients compared to 75% managed by MRI only (p<0.001). Agreement between MRI and US findings was 80% (p<0.001).

Table 1. Performance of US in assessing disease activity and complications

Parameter	Sensitivity	Specificity	Accuracy	PPV	NPV
Localization/Extension	0.80	0.93	0.85	0.95	0.75
Bowel wall enhancement	0.80	0.84	0.82	0.84	0.80
Bowel wall thickening (>3 mm)	0.70	1.0	0.92	1.0	0.91
Strictures	0.76	0.79	0.78	0.72	0.82
Fistulas	1.0	0.97	0.97	0.66	1.0
Abscesses	1.0	0.95	0.95	0.35	1.0
Active disease	0.70	1.0	0.92	1.0	0.91

Conclusions: US was as accurate as the combination CS + MRI in assessing disease activity and complications. Therapeutic decisions based on US findings alone were appropriate in the vast majority of CD patients. US is a non-invasive, easy-to-use tool to manage CD patients in clinical practice.

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Short and long-term surgical outcomes and pouch function following proctocolectomy and pouch formation in paediatric ulcerative colitis: a multicentre-retrospective cohort study from the Porto IBD working group of ESPGHAN

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Background: We aimed to evaluate contemporary surgical complications rate and pouch function following proctocolectomy and ileal pouch anal anastomosis (IPAA) in children with ulcerative colitis (UC)/inflammatory bowel disease unclassified (IBDU) undergoing the procedure before 18 years of age. Outcomes related to pouchitis are reported separately.

Methods: This was a multicentre longitudinal retrospective study involving 17 paediatric IBD centres from the Porto group of ESPGHAN. An electronic REDcap system was used to collate explicit baseline characteristics, clinical, management and surgical data, including short and long term outcomes.

Results: A total of 129 children after IPAA were included (50% male; 93% UC and 7% IBDU). Mean age at diagnosis was 10.5±4.2 years and median disease duration to colectomy was 17 months (IQR 8–36 months). Median post-operative follow-up was 40 months (IQR 26–72 month). Nineteen patients (15%) underwent proctocolectomy before age 10. A two-staged procedure was performed in 76 patients (59%), 3-stage in 45 (35%) and one-stage in 8 (6%). 48 patients (38%) underwent a laparoscopic assisted colectomy. Median number of bowel movements (BM)/24 hours one year after surgery was 5 (IQR 4–6; range 2–12). 42 patients (40%) had nocturnal BM one year post surgery even when pouchitis-free, of whom 48% had up to 1 nocturnal BM and 52% had greater than 1. One month and one year post-IPAA, 31 (28%) and 31 (28%) children used anti-diarrheal medication, respectively. Physician global assessment (PGA) of overall pouch performance was rated good or excellent in 71 (66%) patients at 1 month, 79 (71%) at 1 year post-IPAA, and 86 patients (74%) at last follow-up. Neither number of BM nor PGA were associated with surgical technique (lap/open) or with age <10 at colectomy.

Within 1 month after colectomy, 41 patients (34%) had surgical complications. The most common complications were small bowel obstruction in 14 (12%) and wound infection in 9 patients (7%). Within 1 month of pouch formation 33 patients (30%) had surgical complications. There was no association between surgical com-

plications and surgical technique (lap/open). Patients with colectomy before age 10 had significantly more surgical complications at 1 year post IPAA. Pouch related outcomes included pouch stricture in 14 (11%) patients, pouch fistula in 12 (9%), prolapse in 3 (2.3%), pelvic floor in one (0.8%) and anal sphincter dysfunction in 1 (0.8%).

Conclusions: Surgical complications occurred in many children undergoing IPAA for UC/IBDU. Age younger than 10 years at proctocolectomy was associated with higher long term surgical complications but comparable pouch function. Pouch function was rated excellent or good in the majority of patients at last follow-up (74%).

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Children born to mothers with inflammatory bowel disease – Is there any risk for newborns' complication and development during the childhood?

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Background: Inflammatory bowel disease (IBD-Crohn's disease [CD], ulcerative colitis [UC]) has been associated with increased risk of adverse birth outcome. Limited data are available on the postnatal development in children from IBD mothers. Our aim was to evaluate the effect of disease activity and medical therapy on pregnancy and birth outcome and to compare the prevalence of preterm birth, congenital malformations and postnatal development between children from IBD vs. healthy mothers.

Methods: Data on medical therapy at conception and during pregnancy, data on pregnancy, delivery and newborn complications were assessed retrospectively. Data on postnatal development were retrospectively collected and physical condition of each child was evaluated by a pediatrician. Children from healthy mothers composed the control group. Body composition analysis was performed in every child.

Results: Fifty-six pregnancies of 36 women diagnosed with IBD were studied. Active disease was detected in 8 pregnancies during the first, in 5 cases during the second and 6 cases during the third trimester. IBD-related medication was used at conception in 39 cases. Pregnancy complications occurred in 13 cases. Newborn complications were significantly more common in case of active disease in the 3rd trimester ($p=0.033$ and $p=0.029$ in CD and UC) and in case of steroid use in the 3rd trimester ($p=0.031$). Thirty-six children born to IBD mothers and 16 age-matched healthy controls have been included in the second part of the study. Considering children from IBD mothers, congenital malformations developed in 5 newborns, low birth weight in 4 infants, infectious complication in 7 infants. In control group, none of these occurred. Considering postnatal development, 6 children of IBD mothers developed chronic disease. IBD occurred in one child. The mean growth percentile was 65.6%, and the mean weight percentile was 64.2%. Mean InBody score was 87.6 points (max: 100 points). In control children, 1 suffered from mitral prolapsed, 1 developed asthma. Mean growth percentile was 71%, and the mean weight percentile was 66%. Mean InBody score was 88.1 points. Statistically no difference was found between children with IBD mother vs. controls regarding to growth patterns, gestational

ages, newborn complications, frequency of infectious and chronic diseases, food allergies and InBody scores.

Conclusions: Our results revealed complications in 23% of the IBD pregnancies. Disease activity and steroid use during the 3rd trimester proved to be predictive to newborn complications. Considering postnatal development, no difference was seen between children born to IBD mothers compared to controls despite the higher number of newborn complications.

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Therapeutic drug monitoring of infliximab and adalimumab for detection of patients at risk of loss of response in inflammatory bowel disease

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Background: Due to the high cost of therapeutic drug monitoring (TDM) of infliximab (IFX) and adalimumab (ADA) in inflammatory bowel disease, many algorithms have been proposed to optimize the analysis. Most of them are based on the determination of drug levels and antibodies if patients show loss of response (LOR).

As well as patients who develop drug antibodies, other patients have drug serum levels below the therapeutic range and may present a relapse without evidence of antibodies. For economic impact analysis, it is of vital importance to know the exact percentage of patients that are at risk of LOR due to low serum drug levels, even without the presence of drug antibodies.

The aim of this study was to calculate the percentage of patients at risk of loss of response due to low concentrations of IFX or ADA, analyzing all treated patients of a population, not only those who had experienced LOR.

Methods: A cross-sectional study of a cohort of patients with IBD was carried out. All patients who visited the hospital to receive IFX or ADA were consecutively included. Serum drug concentrations and drug antibodies were measured by an ELISA technique. Patients with IFX levels <3 mcg/mL and ADA <5 mcg/mL were considered at risk of LOR.

Usually, if IFX is present in a sample, antibodies detection could be altered. Therefore, negative antibodies results in these samples are often classified as inconclusive. Anyway, patients with low serum drug levels due to inter-individual pharmacokinetic variations or drug antibodies, are at increased risk of LOR. Results are shown in percentages.

Results: The study included 100 patients, 79 patients with Crohn's disease and 21 with ulcerative colitis, 68 treated with IFX and 32 with ADA. Mean age was 39 [17–69] years. Azathioprine immunosuppressive therapy was used by 40% of the patients.

In the IFX group, 40 patients (58.8%) were at risk of LOR whereas in the ADA group 4 (21.9%) were at risk of LOR. Drug antibodies were detected in 25.0% and 28.6% of the patients in IFX and ADA groups respectively.

The total number of patients with drug serum level below the cutoff without detectable antibodies was 30 in the IFX group and 5 in the ADA (75.0% and 71.4% of patients out of therapeutic range respectively). Only 2 patients with azathioprine developed antibodies.

The proportion of patients detected at risk of loss of response was high (44.1% in IFX group and 15.6% in ADA group).

Conclusions: The percentage of patients at risk of LOR is high, mainly in those treated with Infliximab. Although not always resulting in clinical deterioration, there is a significant number of patients who could benefit from pharmacokinetic monitoring, helping to optimize dosage and prevent relapses.

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Factors at diagnosis associated with disabling disease course in Crohn's disease

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Background: The recognition that chronic uncontrolled inflammation in Crohn's disease (CD) results in poor outcomes has led to the belief that early intervention with immunosuppressive (IS) and biologic therapy is associated with an increased probability of mucosal healing, early sustained remission without steroids and reduction in the need for surgery and hospitalisations. Given the risks of IS therapy, efforts are currently made to predict at diagnosis the subsequent behaviour of the disease, so that only patients with a predisposition for a disabling disease course should be considered for early intensive therapy.

The aim of our study was to identify at diagnosis factors predictive of a subsequent disabling course in CD.

Methods: All patients with a non-stricturing and non-penetrating CD newly diagnosed at our department during January 2009-December 2012 were included. Data regarding demography, phenotype, endoscopy and biochemistry at diagnosis was analyzed. The endpoint was disabling disease, previously defined as sustained disabling symptoms, need for hospitalisation for flare-up or complication (stenosis, abscess or fistulae) of the disease, need for repeated courses of steroids, need for IS therapy and need for intestinal and/or perianal surgery. Statistical analysis: X², Student's t-test, Kaplan-Meier survival curves, Log-rank test, Cox regression. Significance: $p < 0.05$.

Results: Fifty-nine patients were included, 50.8% (n=30) were men, with a mean age of 36 years. Disabling disease occurred in 76.3% (n=45), with a cumulative risk of 76% at 5-years of follow-up. Among the parameters analysed, factors significantly associated with disabling disease included younger ages ($p=0.006$), small-bowel location ($p=0.003$), higher C-reactive protein (CRP) ($p=0.007$), involvement of rectum ($p=0.009$) and severe endoscopic lesions ($p=0.03$). In multivariate analysis, none of the above parameters was independently associated with disabling disease. Conversely, factors significantly associated with time to disabling disease included younger ages ($p=0.008$), small-bowel location ($p=0.004$), colonic location ($p=0.04$), higher CRP ($p=0.01$), steroids requirement at diagnosis ($p=0.03$), perianal disease ($p=0.04$), rectal involvement ($p=0.01$) and severe endoscopic lesions ($p=0.02$). Of these, perianal disease ($p=0.01$) and CRP ($p=0.03$) were independent predictive factors of early disabling disease.

Conclusions: Age of onset, small-bowel location, CRP, rectal involvement and severe endoscopic lesions were associated with disabling disease. Perianal disease and CRP independently predict an early disabling course.

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Does colonoscopy alter the post-procedural fecal calprotectin results in Crohn's disease patients with ileocecal resection?

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Background: For closer follow up in the postoperative (postop) setting there is a tendency to use fecal calprotectin (FC) rather than colonoscopy in resected Crohn's Disease (CD) patients. The aim of the study was to find out whether there was a significant change between pre and post-procedure FC results, which might influence our clinical practice of stool sampling time.

Methods: For this purpose we prospectively gathered the data of CD patients who were referred to our endoscopy unit in the postop setting. Demographic data like age, age at diagnosis, and operation, sex, disease duration, postop follow up time, smoking status and procedure related factors like insertion-withdrawal time and total duration, Rutgeerts score, pre and post-procedure FC levels were all noted. All patients gave a stool sample 24 hours before and after colonoscopy and all of them had their bowel prepared with the same regimen using PEG. Biopsies were taken in none of the procedures as all of the patients had a firm diagnosis of CD and as no additional lesions were noted. FC was determined via ELISA.

Results: A total of 40 ileocecal resected CD patients (20F/20M) were included, their mean age being 42.95 ± 12.4 years, disease duration 143.63 ± 83.94 mo. and postop. follow up time 80.9 ± 70.8 mo. The median pre and post procedure FC levels were $144 \mu\text{g/ml}$ and $113 \mu\text{g/ml}$ disclosing no significant difference (Fig. 1) and no relation with colonoscopy duration. Seventeen of 40 patients (42%) had endoscopic relapse, and when relapses and non-relapses were analyzed separately the difference between pre- and post-colonoscopy FC levels remained insignificant. Of note was that four of 23 patients (17%) in remission and four of 17 patients with relapse (24%) had changing FC results from negative to positive or vice versa after colonoscopy. In the whole group, when FC cut-off was $50 \mu\text{g/g}$ 8 of 40 patients (20%) either changed to positive (6/8) or to negative (2/8) after the colonoscopy. When cut off was $100 \mu\text{g/g}$ nine of 40 (22%) patients' FC changed either to positive (4/40) or to negative (5/40) after the procedure.

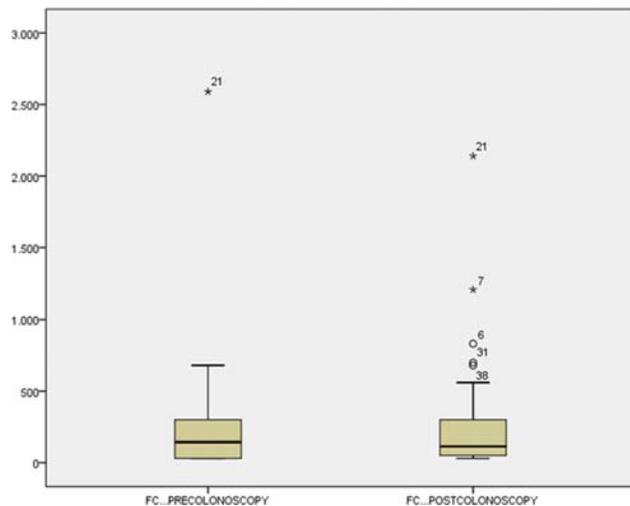


Figure 1. Pre and post colonoscopy FC levels.

Conclusions: The present study shows that pre and post-colonoscopy FC levels are not significantly different. However, one fifth of pa-

tients with alternating results using different cut-offs may suggest that it would be more appropriate not to collect stool samples immediately after colonoscopy for FC determination.

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Quantum blue® adalimumab: development of the first point of care rapid test for therapeutic drug monitoring of serum adalimumab levels

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Background: Adalimumab is a human monoclonal antibody directed against tumor necrosis factor alpha (TNF α) used for the treatment of inflammatory diseases like Crohn's Disease (CD) and Ulcerative Colitis (UC). For efficient treatment trough levels of adalimumab need to be adjusted within a therapeutic window, which is 5 to 10 $\mu\text{g/mL}$ (Moos et al., 2015). A rapid test allows a much faster reporting of trough levels, providing a great advantage over test formats that need samples to be send in to a central lab. Here we report current results of the completed Quantum Blue® Adalimumab test optimization. The test is now under validation.

Methods: The sandwich lateral flow immunoassay uses a TNF α coated gold label and a highly specific monoclonal antibody to detect adalimumab in a diluted human serum sample. Sensitivity of the assay was estimated via Limit of Detection (LoD) and Limit of quantification (LoQ) according to CLSI EP17-A2. Moreover the assay was evaluated regarding cross-reactivity with other therapeutic antibodies targeting TNF α , influence of rheumatoid factors (RF) and high dose hook effect. A method comparison was performed using a commercial available ELISA (RIDASCREEN® ADM Monitoring, Art. No. G09043, R-Biopharm, Darmstadt, Germany) to compare the trough level results of 40 adalimumab treated patients.

Results: The current Quantum Blue® Adalimumab test allows analysis of serum samples within 15 minutes. The samples are diluted 1:20 in chase buffer before application on a test cassette (volume 80 μL). The readout is performed with the Quantum Blue® Reader resulting in concentration levels of adalimumab in $\mu\text{g/mL}$.

The test exhibits a LoD of 0.2 $\mu\text{g/mL}$ and a LoQ of 0.69 $\mu\text{g/mL}$. These data ensure a measuring range of 1 to 35 $\mu\text{g/mL}$ of adalimumab patient samples. No high dose hook effect was detected for samples containing up to 1000 $\mu\text{g/mL}$ adalimumab. Other therapeutic TNF α blockers, like infliximab and golimumab, showed no cross-reactivity with the Quantum Blue® Adalimumab test, furthermore RFs showed no influence on correct measurement of adalimumab at the tested concentrations. The method comparison revealed a slope of 1.12 and a regression coefficient (r^2) of 0.90 (Passing-Bablok). A Bland-Altman analysis showed a bias of 1.88% confirming the overall excellent correlation of the two methods.

Conclusions: The BÜHLMANN Quantum Blue® Adalimumab assay enables the quantitative determination of adalimumab trough level in serum with time to result of only 15 minutes. The developed assay allows to measure adalimumab over a wide range. Hence, it represents a valuable tool for the clinician to assess the adalimumab trough level.

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Ulcerative colitis – presentation during pregnancy or puerperium

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Background: Even though ulcerative colitis (UC) frequently affects young women in reproductive age, it is rare to observe its first presentation during pregnancy. The aim of this study was to assess the characteristics and natural history of UC in patients who had their first presentation during pregnancy or puerperium.

Methods: We performed a retrospective unicentre case-control study, with inclusion of UC patients whose diagnosis was made during pregnancy or in the post-partum period. We used 44 women whose diagnosis was made during reproductive age but without any relationship to pregnancy as a control group (mean age at diagnosis 28 \pm 6.6 years). Demographic, clinical and treatment data was collected through access to electronic medical records. Statistical analysis was performed with SPSS® 20.0.

Results: We included as cases 9 women with a mean age at diagnosis of 28 \pm 4.7 years (range: 16.7–37.2 years). Concerning extension according to Montreal classification, 1 patient (11.1%) had proctitis, 2 patients (22.2%) distal colitis and 6 patients (66.7%) extensive colitis. Three cases occurred in former smokers but in only 2 the cessation of smoking occurred in the months previous to diagnosis.

There was a statistically significant difference regarding smoking status between cases and controls (smokers/former smokers: 50% in cases vs 11.9% in controls; $p=0.05$). Even though the differences weren't statistically significant, we observed a greater proportion of extensive colitis in cases comparatively to controls [66.7% vs 36.4%, $p=\text{non-significant (NS)}$]. Cases also had a greater need of corticosteroids at diagnosis, even after adjustment for confounding variables (OR 6.3; IC95% 1.1–35.9; $p=0.04$), which may indicate a greater severity of the disease at presentation. However, we found no differences between cases and controls in the need of corticosteroids (77.8% vs 50%, $p=\text{NS}$), immunomodulators (11.1% vs 15.9%, $p=\text{NS}$) or biologic treatment (22.2% vs 11.4%, $p=\text{NS}$) during follow up.

Conclusions: Smoking status, namely smoking cessation, appears to have a relationship with the risk of presentation of UC during pregnancy or puerperium, which is in agreement with the known relationship of tobacco and UC described in the literature. Even though the presentation of the disease in this period appears to be more severe, this doesn't seem to affect its natural history, as represented by the need of a more aggressive treatment.

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Usefulness of a multidisciplinary approach combining both rheumatology and gastroenterology for the assessment and treatment of inflammatory bowel disease patients

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Background: More than one third of inflammatory bowel disease patients (IBD) present extraintestinal manifestations, with articular manifestations being the more common, clearly the more incapacitating and which more alter the quality of life of IBD patients. These patients could benefit from a multidisciplinary approach for quicker diagnosis and for optimizing treatments. The aim of the study was to evaluate the impact of a multidisciplinary approach carried out by

both a rheumatologist and a gastroenterologist in the management of these patients.

Methods: From April 2015 to October 2016, all IBD patients reporting articular pain to the IBD-dedicated gastroenterologist were referred to an experienced rheumatologist. The day of the consultation a multidisciplinary committee with a rheumatologist and a gastroenterologist evaluated and discussed in all patients their possible diagnosis and potential changes in their treatment. Assessment was made according to current guidelines and data recorded in a common database regarding the reasons why patients were remitted from IBD, their rheumatologic diagnosis and all changes implemented in their treatments. Results are shown in percentages.

Results: 82 consecutive IBD patients were remitted from the IBD Unit and analyzed by the committee. Mean age 38 years (ranging from 18 to 73). Most patients were women (73%), 19% were smokers and 23% former smokers. 49% had Crohn's disease and 51% ulcerative colitis. The main causes for derivation from IBD were a suspicion of inflammatory arthropathies in 43% and of arthromyalgias in 40%. The more frequent diagnosis after the rheumatology consultation and the committee meeting were inflammatory arthropathies associated with IBD in 41% (52% presented axial arthropathies and 48% presented peripheral arthropathies) and fibromyalgia in 15%. Regarding treatment changes, after the multidisciplinary committee with a rheumatologist and a gastroenterologist, changes were made in 18 patients (22%). In 7 patients methotrexate was added in patients with biologic treatment (in some of them patients were in monotherapy, but in others the drug was introduced for replacing thiopurines). In 6 patients sulfasalazine was introduced instead of mesalamine. In the other patients either other biologics like ustekinumab were introduced or the doses of anti-TNF were optimized in accordance with rheumatologic schedules.

Conclusions: A multidisciplinary consultation combining inflammatory bowel disease and rheumatology allows both an earlier detection of inflammatory arthropathies associated with IBD and earlier changes in treatment, thereby helping to optimize the hospitality resources. Fibromyalgia is common among IBD patients and should not be confused with inflammatory arthropathies.

P286

Evaluation of fecal S100A12 in patients with inflammatory bowel disease

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Background: The diagnosis and evaluation is quite complex for inflammatory bowel disease (IBD). An ideal, noninvasive marker is quite urgent for IBD. Fecal S100A12 is a member of the S100 protein family and secreted by activated neutrophils. We aim to evaluate it as a biomarker for IBD patients in China.

Methods: Fecal S100A12 was measured in 18 Crohn's disease (CD), 21 ulcerative colitis (UC), and 17 healthy controls (HC). Diagnostic value was evaluated by receiver operating characteristic (ROC) analysis in comparison with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The correlation between fecal S100A12 and clinical characters were also evaluated thereby.

Results: There are significantly increase in both UC and CD when compare to HC ($p < 0.01$, $p < 0.01$; respectively). The fecal S100A12 is correlated with fecal occult blood ($p = 0.02$, $r = 0.55$) in UC. However, the fecal S100A12 is correlated with disease duration, ALB, and PLT in CD ($p = 0.01$, $r = 0.53$; $p < 0.01$, $r = -0.65$; $p = 0.04$, $r = 0.45$.

respectively). There are no correlation between fecal S100A12 and other clinical characters.

Conclusions: Fecal S100A12 is valuable in distinguish IBD patients with HC. However, the sensitivity and specificity is limited when compared with western countries. The correlation between S100A12 and clinical characters is limited as well. More research need to do to explore it in Chinese patients.

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Lipid peroxidation levels and antioxidant status in serum, plasma and saliva of patients with active and inactive Crohn's disease

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Background: The destructive effects of oxidative stress has been proposed as a mechanism underlying the pathophysiology of Crohn's disease (CD). Lipid peroxidation induced by oxidative stress is indicated by malonyldialdehyde (MDA), glutathione (GSH) and ferric reducing ability of plasma (FRAP) as antioxidant systems protect from the pathological effects of free radical activity, and can limit the tissue injury. The aim of the study was to evaluate in serum, plasma and saliva the redox homeostasis based on lipid peroxidation factor MDA and antioxidants GSH and FRAP levels in patients with active and inactive CD and in healthy controls.

Methods: We enrolled 58 patients with CD (32 male, 26 female), age 18–63 years, 35 with active and 23 with inactive CD, and 25 age- and gender-matched healthy individuals. Patients with CDAI < 150 were considered inactive, and patients with CDAI > 150 were considered as active CD. Patients were chronically treated with azathioprine according to the ECCO guidelines. The blood samples (both serum and plasma) and unstimulated whole saliva were obtained in patients of the three groups, however, in patients with active CD samples were taken prior to the start of anti-inflammatory treatment. MDA, GSH and FRAP levels were measured in serum, plasma and saliva. Routine blood morphology and CRP levels in serum were also investigated in the hospital laboratory.

Results: MDA levels were significantly increased in serum (median: 12,174 nmol/g of protein), plasma (14,135 nmol/g) and saliva (28,051 nmol/g) in patients with active CD as compared to inactive CD and controls (respectively, 2,638, 2,851, 4,467 nmol/g; $p < 0.0001$; Kruskal-Wallis test), and positively correlated with CDAI ($r = 0.740$, $p < 0.0001$; Spearman's correlation). GSH and FRAP levels were significantly decreased in serum, plasma and saliva in both CD groups as compared to controls, and negatively correlated with CDAI (GSH: $r = -0.775$, $p = 0.0001$; FRAP: $r = -0.800$; $p < 0.0001$).

Conclusions: Increased level of MDA and decreased levels of GSH and FRAP in patients with active CD and to lower extent in inactive CD as compared with healthy controls underline the importance of oxidative stress in the physiopathology of CD. Due to the high availability of saliva samples

P288 Treating beyond symptoms in inflammatory bowel disease (IBD): the Kent IBD Nurse Experience with the Steroid assessment tool

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Background: Treatment for IBD has two main goals – eliminate symptoms of active disease and maintain remission. For over 50 years clinical studies demonstrate that steroids help induce remission in CD and UC. However, further research demonstrates steroids do not modify disease, they are not able to main remission, only one in three patients have mucosal healing and long-term use can increase adverse reactions.

In 2014, in an effort to optimise the use of steroids in the treatment of IBD in the UK, a collaboration between 14 UK based IBD consultants and nurses and AbbVie resulted in the development of a secure web-based steroid assessment tool SAT, enabling clinicians to monitor steroid use within their clinic setting. The results of this initial study were presented at ECCO 2016 and the British Society of Gastroenterology congress 2016.

Methods: As with the National Steroid Audit, the Kent Steroid Audit used the SAT (Steroid Audit Tool) to collect the data:

In Kent, 3 IBD nurses were keen to work with AbbVie on a collaboration using the SAT. In contrast to the national steroid audit that audited 8 university hospitals and 3 district general hospitals, the Kent IBD audit audited 4 district general hospital.

The 6 district hospitals were selected as each nurse was able to run IBD clinics at each hospital.

Results: 500 IBD patients in Kent were input into the SAT.

Similarly to the National Steroid Audit, a larger proportion of IBD patients in Kent were diagnosed with UC vs. CD.

A higher proportion of IBD-Unknown patients (8%) were reported in Kent steroid audit vs. the National Steroid Audit (3%). Overall, 40% of Kent IBD patients entered into the SAT had received an oral corticosteroid in the past 12 months.

Steroid excess for Kent IBD patients: 28%, 6% of patients had been given 6 or more courses of steroids within 12 months.

National Steroid Audit reported steroid excess: 13.8%.

Conclusions: 500 Kent IBD patients were entered into the SAT which showed 40% of them received an oral corticosteroid in the past 12 months.

The Kent IBD Steroid Audit met its primary objective and reports that within Kent the IBD population in steroid excess of ECCO guidance is more than double the national level 28% in Kent vs. 13.8% nationally.

The SAT also identified inconsistent bone protection between hospital trusts, possibly due to IBD patients hoarding steroids and not being aware the need to take a bone protection agent, or physicians not prescribing a bone protection agent along side an oral steroid. A Kent IBD pathway has been formalised to incorporate the correct steroid dosages and monitoring. A greater awareness through patient and healthcare professional education has been stated in Kent.

P289 Outcome of endoscopic ally resected dysplastic lesions in ulcerative colitis

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Background: For a long time, dysplastic lesions in ulcerative colitis were only treated by surgery. Recent guidelines recommend the complete endoscopic resection of dysplastic lesions in ulcerative colitis.

The aim of this study was to determine the outcome of dysplastic lesions resected endoscopically in ulcerative colitis.

Methods: in this prospective study between January 2008 and January 2015; dysplastic lesions detected in patients with longstanding ulcerative colitis were assessed for their resectability, then when it was possible were resected. The patients were followed, and an endoscopic control was done at 6 months than every one year.

Results: 36 dysplastic lesions were identified in 25 patients; 5 lesions were judged not resectable and referred to surgery. 31 lesions were resected in 21 patients: 22 low grade dysplasia, 7 lesions indefinite for dysplasia, and 2 high grade dysplasia.

18 patients (85.7%) had endoscopic control: mean 2.8 (maximum: 5 minimum: 1).

2 patients refused next colonoscopy, one patient was not controlled because of a bad bowel preparation for 4 times.

In 13 patients (72.2%) no dysplasia was detected after a mean follow up of 30.16 months (marges: 7.56–62.5). Neoplastic lesions were found in 5 patients (27.7%): one adenocarcinoma of the sigmoid detected in a woman that have had a high grade dysplasia resected in the sigmoid; in 3 patients new dysplastic lesions localized in other segments of the colon than those initially resected. In one patient a serrated rectal adenoma was found in the same place where was resected a serrated adenoma, reflecting an incomplete resection.

Conclusions: Our results confirm that a complete endoscopic resection may be sufficient in dysplastic lesions occurred in ulcerative colitis. Nevertheless a closer follow up is necessary because these patients may develop newer neoplastic lesions.

P290 Evaluation of patients with retained patency capsule

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Background: Capsule endoscopy (CE) is a non-invasive method for examining the small bowel. Nevertheless capsule retention is the most significant complication of these devices and may occur in any location of the gastrointestinal tract. Patency capsule (PC) was developed to avoid this risk of capsule retention. The aim of this study was to characterize the patients that presented PC retention.

Methods: Retrospective study of patients with PC retention between 2010–2014. The main indications for PC were Crohn's disease (CD), subocclusive symptoms, NSAID use or previous abdominal surgery.

Results: Between 2010–2014 there were performed 433 PC, of which 119 (28%) patients had PC retention. The most frequent indication for CE study was CD staging (45%). The 119 patients included were 65% women, mean age 43±17 years, 30% had history of abdominal surgery and the mean follow-up was 20±18 months. Previously, 27% had performed CT/MRI enterography, with bowel wall thickening in 53%, evidence of luminal narrowing/stricture in 28% cases

and in 19% no lesions. PC retention was symptomatic in only 5% of patients, all with CD ($p=0.006$), which was self-limited and resolved without surgery. After negative PC test, other 32% patients performed CT/MRI enterography with bowel wall thickening in 42%, evidence of luminal narrowing/stricture in 18% cases and in 40% no lesions. During follow-up, 9% of patients were submitted to intestinal resection surgery (6 cases of CD, 4 of intestinal neoplasia and 1 of diverticulitis), 3% were diagnosed with small bowel tumor and 2% died from neoplasia related complications.

Conclusions: The PC test has proven to be a safe examination, with reduced frequency of symptomatic retention, which occurred only in patients with CD. Most patients had lesions on CT/MRI enterography study and some needed to perform surgery. The incidence of tumors was relevant and should always be considered in the differential diagnosis.

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Proteinase 3-antineutrophil cytoplasmic antibodies (PR3-ANCA) would be a predictive biomarker for the clinical course of ulcerative colitis

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Background: Antineutrophil cytoplasmic antibodies (ANCA) are antibodies directed against cytoplasmic antigens localized in granules of neutrophils and monocytes which play a crucial role in the pathogenesis of ulcerative colitis (UC). In this study, we evaluated whether ANCA is a useful serologic-biomarker in the clinical course of UC patients.

Methods: 58 UC patients, in whom proteinase 3 (PR3)- and myeloperoxidase (MPO)-ANCA were evaluated at Kitano hospital from October 2007 to June 2016, were analyzed, retrospectively. Clinical and endoscopic activities were evaluated with Lichtiger index and Mayo score, respectively. The positivity of PR3-ANCA and MPO-ANCA were defined to be more than a titer of 1.0 (U/ml). Clinical remission (CR) was defined as less than 5 points of Lichtiger index, and endoscopic mucosal healing (MH) was defined as Mayo-0 or 1, respectively. We analyzed the ratio of positive for PR3- and MPO-ANCA in UC patients, and also evaluated the differences of clinical-features and -course of UC between ANCA-positive and -negative group.

Results: Out of 58 UC-patients, 37 (63.8%) and 6 (10.3%) were positive for PR3-ANCA and MPO-ANCA, respectively. All the patients positive for MPO-ANCA were also positive for PR3-ANCA.

The ratio of patients with extensive or left-sided colitis in the PR3-ANCA-positive group was significantly higher than that in the PR3-ANCA-negative group (97.3% and 66.7%, respectively; $p<0.01$). On the other hand, there was no significant difference in clinical characteristics at evaluating ANCA, such as Lichtiger index, serum level of C-reactive protein (CRP) and albumin between the PR3-ANCA-positive group and -negative group.

However, regression analysis demonstrated that the titer of PR3-ANCA was significantly related with the serum level of albumin at evaluating ANCA ($r=0.54$, $p<0.01$), although there was no significant relationship between the titer of PR3-ANCA and clinical-markers, such as Lichtiger index ($p=0.59$), and the serum CRP level ($p=0.08$).

The ratio of patients with history of intensive therapies such as immunomodulators (IM) and anti-tumor necrosis factor (TNF)-alpha agents in the PR3-ANCA-positive group was significantly higher

than that in the PR3-ANCA-negative group (IM; 56.8% and 23.8%, respectively; $p=0.03$, anti-TNF-alpha agents; 37.8% and 4.8%, respectively; $p<0.01$).

In the subsequent clinical course, the ratio of UC-patients requiring surgery in the PR3-ANCA-positive group was also high compared with the PR3-ANCA-negative group, although there was no significance (10.8% and 4.8%, respectively; $p=0.64$).

Conclusions: Our data suggested that PR3-ANCA might be a useful serum biomarker for predicting the refractoriness of UC.

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Perianal disease: far beyond a simple feature of Crohn's disease

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Background: Perianal disease is a significant source of morbidity and impairs the quality of life of affected patients with Crohn's disease (CD). We aimed to access the impact of perianal involvement in disease outcomes.

Methods: Retrospective unicentric study including patients with definite diagnosis of CD with a follow up of at least 12 months. All patients with documented perianal disease (anal fistula and perianal abscess) were included while controls were randomly selected. Clinical and analytical variables were assessed, and disease outcomes (hospitalization, surgery, need for steroids and behavior progression) during the follow-up were reviewed. Statistical analysis was performed using SPSS v21.0 and a two-tailed p value <0.05 was defined as indicating statistical significance.

Results: Included 198 patients, of which 53 (26.8%) had perianal disease. Patients had a mean age of 41 ± 13 years and 52.5% were females. When comparing patients with and without perianal disease, no significant differences were found between groups regarding gender, age, Montreal classification at diagnosis (age, location and behavior-excluding perianal involvement), family history and smoking habits. Patients with perianal disease had more frequently proctitis at diagnosis (32.1% vs 5.6%, $p<0.01$), and this difference was statistically significant. During follow-up, these patients were more frequently submitted to surgery (excluding perianal disease interventions) (41.5% vs 24.8%, $p=0.02$), were more frequently hospitalized (66.0% vs 49.7%, $p=0.04$), had longer in-stay (23 days vs 12 days, $p=0.01$) and were more frequently treated with anti-TNF agents (56.9% vs 38.1%, $p=0.02$). Also, these patients were more likely to have a change in disease behavior, with development of penetrating disease (18.9% vs 6.9%, $p=0.01$). No differences were found between the two groups regarding extra-intestinal manifestations, need for steroids, time from diagnosis to first surgery and development of stricturing disease.

Conclusions: Patients with perianal disease had significantly higher disease burden, with greater need for surgery, hospitalization and more frequently displayed penetrating disease progression. These results support that perianal CD represents a particularly aggressive disease phenotype that should be treated aggressively, not only due to the perianal involvement but also, very importantly, because of its association with worse outcomes.

P293 Histological risk factors to predict clinical relapse in ulcerative colitis in mucosal healing

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Background: Currently, the target of treatment for ulcerative colitis (UC) have been changing from clinical remission to include mucosal healing, and finally histological remission. We evaluated the correlation between future clinical relapse and histological findings in patients with UC who achieved mucosal healing.

Methods: Patients with UC who underwent colonoscopy with biopsies and achieved mucosal healing were enrolled into a retrospective cohort. Data were collected from April 2013 to October 2016. Mucosal healing was defined as Mayo endoscopic subscores 0 or 1. Histological findings based on Japanese criteria for the diagnosis of UC, were evaluated as the presence or absence of inflammatory cell infiltration, erosion, crypt abscess, goblet cell depletion and crypt distortion. Assessment of histologic inflammation was done by two experienced pathologists. Clinical relapse was defined by the addition of medical treatment for the clinical symptoms. Multivariate analysis by Cox proportional hazards regression tests were used to generate a prediction model of clinical relapse.

Results: A total of 189 UC patients were enrolled. Clinical relapse occurred in 64 patients (33.9%) during the observation period. There was no difference in the time to relapse between Mayo endoscopic subscores 0 and 1 ($p=0.3613$). The rate of Clinical relapse was significantly higher in patients with erosion and/or crypt distortion compared to patients without them ($p=0.0244$; and $p=0.0178$, respectively). No significant difference was observed in patients who have inflammatory cell infiltration, crypt abscess, and/or goblet cells depletion.

Multivariate analysis indicated that the presence of erosion (hazard ratio, 1.910; 95% confidence interval, 1.105–3.302, $p=0.02052$) and crypt distortion (hazard ratio, 2.611; 95% confidence interval, 1.125–6.059, $p=0.02547$) significantly affect the time to relapse, respectively.

Conclusions: Presence of erosion and crypt distortion are considered to be histological risk factors for future clinical relapse in UC patients in remission who achieved mucosal healing, while Mayo endoscopic subscores did not show significant predictive values for relapse.

P294 Iron-deficiency without anemia in Crohn's disease: what are the predictive factors of recovery?

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Background: Iron-deficiency without anemia (IDWA) is a common but little explored clinical situation in patients with Crohn's Disease (CD). Despite being at risk for developing iron-deficient anemia, some patients will present recovery of the IDWA during the follow-up. The aim of this study was to identify predictive factors of IDWA recovery after one year of follow-up.

Methods: Retrospective single-center evaluation of patients with CD who had at least on episode of IDWA between January/2011 and December/2014, with a minimum follow-up of 1 year. Iron-deficiency was defined as a serum ferritin value below 30 $\mu\text{g/L}$ in the absence of inflammation or when serum ferritin value was between 30–100 $\mu\text{g/L}$ and inflammation was evident. Two groups of patients (those who had recovery of IDWA and those who maintained IDWA or developed anemia) were compared regarding demographic and clinical characteristics using the χ^2 and Fisher's exact tests.

Results: From the 136 identified patients with CD and IDWA, 97 (71,3%) were women. During the following year after the identification of IDWA, 37 patients (27,2%) recovered the serum ferritin levels, 24 (17,6%) developed iron-deficient anemia, and 75 (55,2%) had persistent IDWA. Recovery of the IDWA was significantly more common in men ($p=0.006$), in patients with serum ferritin values between 30–100 $\mu\text{g/L}$ ($p=0.035$), in patients with a penetrating behavior of the disease ($p=0.026$), and in those with perianal disease ($p=0.029$). No significant differences were found regarding disease extension ($p=0.121$), upper gastrointestinal tract involvement ($p=0.908$), age at the diagnosis ($p=0.913$), smoking habits ($p=0.236$) or family history of inflammatory bowel diseases ($p=0.313$). The use of iron supplements was not more common in those patients who had recovery of IDWA during the follow-up ($p=0.683$).

Conclusions: Only a fourth of the patients will present recovery of IDWA during the following year, which is more common in men and in those with higher levels of serum ferritin. These findings emphasize the need of a close monitoring of IDWA, particularly in women or in patients with lower serum ferritin values, in whom the recovery is not so common.

P295 Absence of mucosal healing in patients undergoing assessment of mucosal healing with a normal PUCAI score in pediatric ulcerative colitis

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Background: Mucosal healing (MH) is an important treatment goal, and is usually assessed by endoscopic evaluation in ulcerative colitis. Recent guidelines have noted that there is a good correlation between the paediatric ulcerative colitis activity index (PUCAI) and endoscopic Mayo Score, and a recommendation that the PUCAI can be used as a proxy for MH. However, no previous study has prospectively validated the use of PUCAI as a proxy for MH specifically during clinical remission. The goal of the present study was to evaluate if the PUCAI accurately reflects MH in children with clinical remission. **Methods:** Single center prospective observational cohort with blinded assessment of endoscopic Mayo score, involving consecutive pediatric patients ≤ 18 years old in clinical remission or borderline clinical remission due to occasional symptoms. All children with UC underwent sigmoidoscopy 3–4 months after obtaining remission. PUCAI was calculated and registered prior to endoscopy. Complete clinical remission was defined as PUCAI < 10 . Borderline clinical remission was defined as involvement of only one symptom category that was inconsistent (i.e. occasional mild bleeding, abdominal pain or liquid stools without blood). Mayo endoscopic score was performed at time of endoscopy by the endoscopist and rectum

and sigmoid were photographed. Mayo score was reviewed independently by another experienced gastroenterologist blinded to both the PUCAI and endoscopists assessment. The highest Mayo score of either segment was used as the patient endoscopic Mayo score.

Results: 19 patients (47.4% male, 52.6% female) mean age 15.7±2.2 met study inclusion criteria. 79% were asymptomatic with normal PUCAI, the rest had suspected clinical remission with occasional symptoms. There was a good interobserver agreement between the Mayo score that evaluated between the two experts independently (Phi coefficient 0.772, Cramer's V 0.772). Among patients with PUCAI <10, Mayo score 0 were seen in 66.7%, Mayo 2–3 were seen in 33.3%. Among patients in questionable remission, Mayo score 0 were seen in 75%, Mayo 1 were seen in 25%. There was poor agreement between Mayo score and PUCAI, knowing one value did not significantly increase the chances of knowing the other value (Phi coefficient 0.073, Cramer's V 0.073, The Goodman and Kruskal tau coefficient 0.005, all were not significant p=0.75).

Conclusions: The data from this cohort of patients assessed prospectively during clinical remission suggests that a clinically relevant proportion of patients had active endoscopic disease, despite normal PUCAI scores. Caution should be used in extrapolating from PUCAI to MH specifically among patients with clinical remission after therapy.

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Persistent symptoms, CRP elevation and treatment changes over time in Crohn's disease patients are associated with bowel damage progression as expressed by deterioration of Lemann Index score

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Background: Crohn's disease (CD) is a chronic and progressive disease causing bowel damage (BD) which will lead to complications and surgery. Recently, the Lemann Index (LI) has been developed to measure the cumulative structural BD at a given time independent of disease activity. In this retrospective study, we investigated factors potentially related to structural BD progression in CD as expressed by changes in LI score over time.

Methods: We studied a cohort of 63 patients with 2 serial abdominal cross-sectional imaging studies (CT and/or MRI) at least 24 months apart, over a period of 5 years of follow-up at a tertiary IBD centre. Imaging and endoscopic data were used to compute LI using a Microsoft Access-based calculator. Changes in LI between the 2 time-points were calculated (delta LI, DLI = LI2-LI1) and patients were classified into 2 groups: those with zero or negative DLI values (stable or improved, iDLI) and those with positive DLI values (deteriorated, dDLI). The percentages of interval time (IT) with symptomatic disease luminal and/or perianal, increased CRP and exposure to various treatments were estimated. Non-parametric statistical analyses for independent and paired groups were performed to identify factors related to BD progression.

Results: In the entire CD cohort, median LI2 score increased significantly (median LI2, 8.5 versus median LI1, 7.5; p=0.021) over a median period of 30 months. LI increased (dDLI) in 32 patients (51%) and remained stable or decreased (iDLI) in 31 patients (49%). There were no significant differences in baseline characteristics between the 2 groups except for more common prior exposure to 2 biologics and more frequent active disease in dDLI group (Table 1). Factors independently associated with a significant increase in median LI2 were: persistent symptomatic disease during >50% IT (DLI=1.62, z=2.685, p=0.007), persistent CRP elevation >50% IT (DLI=1.31, z=2.103, p=0.035), frequent or continuous steroid use

Table 1. Baseline demographic and clinical characteristics of Crohn's disease patients according to Lemann Index (LI) score changes over time

Parameter	LI increased		LI stable or decreased		P
	N=32		N=31		
Males, n [%]	22	[69]	15	[48]	0.128
Age, median [IQR], yrs	37	[25-51]	30	[20-43]	0.193
Age at diagnosis, median [IQR], yrs	22	[16-31]	18	[15-24]	0.382
Disease duration, median [IQR], yrs	12	[6-19]	13	[6-16]	0.700
Disease location, n [%]					
L1, L2, L3	11, 7, 14	[34], [22], [44]	10, 6, 15	[32], [19], [49]	0.931
L4 (upper tract)	7	[22]	6	[19]	1
Disease behavior, n [%]					
B1, B2, B3	7, 10, 15	[22], [31], [47]	5, 12, 14	[16], [39], [45]	0.766
Perianal disease, n [%]	20	[63]	16	[52]	0.450
Current smoking, n [%]	3	[9]	7	[23]	0.278
Prior CD-related surgery, n [%]	20	[63]	18	[58]	0.799
Prior biologics treatment, n [%]	23	[72]	21	[68]	0.788
1	9	[28]	16	[52]	
2	14	[44]	5	[16]	0.044*
Baseline disease activity, n [%]	27	[84]	19	[61]	0.05*
Baseline treatment, n [%]					
No treatment	5	[16]	8	[26]	0.534
Steroid use	6	[19]	3	[10]	0.474
Immunomodulators use	12	[38]	7	[23]	0.275
Biologics use	20	[65]	19	[61]	1
Baseline elevated CRP levels, n [%]	18	[55]	17	[60]	0.797
Lemann Index (LI) 1, median [IQR]	6.6	[3.3-14]	7.9	[4.9-9.6]	0.747

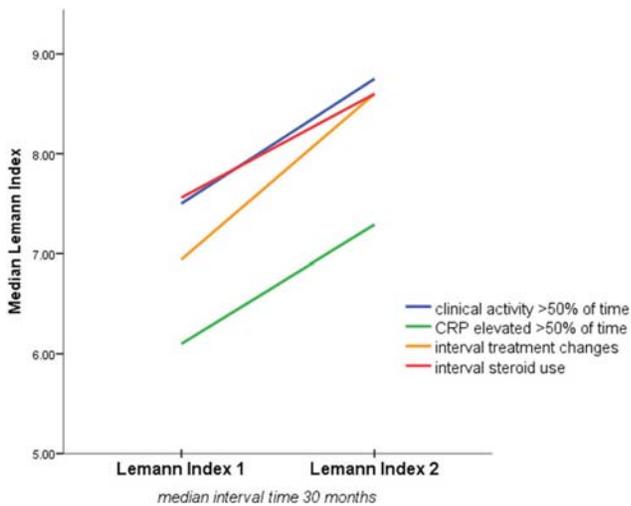


Figure 1. Lemann Index in Crohn's disease patients at 2 time points.

(DLI=2.2, $z=3.309$, $p=0.001$) and significant changes in treatment (DLI=2.2, $z=2.418$, $p=0.016$) during the interval period (Wilcoxon signed-rank test, Figure 1).

Conclusions: Our results show that ongoing Crohn's disease activity as indicated by persistent symptomatic disease, persistent CRP elevation, frequent steroid use and changes in treatment is associated with progressive bowel damage.

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Fecal calprotectin accurately predicts symptomatic relapse in children and adolescents with inflammatory bowel disease in clinical remission

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Background: In children and adolescents with inflammatory bowel disease (IBD) in clinical remission, it is difficult to predict when a relapse will occur. Reliable data on the value of biomarkers of inflammation for predicting relapse in these young patients are lacking. Therefore, we aimed to investigate the predictive value of fecal calprotectin (FC) and CRP for symptomatic relapse in pediatric IBD in clinical remission.

Methods: In this cross-sectional cohort study, patients aged <18 years with Crohn's disease or ulcerative colitis in clinical remission ≥ 3 months were included. At baseline, clinical and biochemical disease activity were assessed using the abbreviated-Pediatric Crohn's Disease Activity Index (aPCDAI) or Pediatric Ulcerative Colitis Activity Index (PUCAI), and FC and CRP, respectively. Clinical remission was defined as an aPCDAI or PUCAI <10. Disease course over the subsequent 12 months was retrospectively assessed. Symptomatic relapse was defined as an aPCDAI or PUCAI score ≥ 10 , with the need for treatment intensification. Multivariate Cox regression analysis was performed to evaluate whether FC and CRP were independent predictors for symptomatic relapse.

Results: In total, 114 patients in clinical remission were included

(56% males; median age 14.9 years). Baseline FC level was higher in patients that developed a relapse compared to patients without symptomatic relapse (median 367 $\mu\text{g/g}$ vs. 117 $\mu\text{g/g}$, $p=0.014$). FC level was an independent predictor for symptomatic relapse within 6 months from baseline (HR per 100 $\mu\text{g/g}$: 1.15 [95% CI: 1.06–1.24], $p<0.001$), corresponding to a 15% increase in the probability of relapse per 100 $\mu\text{g/g}$ increment, with fair predictive accuracy (AUC: 0.77, $p<0.001$). The optimal FC cut-off was 350 $\mu\text{g/g}$, with a sensitivity and specificity of 76% and 78%, respectively.

Baseline CRP level did not differ between patients with or without symptomatic relapse. CRP level was an independent predictor for symptomatic relapse within 6 months from baseline (HR per 1 mg/L: 1.10 [95% CI: 1.01–1.19], $p=0.025$), corresponding to a 10% increase in the probability of relapse per 1 mg/L increment, with poor predictive accuracy (AUC: 0.67, $p=0.036$). The optimal CRP cut-off was 0.6 mg/L, with a sensitivity and specificity of 88% and 38%, respectively.

Conclusions: Levels of FC and CRP were both independent predictors of symptomatic relapse in pediatric IBD in clinical remission, with superior predictive test characteristics of FC. High FC levels at routine measurement justify careful disease monitoring and evaluation of current treatment.

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Comparison between clinical and patient-reported symptoms among Crohn's disease and ulcerative colitis patients

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Background: There is no symptom-based patient-reported outcomes (PRO) measurement available in IBD. Disease scores contain a mixture of PRO and physician's observations and have shown serious limitations in clinical trials. Comparison between healthcare professionals (HCP) and patient (P) reports on scores' items is a first step toward disease scores refinement. In our IBD cohort study, we were able to collect P and HCP-reported symptoms independently. We assessed the agreement between both measures, and tested the correlation between the general well-being item (GWB) and two health-related quality of life (HRQoL) measures.

Methods: Between 2012 and 2015, we collected CDAI and MTWAI items 1) during follow-up medical visits, 2) through P self-reported follow-up questionnaire, except lab values. We compared items independently reported by HCP and P, stratified by diagnostic and Δt HCP-P reports. We calculated the Cohen's kappa (κ) statistic for agreement. A quadratic weight was applied for more severely serious disagreements. For EIM & complications, we computed a pooled κ based on the average between observed and expected probability of agreement over sub-items. A pooled κ was computed to summarize agreement over all examined variables. We also collected SF-36 and IBDQ scores. Pearson correlation coefficients r were calculated between both scores and GWB reports of HCP and P.

Results: 2427 reports could be evaluated (Δt : 537 <1 month, 390 1–2, 1500 2–6), referring to 1385 patients (52% females, 58% CD). The best overall κ was found at Δt 1–2 months, moderate for number of stools/wk and antidiarrheal treatment (AT) in CD, moderate

Abstract P298 – Table 1. Cohen's Kappa scores for GI-P agreement among activity index items (0–0.2: very low, 0.2–0.4: low, 0.4–0.6: moderate, 0.6–0.8: high, 0.8–1: perfect).

CD	Δt					
	<1	1-2	2-3	3-4	4-5	5-6
Nb soft stool during last week	0.457	0.484	0.500	0.357	0.469	0.444
Abdominal pain	0.265	0.363	0.336	0.318	0.385	0.288
General well-being	0.161	0.338	0.222	0.240	0.268	0.355
Antidiarrheal treatment	0.292	0.441	0.288	0.166	0.186	0.125
EIM & complications	0.379	0.382	0.252	0.309	0.180	0.265
Overall	0.336	0.423	0.370	0.297	0.355	0.351
UC						
Nocturnal diarrhea	0.281	0.749	0.318	0.378	0.317	0.438
Bloody stools	0.243	0.540	0.284	0.256	0.240	0.217
Fecal incontinence	0.252	0.055	0.250	0.268	0.177	0.312
Abdominal pain	0.378	0.366	0.147	0.302	0.218	0.378
General well-being	0.316	0.201	0.340	0.318	0.198	0.304
Antidiarrheal treatment	0.255	0.069	0.360	0.284	0.427	0.202
Overall	0.296	0.325	0.298	0.309	0.264	0.316

to good for nocturnal diarrhea and bloody stools in UC. Agreement on GWB was low to very low. P-reported GWB were well correlated with IBDQ (CD: $r=0.65$, UC: $r=0.67$), SF-36 physical (PCS) (CD: $r=0.52$, UC: $r=0.58$) an SF-36 mental (MCS) component scores (CD: $r=0.47$, UC: $r=0.46$). Correlation of PCS resp. IBQD with HCP-reported CD-GBW was moderate at $\Delta t < 1$ and 2–3 months ($r=-0.45$ and -0.53 , resp. -0.43 and -0.48), but correlation with MCS remained low ($r < 0.40$) whatever Δt . For UC, HCP-reported GBW moderately correlated with IBDQ at $\Delta t < 1$ and 1–2 months ($r=-0.48$ and -0.47), but was low when $\Delta t > 2$. Correlation with PCS and MCS remained low whatever Δt .

Conclusions: The agreement was low for many scores' items, except two per disease. Among scores' items with high weight, eg CDAI AT or GWB, agreement was surprisingly low. P-GWB correlated with HRQoL scores better than HCP, especially for scores related to mental or emotional aspects.

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Identification of a prognostic biomarker able to predict ulcerative colitis patients that will not respond to standard therapy

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Background: Ulcerative Colitis (UC) is associated with high rate of morbidity and disability. There is an urgent unmet need to identify a specific biomarker that early in the disease course select suitable patients for appropriate therapy, avoiding thereby unnecessary step-up therapies and patients' disability due to prolonged inflammation. Recently, we showed that aberrant glycosylation of T cells plays a crucial role in UC pathogenesis [1,2]. We herein studied whether this molecular marker is able to predict therapy response in UC patients, early in disease course.

Methods: 131 formalin fixed paraffin-embedded colonic biopsies collected at the time of diagnosis from 131 UC patients were analyzed by immunohistochemistry in order to evaluate the expression of our biomarker (glycosylation levels in intestinal T cells). The relationship between biomarker expression and clinicopathological/therapeutic features of UC patients was analyzed. ROC curves

were performed and the predictive value of the biomarker in the response to therapy was determined.

Results: Univariate analysis showed that our biomarker is able to predict patients' therapeutic outcome, early in disease course, by distinguishing patients that will display a stable disease course (always under 5-ASA) from those that will step-up therapy. High levels of biomarker expression, at/near to diagnosis can predict 78% (Negative Predictive Value - NPV) of the patients that will display a good disease course (always under 5ASA; $p < 0.05$). When the biomarker is analyzed in severe UC patients (MayoE 3) at diagnosis, the sensitivity of the biomarker increase (from 46% to 64%), in which low levels of biomarker are able to predict 78% (Positive Predictive Value - PPV) of the UC patients that will step-up therapy to biologics (with bad disease course). Multivariate analysis revealed that only our biomarker and C Reactive Protein are shown to be independent predictors of non-response to standard therapy (5ASA; corticosteroids; immunomodulators). Interestingly, the ROC curve ($AUC=0.714$, $p=0.001$) revealed a powerful effect of both molecular parameters when analyzed together, suggesting an additive value in the prediction of the failure to standard therapy. This additive predictive effect was stronger when analyzed in severe patients (MayoE 3) in which the association of both biomarkers is able to predict 70% of the UC patients (PPV), early in the disease course, that will not respond to standard therapy.

Conclusions: Our results reveal a potential novel molecular tool in the prediction of failure to standard therapy in UC patients with promising prognostic value to be included in the algorithm of the therapy-decision making of UC patients.

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P300

Illness perceptions and coping with health-related quality of life in patients with inflammatory bowel disease

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Background: Inflammatory bowel diseases (IBD) affect patients' health-related quality of life (HRQoL) and are associated with higher levels of anxiety and depression. We aimed to investigate whether illness perceptions and coping strategies were associated with mental adjustment (depression and anxiety) and HRQoL in IBD.

Methods: Patients were prospectively recruited at a tertiary IBD Center. Self-administered questionnaires evaluating patients' demographics, illness perceptions, coping strategies, catastrophization, HRQoL, depression and anxiety were completed. Analysis was performed using Pearson's product moment correlation coefficient, hierarchical regression and structural equations modeling.

Results: IBD patients (n=156, 117 Crohn's disease, 30 ulcerative colitis, and 9 IBD-undetermined), 49% females, mean age 41.6±14.79 (19–77) years, mean disease duration 12±9.42 (1–37) years were included. Severe anxiety was reported in 30% (n=45) and 23% reported severe depression (n=33). Mean HRQoL was 5.12±1.09.

Illness perceptions that had an association with all or most HRQoL subscales were: Perception of the treatment as effective ($\beta=0.28$, $p<0.01$), perception of understanding the disease ($\beta=0.28$, $p<0.01$), and the perception of the disease as cyclical, which was negatively correlated to HRQoL ($\beta=-0.22$, $p<0.05$). Coping strategies that were more beneficial to IBD are characterized by acceptance of IBD and its challenges while trying to go on with life and engage in meaningful activities. Coping strategies that indicate inability to accept the disease, giving up, or using distractions, were all related to lower HRQoL and higher levels of depression and anxiety. Two coping strategies mediated the association between illness perceptions and HRQoL: "comparison to others" and "activities engagement".

Gender, education level and coping strategies predicted 73% of the explained variance in HRQoL of these patients.

Conclusions: Illness perceptions and coping strategies may promote patients' HRQoL and mental state. Therefore, modifying illness perceptions and coping strategies using psychosocial interventions may contribute to HRQoL in patients with IBD.

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Non-familial small bowel carcinomas in Crohn's disease: clinico-pathological, molecular and prognostic features

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Background: An increased risk for small bowel carcinoma (SBC) has been reported in Crohn's disease (CrD). We aimed to explore clinical, histopathologic, molecular and prognostic features of CrD-associated SBC (CrD-SBC) in comparison to both coeliac disease (CD)-associated SBC (CD-SBC) and sporadic SBC (spo-SBC).

Methods: Seventy-six patients, who underwent surgical resection for non-familial SBC (25 CrD-SBC, 26 CD-SBC and 25 spo-SBC), were retrospectively recorded to investigate survival together with histological and molecular features detected by immunohistochemistry, multiplex PCR and sequencing.

Results: CD-SBC showed a significantly ($p=0.004$) better sex-, age- and stage-adjusted overall and cancer-specific survival in comparison to CrD-SBC, while no significant difference was found between spo-SBC and either CD-SBC or CrD-SBC. CD-SBC exhibited a significantly ($p=0.001$) higher rate of microsatellite instability (MSI, 65%) compared to both CrD-SBC (16%) and Spo-SBC (16%). The median number of tumor-infiltrating lymphocytes (TIL) correlated with MSI status and was significantly higher in CD-SBC than in both CrD-SBC ($p<0.001$) and spo-SBC ($p=0.002$). Among CD-SBC, MSI allowed to separate two subgroups with different outcome, stage and TP53 mu-

tation rate. MSI was the result of MLH1 methylation in all cases (with the exception of one case of CrD-SBC). No BRAF mutation was observed in any SBC. Mutations in KRAS, NRAS, and PIK3CA were detected in 30%, 4% and 13% of cases, respectively. HER2 gene amplification was identified in two CD-SBC, two CrD-SBC and one spo-SBC.

Conclusions: In comparison to CrD-SBC, CD-SBC harbor much more frequently MSI and show a more favorable prognosis, likely related to their high density of TILs, which have independent prognostic value in SBC. MSI status, KRAS/NRAS mutations and HER2 amplifications might contribute to stratify patients for targeted anti-cancer therapy.

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Cytomegalovirus infection in pediatric acute severe ulcerative colitis – a multicenter case-controlled study from the Pediatric IBD Porto group of ESPGHAN

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Background: Data on the clinical course and outcomes of pediatric patients with cytomegalovirus (CMV) infection complicating acute severe ulcerative colitis (ASC) is very limited. The aim of our study was to compare the outcome of CMV-positive and negative pediatric ASC.

Methods: This was a multicenter retrospective case-controlled study, from centers in Europe and Israel. We included CMV-positive pediatric patients hospitalized for acute severe colitis and compared their outcomes (rate of colectomy during hospitalization and up to 1 year from the hospitalization) to matched CMV-negative controls

Results: A total of 56 children from 10 centers were included. The patient cohort included 23 (41.1%) males/ 33 (58.9%) females, with a median age of 11.5 (interquartile range (IQR) – 7–14) years. Fifty-two (92.9%) of the patients had extensive/pan-colitis colitis and the rest left sided colitis, with severe disease in 52 (92.9%) of the patients and moderate in 4 (7.1%). Fifteen patients were CMV-positive and 41 – CMV-negative. Significantly higher proportion of CMV positive patients were resistant to intravenous corticosteroids (p=0.009). After diagnosis of CMV infection, 14/15 patients were started on gancyclovir (5 mg/kg – 5/14 (35.7%) and 10 mg/kg – 9/14 (64.3%). During hospitalization, 3 (20%) CMV positive and 3 (7.8%) CMV-negative patients required colectomy (p=0.17). By 12 months of follow-up, 5 (33.3%) and 5 (12.5%) CMV positive and negative

patients required colectomy, respectively (p=0.049). Previous anti-TNF exposure and Pediatric Ulcerative Colitis Activity Index score on index date were significantly associated with the risk of colectomy during hospitalization and by 12 months (p=0.037 and p=0.01 for previous anti-TNF exposure and p=0.021 for PUCAI) on univariate analysis, however none of the factors including CMV positivity retained significance on multivariate analysis.

Conclusions: A higher prevalence of CMV positivity was found in pediatric UC patients who required colectomy within 12 months of index hospitalisation, however the difference was not statistically significant on multivariate analysis. Further studies are merited to clarify the impact of CMV infection on the outcome of acute severe colitis in pediatric patients

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Gastrointestinal infectious agents detected by Biofire FilmArray GI PCR panel stool testing in active inflammatory bowel disease are common and associated with a more benign course of IBD

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Background: Using standard techniques, only 10% of inflammatory bowel disease (IBD) patients with symptoms have detectable gastrointestinal (GI) tract infections. Detection is limited by the sensitivity of these tests. *Clostridium difficile* infection can worsen the course of IBD, but it is not known if other infections can also. Our primary aim was to determine the risk of GI infections in IBD patients during symptomatic flares using the BioFire FilmArray GI Panel test. This multiplex PCR test detects 22 organisms, including bacteria, viruses, and protozoa. Our secondary aim was to compare the IBD course between the patients with positive and negative tests for infection.

Methods: We reviewed BioFire GI stool results for all adult IBD patients from April to October 2016 at our center. We excluded patients on antibiotics in the last 2 weeks, UC patients status post colectomy, and patients with symptoms from other causes, e.g. pancreatitis or infections outside GI tract. We compared the risk of GI infection between those with active and inactive IBD defined by inflammatory markers (using QuantumBlue fecal calprotectin), imaging findings, or endoscopic /biopsy findings. Among actively inflamed IBD patients, we compared clinical characteristics, medication use, and disease course (need for escalation of immunosuppressive agents and need for surgery) between those with positive and negative tests.

Results: 131 IBD patients (60 active CD, 14 inactive CD, 54 active UC, and 3 inactive UC) were included. Most (88.6%) were inpatients. Thirty-nine had positive results; common types of infection included Norovirus, *C. difficile*, and *E. coli*. The risk in the IBD group with active inflammation was significantly higher than the inactive IBD group [38/114 (33.3%) vs 1/17 (5.9%), p=0.02]. In the inflammation group, shorter duration of presenting symptoms and use of biologics were significant predictors of a positive test. The proportions of escalation of immunosuppressive therapy and surgery were significantly lower in the group with positive tests for infection vs. those with negative tests [escalation, 23/38 (60.5%) vs

68/76 (89.5%), $p < 0.01$], and [surgery 4/38 (10.5%) vs 21/76 (28%), $p = 0.034$], respectively.

Conclusions: A surprisingly large fraction, one-third of IBD patients with symptoms and objective evidence of gut inflammation, had infectious agents detected in their stool. The course of IBD in patients with these infections was more benign than those with negative tests. It appears that more sensitive testing for acute infections can be prognostically helpful, particularly in IBD patients with acute worsening of symptoms, and the use of steroids and escalation of IBD therapy could be reduced if stool infections are identified early.

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Zinc levels, interplay with ATG16L1 and disease outcome in Crohn's disease patients in the Swiss IBD cohort study

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Background: Zinc deficiency (ZD) in Crohn's disease (CD) is common, may exacerbate disease activity and is found even in patients with clinical remission. Previous literature indicates positive effects of zinc on intestinal repair and tight junction permeability as well as anti-inflammatory activity via zinc homeostasis and activation of autophagy. In view of the latter, ZD might increase the impact of the autophagy-related 16-like 1 (ATG16L1) single nucleotide polymorphism (SNP), a key player in autophagy, which is known to be associated with an increased risk of CD. We aimed to assess the prevalence of ZD in CD patients in clinical remission and to analyze both a potential impact on future disease course as well as an interplay with the presence of mutated ATG16L1.

Methods: Zinc levels from CD patients in clinical remission at baseline and an uncomplicated disease course within the next 3 years ($n=47$) were compared with those from patients developing complications ($n=50$) defined as either 1) flare up or 2) need for new anti-TNF or 3) development of stenosis, abscess, fistula or anal fissure. All data was available from the Swiss IBD cohort study.

Results: Mean zinc level in the 97 patients (mean age 40.4 ± 15.7 y, 44.3% males, median CDAI at baseline 34.0 [IQR 11.0–53.0]; no prior or current anti-TNF treatment) was 18.0 ± 4.7 $\mu\text{mol/L}$. No absolute ZD (defined as < 11 $\mu\text{mol/L}$) was observed. Low zinc levels (defined as < 15.1 $\mu\text{mol/L}$) were found in 28 patients (28.9%). Males had significantly higher zinc levels compared to females (19.4 ± 5.7 vs. 16.8 ± 3.3 , $p = 0.006$) and proportion of patients with low zinc levels was higher among females (20/54, 37.0% vs. 8/43, 18.6%, $p = 0.047$). Zinc levels of patients with a future complicated disease course were not different from those of patients without complications (17.7 ± 4.3 vs. 18.3 ± 5.1 , n.s.). ATG16L1 SNP analysis was available for 61 patients (62.9%) with 25 (25/61, 41.0%) carrying the SNP rs2241880 (T300A). Zinc levels of patients with ATG16L1 (T300A) did not differ from those of patients without (16.3 ± 2.7 vs. 17.1 ± 3.2 , n.s.). Looking only at ATG16L1 (T300A) carriers, no difference in zinc levels between patients with vs. without a complicated disease course was seen (16.0 ± 2.6 vs. 17.3 ± 2.9 , n.s.). In a multivariate regression model adjusted for age, sex, diagnostic delay, prior/current

immunomodulation and presence of ATG16L1 (T300A), zinc levels at baseline did not predict complicated disease outcome (OR 0.80, 95% CI 0.60–1.06).

Conclusions: We did not observe ZD in CD patients in clinical remission. However, zinc levels among females were lower compared to those among males. Zinc levels at baseline did not predict complicated disease course, neither in CD patients overall nor ATG16L1 (T300A) carriers.

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Indirect comparison of two novel biologics for the treatment of Crohn's disease : network-meta analysis of ustekinumab vs vedolizumab

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Background: Long-term remission is an important treatment goal for patients with Crohn's disease (CD). While anti-TNF inhibitors are effective at inducing and maintaining remission in patients with moderate to severe CD, a considerable proportion of patients do not respond or lose response to these therapies over time. Therapies with new MOAs are emerging to address this unmet need but clinical trials often do not include direct comparison of these agents. Better understanding of relative clinical efficacy and safety is needed to determine optimal positioning of biologic therapies in the treatment algorithm. The aim of this analysis was to conduct an indirect comparison of efficacy of two novel MOA biologics: vedolizumab (VDZ), an anti- $\alpha 4\beta 7$ integrin, and ustekinumab (UST), an antibody directed against the p40 subunit of IL-12 and IL-23, as therapy for patients with moderately to severely active CD.

Methods: Induction and maintenance data from Phase 3, randomized, double-blind, placebo-controlled studies were used in the analysis: GEMINI II [1] for VDZ and UNIT-1, UNIT-2, and IM-UNITI [2] for UST. Bayesian Network Meta Analysis comparing VDZ and UST was performed with OpenBUGS v3.2.2. A binomial likelihood and a logit link function in a fixed effect model were used to account for variability in the placebo (PLA) effect across trials. Week 6 induction data were extracted for PLA, VDZ 300mg, UST 6mg/kg. Week 52 maintenance data were extracted for PLA, VDZ 300mg Q8W and Q4W, UST 90mg Q12W and Q8W. Results were stratified by prior exposure to anti-TNFs (induction: non-anti-TNF refractory, anti-TNF refractory; maintenance: anti-TNF naïve, anti-TNF refractory). Clinical remission was defined as CDAI ≤ 150 . Odds Ratios (ORs) were estimated for the probability of remission. Median and 95% credible intervals of the posterior distribution of each OR were calculated.

Results: The OR for clinical remission at 6 weeks of treatment of UST 6mg/kg vs VDZ 300mg was 0.99 for non-anti-TNF refractory and 1.63 for anti-TNF refractory patients. The OR for clinical remission at 52 weeks of treatment of UST 90mg Q8W vs VDZ 300mg Q8W was 0.67 for anti-TNF naïve patients and 0.73 for anti-TNF refractory patients. None of the ORs were statistically significant. Results for other dosing regimens in the maintenance phase are shown in Table 1.

Conclusions: There appears to be a positive trend with VDZ demonstrating numerically superior odds of clinical remission vs UST in

Table 1. Indirect comparison of GEMINI II (VDZ) vs. IM UNITI (UST): Odds ratio for remission at 52 weeks.

Population	UST 90mg	VDZ 300mg	Odds ratio for UST vs VDZ [95% CI]
Anti-TNF naive	Q12W	Q8W	0.46 [0.16, 1.34]
	Q8W	Q8W	0.67 [0.23, 1.99]
	Q12W	Q4W	0.57 [0.2, 1.65]
	Q8W	Q4W	0.83 [0.28, 2.44]
Anti-TNF refractory	Q12W	Q8W	0.65 [0.2, 2.05]
	Q8W	Q8W	0.73 [0.23, 2.28]
	Q12W	Q4W	0.68 [0.21, 2.15]
	Q8W	Q4W	0.76 [0.24, 2.38]

95% CI: 95% Credible Intervals

the maintenance phase of treatment. Direct head-to-head studies are required to confirm this trend.

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P306

What is the impact of perianal disease on anorectal function and quality of life of IBD patients? A prospective observational study

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Background: The perianal disease is a common feature of patients affected by inflammatory bowel disease (IBD), with a detrimental effect on quality of life (QoL). The anorectal function of IBD patients is still poorly understood, with contrasting results. Aim of this prospective observational study was to analyze the effect of perianal disease on anorectal function and QoL of IBD patients, and to compare the results with healthy volunteers.

Methods: Patients were assessed by a full clinical examination (including the Wexner score, the Harvey Bradshaw score, the Clinical Mayo score), anorectal manometry, three-dimensional endoanal ultrasound (3D-EAUS), and endoscopy. The Inflammatory Bowel Disease Questionnaire (IBDQ) was adopted to evaluate patients' QoL.

Results: From January to November 2016, 37 IBD patients (21 males; mean age 40.6±14.0 years) and 20 healthy volunteers (9 males, mean age 46.9±15.1 years) were enrolled in the study. Thirty patients were affected by Crohn's disease (CD), and 7 by ulcerative colitis (UC), with a mean Harvey Bradshaw score and a mean Clinical Mayo score of, respectively, 4.5±3.9 and 3.3±2.9. Twenty-nine patients had a history of perianal fistula, 9 patients were affected by fecal incontinence (mean Wexner score 7.2±4.3), 2 patients by anal fissure. Fecal incontinent patients were older (p=0.025), had a longer duration disease (p=0.015), and a higher bowel movements number (p=0.006) than continent patients. A perianal fistula was

more frequent in CD patients (p=0.014), and in smoking patients (p=0.018). The 3D-EAUS was normal in all healthy volunteers, while 31/37 IBD patients had some pathological features (fistula, sphincter lesion, fibrosis). At the anorectal manometry, the maximum anal resting pressure, the maximum squeeze pressure, and rectal sensations did not differ between IBD patients and the control group; however the rectoanal inhibitory reflex was present in all healthy volunteers, and only in 32/37 IBD patients (p=0.080); 25/37 IBD patients had a dyssynergic defecation pattern. No differences emerged at the anorectal manometry between CD or UC patients, while the presence of rectal inflammation (p=0.046) and incontinence (p=0.050) were associated to a lower maximum anal resting pressure. Overall, the mean IBDQ score was 167.6±38.8, but it was lower in UC patients when compared to CD patients (132.5±44.4 versus 170.4±32.9, p=0.018); the QoL score was significantly lower in fecal incontinent patients (146.4±27.9 versus 173.6±39.8, p=0.040).

Conclusions: The anorectal manometry and the 3D-EAUS are useful tools to evaluate IBD patients with a perianal complaint. The anorectal function of IBD patients with a perianal disease is impaired. Patients' QoL is lower in UC, and in fecal incontinent patients.

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Fecal Lactoferrin levels are stable during pregnancy

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Background: During pregnancy it is difficult to reliably monitor inflammatory bowel disease (IBD) activity. Common biomarkers as C-reactive protein (CRP) and fecal calprotectin (FC) were shown to increase throughout normal pregnancy. Fecal lactoferrin (FL) has been shown to be a reliable biomarker for IBD activity. The stability of FL has never been examined during pregnancy. The aim of the study was to compare FL levels during different stages of pregnancy

Methods: 83 stool samples were collected for FL analysis during years 2014–2015 at Shaare-Zedek Medical Center. All patients were one of four groups; 44 (53%) were pregnant with IBD, 12 (15%) pregnant without IBD, 16 (19%) with IBD but not pregnant and 11 (13%) were healthy not pregnant women. The results were compared with other IBD biomarkers and during various stages of pregnancy.

Results: Median FL (µg/mL) for pregnant women was similar to non-pregnant women (7 vs. 6, respectively, p=0.61). Median FL was higher in IBD compared to non IBD patients (9.5 vs. 2, respectively, p=0.035). Comparing the four groups showed median FL levels were 8, 17.5, 2 and 2 for IBD-pregnant, IBD-non pregnant, pregnant-non IBD and non pregnant-non IBD patients, respectively. In trimesters one, two and three median FL levels were 12, 8 and 7, respectively, p=0.18). FL correlated positively with FC (Pearson correlation <0.001), but did not correlate with CRP, hemoglobin or erythrocyte sedimentation rate.

Conclusions: FL is steady throughout pregnancy. IBD patients had higher FL than healthy patients. This test may be used as the ideal biomarker to reliably monitor disease activity of pregnant patients with IBD

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Safety of the given patency capsule in patients with Crohn's disease or suspected Crohn's disease

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Background: Videocapsule endoscopy (VCE) is a non-invasive method for examining the small bowel. Nevertheless VCE retention is the most significant complication of these devices and may occur in any location of the gastrointestinal tract. A patency capsule (PC) is used to safely perform VCE, in patients with an increased risk of VCE retention. A recent report raised some concerns about PC safety in 2 patients with suspected CD, but there were some limitations since one of the PC expiry date was exceeded <https://planner.smart-abstract.com/ecco2017/submission/en/abstract/4483/content#>. Our aim was to assess the safety of PC in patients with Crohn's disease (CD) or suspected CD, in routine clinical practice.

Methods: Retrospective single-center study including patients with CD or suspected CD with clinical indication for VCE, between January 2011 and October 2016. PillCam PC (Given Imaging®) was performed in all patients to access small-bowel patency, without previous bowel preparation. PC detection was performed 30 hours after ingestion with radiofrequency identification (RFID) scanner. Patients with a positive identification of PC were considered to not have patency of the gastrointestinal tract and did not perform VCE. Symptomatic PC retention was defined as the presence of typical obstructive abdominal symptoms (i.e. postprandial colicky abdominal pain/bloating/vomiting).

Results: During the period of the study, were performed 451 PC (60% women, with a mean age of 39±13 years). Fifty-eight per cent of cases had a suspected CD and 42% of cases had a previous diagnosis of CD. Twenty-seven per cent of cases had a known or suspected small-bowel stenosis detected by previous ileocolonoscopy or abdominal imaging and 26% of cases had a history of previous abdominal surgery. The retention rate 30h after PC ingestion was 27% (31% in patients with CD vs. 24% in patients with suspected CD, $p>0.05$). All 322 patients with confirmed small bowel patency performed VCE, without incidents. Six (1.3%) patients presented a symptomatic PC retention (5 with CD and 1 with suspected CD, $p>0.05$). Two (0.4%) cases (with CD) were admitted due to small-bowel obstruction, which was successfully managed with corticosteroids.

Conclusions: The PC test has proven to be a safe modality for securing small bowel patency prior to capsule endoscopy, with reduced frequency of symptomatic retention, which occurred almost exclusively in patients with a previous diagnosis of CD.

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P309

Impact of rapid access MR on clinical decision making and patient management in Crohn's disease in a tertiary referral center

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Background: Assessment of disease activity in CD patients should be based on the complex evaluation of clinical symptoms and objective measures including laboratory and imaging data. Our aim was to

evaluate the impact of rapid access MR (within 2 weeks) on the clinical decision making in a specialized tertiary care center and analyze correlation between MR findings and laboratory findings, clinical activity and outcomes.

Methods: 93 rapid access MRI/MRE scans were available in a cohort of 75 referral CD patients (male/female: 51/49%, median age: 34 IQR: 25–43 years) between January 2014 to June 2016. Active disease was the indication for MRI in 51%. Location of CD was ileocolonic in 61% and colonic in 28% with perianal fistulas in 39% and previous surgeries in 53% of CD patients. MRI results were compared to clinical activity scores, CRP and changes in medical management or surgery requirements. The MR Enterography was carried out by 3T MR Scanners (Philips Achieve and Insignia) on prone position after the administration of oral contrast agent (polyethylene glycol or methylcellulose), using the breath hold technic and coronal and axial single-shot T2-weighted turbo spin echo, axial 3D DWIBS sequences for the abdomen. We used the sagittal, coronal T2, axial T2 fs, axial 3D DWIBS and axial 3D Wave (T1 native and post contrast fs) sequences for the pelvis. We used 16-channel torso and multi coils.

Results: The indication for MRI was active disease in 51% of the patients. MRI confirmed any activity in 76% and significant activity based on the MRI result in 68% of the patients. Luminal activity, fistula, abscess and/or stenosis was confirmed in 45%, 36%, 25% and 16% of the patients. Agreement between clinical and MRI activity was weak for any MRI activity (κ : 0.31) and moderate for significant MRI activity (κ : 0.61, sensitivity: 68%, specificity: 92%, PPV: 90% and NPV: 74%). There was an association between activity on MRI and elevated CRP ($p=0.01$ for significant MRI activity, $p=0.1$ for any activity). The MRI results led to a change in medical therapy in 73% of the patients, while 31% of patients with significant MRI activity required surgery. Any MRI activity was detected in 46% of patient undergoing MRI for disease control/follow-up with significant MRI activity in 8% of these patients. The MRI result led to a change in the therapeutic strategy in 22% of these patients, while 1 patient with significant MRI activity required surgery.

Conclusions: Rapid access MR is an accurate imaging method with a great impact on the everyday clinical decision making in both patients with clinically active and quiescent disease, enabling rapid patient stratification and selecting patients for the appropriate therapeutic strategy.

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Development of a new clinico-biological score associated with disease activity in patients with inflammatory bowel disease treated with thiopurine

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Background: To date, there is no simple surrogate biomarker for monitoring thiopurine efficacy in patients with inflammatory bowel diseases (IBD).

Aims: To develop a clinico-biological score that would be associated with disease activity in IBD patients treated with thiopurine.

Methods: This was a multicenter translational study (NCT-02367326) performed in 2015 that included all patients with Crohn's disease (CD) or ulcerative colitis (UC), naive of biologics, treated for at least three previous months with a thiopurine. Additional corticotherapy was allowed. At inclusion, patients were defined in remission with HBI <5 and CDEIS <4 for CD, and with total Mayo score ≤2 for UC. Blood tests performed at inclusion were prospectively collected. Best clinico-biological score model was reached based on cut-offs that would be associated with disease activity for each numeric variables determined by ROC curves, and on weights of each variables in the association of disease activity using random Forests and logistic regression analyses. Diagnostic performances of this score for active disease were then assessed by ROC curve in the overall population.

Results: A total of 339 eligible patients was recorded (median age: 37 years [27–48.5]; female: 58.4%; CD: 68.4%). Clinical characteristics were similar for patients with active or inactive disease at inclusion. Statistical significant differences were observed between the two groups for median values of inflammation-related parameters (including MCV, CRP), and liver function test (ALP, AST). In contrast, excluding MCV, there was no difference between the two groups regarding median values of thiopurine metabolism-related parameters (lymphocytes, 6-TGN (n=76), 6-MMP (n=61)). The following model of clinico-biological score reached by the addition of attributed points (pts) per variable was assessed: BMI <30, ALT ≤50 UI/L (6 pts), RBC >3 (10 pts), MCV <90fL, CRP >3mg/L (5 pts), lymphocytes ≥1200/mm³, GGT ≥120 UI/L, white leucocytes ≥6000/mm³ (3 pts), age <52 years, AST ≤50 UI/L, ALP >100 UI/L, neutrophils ≥3700/mm³ (1 pt). The area under the curve (AUC) was 80% [95% CI: 74.2%-85.7%], with sensitivity and specificity of 84.7%, and 65.6%, respectively, for a score over 30 points. Positive (PPV) and negative (NPV) predictive values were 48.4%, and 91.6%, respectively. This low PPV may be compensated by that of CRP assay for a cut-off at 4mg/L (PPV: 82%; AUC: 71% [95% CI: 64.6%-77.4%]). However, diagnostic performances of this new clinico-biological score were overall better than CRP for disease activity (p=0.041).

Conclusions: This new simple clinico-biological score appears associated with disease activity in IBD patients with ongoing thiopurine therapy, and should be validated in an independent prospective cohort.

P311 Microscopic inflammation and myenteric plexitis at the margin of resection do not predict endoscopic recurrence in patients with Crohn's disease after ileocolic resection

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Background: Studies have produced conflicting results regarding the predictive value of histological inflammation and myenteric plexitis at the margin to identify patients at risk of recurrence after resection for Crohn's Disease (CD). The aim of this study is to determine whether these features predict endoscopic recurrence after ileocolic resection (ICR).

Methods: Patients with CD referred for ICR with a primary anastomosis were enrolled in a prospective study at a tertiary centre. Clinical information and demographics were recorded. Hematoxylin and eosin stained slides from resection specimens were evaluated for grade of microscopic activity (None, focal, mild, moderate or severe) at proximal and distal margins, and the presence of submucosal plexitis. Gross inflammation at the margins was recorded. Post-operatively, patients underwent colonoscopy with mucosal biopsies at 3–6 months and 12–18 months post resection. Neo-terminal ileum Rutgeert's score > i2 determined recurrence. Bivariate analysis was performed with Fisher's exact test and relative risk calculated by Koopman score using Graphpad.

Results: 45 patients were enrolled in this study. Correcting for withdrawals, incomplete follow-up and unavailable specimens, 29 patients were included. Twenty-seven patients (93.1%) had at least 2 post-operative colonoscopies with a median follow-up interval of 18 months (4–144 months). The cumulative recurrence rate was 41.4% (12/29). Risk factors including age, disease phenotype and smoking status were not related to recurrence. Shorter time to first resection for CD (median 1 vs 8 years, p=0.017, Mann Whitney U test) and no post-operative anti-TNF therapy use (n=5/29 [0% with recurrence vs 23.5% without]; p=0.001) increased risk of recurrence over the total follow-up period. Patients on anti-TNF at first follow up were excluded from this analysis (n=4). Gross inflammation at the proximal margin was present in 25% (3/12) with and 15.4% (2/13) without recurrence (p=0.622). Neither presence nor degree of microscopic inflammation at the proximal or distal resection margins was associated with endoscopic recurrence at any time point (n=5/12 vs 6/13) p>0.9). We found no association between submucosal plexitis and risk of recurrence (33.3% in recurrence vs 23% without; p=0.67).

Conclusions: Independent of concurrent anti-TNF therapy, histological or gross inflammation at the proximal or distal resection margins at the time of resection did not predict early or subsequent endoscopic recurrence. In addition, myenteric plexitis did not predict disease recurrence. Confounding factors which may influence these results include cohort size and the median duration of follow up.

P312 Trabecular bone score in patients with inflammatory bowel diseases

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Background: Osteopenia and osteoporosis are known chronic complications of inflammatory bowel diseases (IBD). It is known that areal bone mineral density (aBMD) does not sufficiently reflect bone strength and quality. The trabecular bone score (TBS) provides an indirect measurement of bone microarchitecture, independent of aBMD.

Methods: The aim was to assess TBS and BMD of lumbar spine (LS) in IBD patients. Furthermore we analyzed the impact of clinical factors on TBS. The cohort consisted of consecutive IBD patients from tertiary IBD centre. Clinical characteristics i.e. age, gender, anthropometry, clinical behaviour, medication were recorded. The BMD was determined by dual-energy X-ray absorptiometry (DXA, Hologic Discovery) at the lumbar spine. TBS was determined by TBS Insight[®] software (Medimaps, France).

Results: The cohort consisted of 84 IBD patients (53 with Crohn's disease (CD) and 31 with ulcerative colitis (UC)). The mean age was 42.0±14.2 years with the mean disease duration of 11.0±7.0 years. There were 14% (12/84) postmenopausal women, 8 patients (9.5%) were on long term corticosteroids and 21 CD patients had prior major IBD surgery. The percentage of patients with substitution of vitamin D (800IU) and calcium (0.5–1g) was similar between CD and UC (24.5% vs. 29.0%), none of the patients was on anti-osteoporotic treatment. The mean LS BMD of the cohort was 0.964±0.113 g/cm² and TBS 1.36±0.14. We observed significantly lower mean TBS LS in patients with fistulising CD compared to luminal CD, 1.36±0.09 and 1.47±0.05 (p=0.0039) respectively. No similar finding was observed using BMD. We did not observe any significant impact of clinical characteristics nor medication in UC patients.

Conclusions: We observed that spine TBS can identify quality of bone mineral density in patients with Crohn's disease better than BMD itself. CD patients with severe disease are at higher risk of low bone mineral density.

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Glycan antibodies and pANCA in newly diagnosed inflammatory bowel disease patients at presentation and during follow-up

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Background: Serum antibodies in inflammatory bowel disease (IBD) patients have been extensively investigated. However, data on adult patients at diagnosis is scarcely available and results on stability over time are inconsistent. Our aim was to investigate serological antibodies in newly diagnosed untreated IBD patients and to relate them to disease severity, -location and response to therapy. Furthermore, we analysed antibody stability over time.

Abstract P313 – Table 1. Serum antibodies at diagnosis in patients with Crohn's Disease (CD), Ulcerative Colitis (UC), Inflammatory Bowel Disease Unclassified (IBDU) and in healthy controls (HC)

	CD (n=86)	UC (n=29)	IBDU (n=5)	HC (n=19)	P-value
gASCA positive, n (%)	20 (23%)	1 (3%)	0 (0%)	0 (0%)	CD-UC 0.011, UC-HC 0.604, CD-HC 0.012
AMCA positive, n (%)	8 (9%)	1 (3%)	0 (0%)	0 (0%)	CD-UC 0.284, UC-HC 0.604, CD-HC 0.190
ALCA positive, n (%)	11 (13%)	0 (0%)	0 (0%)	0 (0%)	CD-UC 0.034, CD-HC 0.098,
ACCA positive, n (%)	5 (6%)	0 (0%)	0 (0%)	1 (5%)	CD-UC 0.227, UC-HC 0.396, CD-HC 0.703
pANCA positive, n (%)	4 (5%)	13 (45%)	1 (20%)	0 (0%)	CD-UC 0.0001, UC-HC 0.0001, CD-HC 0.444
Glycan ⁺ pANCA/	33 (38%)/	1 (3%)/	0 (0%)/	1 (5%)/	CD-UC 0.0001
Glycan ⁻ pANCA ⁺ n (%)	2 (2%)	13(45%)	1 (20%)	0 (0%)	

Methods: Baseline anti-Saccharomyces cerevisiae antibodies (ASCA), anti-chitobioside carbohydrate antibodies (ACCA), anti-laminaribioside carbohydrate antibodies (ALCA) and anti-mannobioside carbohydrate antibodies (AMCA) were measured with enzyme-linked immunosorbent assays and perinuclear anti-neutrophilic cytoplasmic antibodies (pANCA) was measured by indirect immunofluorescence in serum samples of 120 untreated IBD patients at diagnosis (86 Crohn's Diseases (CD), 29 ulcerative colitis (UC), five IBD unclassified (IBDU)) and 19 gender and age-matched healthy controls. Presence and levels of antibodies were associated with disease outcomes. Serial assessment of antibodies was available in 71 IBD patients.

Results: At baseline, 43% of CD patients were positive for any antibody (mainly ASCA) and 41% of UC patients (mainly pANCA) (Table 1). There was a clear difference in antibody profile between UC (Glycan⁻pANCA⁺) and CD (Glycan⁺pANCA⁻) but no association was found with disease phenotype or disease activity scores at diagnosis.

Furthermore, no independent associations were found with future disease course like treatment response, progression to complicated disease behaviour, anti-TNF therapy or surgery.

An antibody status change occurred in 6–15% of IBD patients (see Table 2).

Table 2. Status change of antibodies at serial measurement

Marker	IBD (n=71)	CD (n=49)	UC (n=18)	IBDU (n=4)
ASCA				
No change	64 (90%)	42 (86%)	18 (100%)	4 (100%)
+ to -	5 (7%)	5 (10%)	-	-
- to +	2 (3%)	2 (4%)	-	-
AMCA				
No change	65 (91%)	43 (88%)	18 (100%)	4 (100%)
+ to -	4 (6%)	4 (8%)	-	-
- to +	2 (3%)	2 (4%)	-	-
ALCA				
No change	64 (90%)	42 (86%)	18 (100%)	4 (100%)
+ to -	2 (3%)	2 (4%)	-	-
- to +	5 (7%)	5 (10%)	-	-
ACCA				
No change	67 (94%)	46 (94%)	17 (94%)	4 (100%)
+ to -	2 (3%)	2 (4%)	-	-
- to +	2 (3%)	1 (2%)	1 (6%)	-
pANCA				
No change	60 (85%)	46 (94%)	12 (66%)	2 (50%)
+ to -	5 (7%)	2 (4%)	3 (17%)	-
- to +	6 (8%)	1 (2%)	3 (17%)	2 (50%)

Conclusions: This study does not support the routine use of serological antibodies in adult IBD patients as tool for disease activity or to predict future disease course. At most, the antibody profile supports the distinction between CD and UC and could be useful in IBDU patients. As antibodies are relatively stable over time and during therapy, the moment of analyses does not seem to be crucial.

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Management of perianal disease in patients with Crohn's disease

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Background: Perianal disease (PD) in patients with Crohn's disease (CD) can determine the treatment and it is cause of substantial morbidity. Our aims were to describe the multidisciplinary management of patients with CD and associated PD and to analyze the possible relationship between PD relapse and the type of fistula and treatments used

Methods: Retrospective case series study. Epidemiological and clinical data were collected from each patient. The type of fistula was determined by Parks classification. Complete response was defined as closure of the fistulous orifice and cessation of drainage in all fistulas and partial response as cessation of drainage in at least 50% of fistulas

Results: 66 patients with PD from a total of 300 patients with CD were included; 56% men, mean age: 44±12 y, 48% smokers. The mean time to diagnosis of PD was 43.1 months, although in eight patients (12%) the fistula diagnosis was prior to the diagnosis of CD. 13 fistulas were simple (28% superficial, 32% intersphincteric, and 40% low transsphincteric) and 49 were complex (15.9% low fistulas with proctitis or multiple external openings, 34.2% high transsphincteric, 26.3% suprasphincteric, 15.7% extrasphincteric and 7.9% rectovaginal). 79% of the patients had associated perianal abscess at diagnosis. Regarding the treatment used, 51 patients (77.4%) were treated with antibiotics (metronidazole, ciprofloxacin and levofloxacin, 91.5% with improvement of symptoms), 59 patients (89%) required immunomodulators (49 after diagnosis of PD) and 34 patients needed anti-TNF treatment (n=32, 94% of cases). The first line biological drug was infliximab (n=32, 94% of cases) with complete response in 14 patients (43.7%), partial response in 6 patients (18.7%) and unresponsive in 12 patients (37.5%, 9 of these patients were switched to adalimumab 3, of them with complete response). Surgery was required in 49 patients (75.4%) and in 24 of them (49%) setons were used, most of them (73.7%) for more than 12 months. Fistulotomy was used in both simple (33.3%) and complex fistulas (29.4%) with a complete response in 62.8% of the cases treated with this technique. Globally, 46.6% of patients had recurrence of PD. Patients with complex fistulas required more frequent surgical treatment (p=0.012) and had more recurrence (p=0.036). Significant differences between PD recurrence and sex, age at diagnosis or smoking were not found

Conclusions: Half of the patients require anti-TNF drugs to control PD, these patients present a more complex PD and with more recurrences. Despite the relapses, the effectiveness of biological drugs is acceptable in this type of patients, showing the importance of multidisciplinary and combined treatment (antibiotics, immunomodulators, biological drugs and surgery)

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Gastrointestinal immune related adverse events associated with programmed-Death 1 blockade

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Background: Immunotherapy for cancer is coming of age. The main class of check-point blockade agents, anti-Programmed-death 1 (PD-1) antibodies, is associated with various immune-related adverse events. The aim of this study was to describe the gastrointestinal immune-related adverse events (GI-irAE) associated with anti PD-1

Methods: This is a retrospective study of all consecutive adult patients who had a suspected GI-irAE related to anti-PD-1 antibody between 2013 and 2016. Patients were recruited through a pharmacovigilance registry (REISAMIC)[1]. Data was reviewed by a multidisciplinary team, including a pathologist who reviewed endoscopic biopsies. Frequency calculation was restricted to Gustave Roussy patients. Quantitative variables are described by median (range), qualitative variable by frequency (percentage).

Results: From January 2013 to August 2016, 909 patients received anti-PD1 or anti-PDL1 at Gustave Roussy. 43 consecutive patients with digestive symptoms were screened to search for GI-irAE. Finally, nineteen patients had a confirmed GI-irAE related to anti-PD-1 treatment. Frequency of GI-irAE was therefore 19/909 (1.3%). Median time between first infusion of anti PD-1 and onset of GI-irAE was 4.3 [1–33] months. Symptoms were diarrhea (n=16, 84%), abdominal pain (n=13, 68%), nausea and vomiting (n=8, 42%), severe constipation (n=2), and hematochezia (n=2). Lower endoscopy was normal in 7 patients (36%); it showed erythema in 5 patients (26%) and ulcerations in three patients (16%). All endoscopic lesions were accessible to a flexible sigmoidoscopy. GI-irAE associated with anti PD-1 could be classified into 4 distinct clinicopathological entities: acute colitis (n=8), microscopic colitis (n=7), severe ulcerative gastritis (n=2) and coprostitis (n=2). One patient with coprostitis died from necrotizing enterocolitis. Response rates to corticosteroids were of 87.5% (7/8) in acute colitis (resolution of symptoms in 36 days (6–172)) and of 57% (4/7) in microscopic colitis (resolution of symptoms in 98 days (42–226)), respectively.

Conclusions: This study suggests that GI-irAE associated with anti PD-1 are much less frequent than with anti CTLA-4 (1.3% vs 8–20%) [2]. It describes four entities with distinct features and outcomes, the most frequent being acute colitis and microscopic colitis.

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New approaches for IBD management based on text mining of digitalised medical reports and latent class modelling

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Background: Inflammatory bowel diseases (IBD) are characterized by a chronic inflammation of the gastrointestinal tract. The course of the diseases is variable, ranging from a quiescent course to multi-

ple (severe) flares, often necessitating surgery. Early identification of patients with an expected poor prognosis may be of importance, to adapt treatment strategies accordingly. Currently used clinical markers for severe disease course have limited value for decision making in daily clinical practice. Although diagnostic medical reports, e.g. endoscopy, pathology and imaging reports, may comprise relevant information, these are not used to stratify patients.

Methods: We aimed to apply Natural Language Processing of diagnostic reports of all IBD patients of a population-based cohort to test whether we could identify new disease characteristics within 6 months of diagnosis that can predict disease outcome. We converted and cleaned diagnostic medical reports for text mining approaches. Predictive models were used to characterise clusters obtained by unsupervised classification with Latent Class Modelling of disease events.

Results: Detailed health records with complete clinical follow-up since diagnosis, were available of 1142 newly diagnosed Crohn's disease patients within the population-based IBD South Limburg cohort. The mean follow-up was 101 months (SD 71 months). A total of 9760 imaging, endoscopy and pathology reports were digitalised and de-identified in order to remove any protected health information using pattern matching rules. We successfully corrected miswritten or misrecognised words and compounds with algorithms specifically adapted for Dutch language particularities. Three clusters were obtained with varying disease course based on flares, surgery, hospitalization, and medication changes. Subsequent steps include the identification of consecutive groups of words and their modality and/or negativity for relevant patient groups, aiming to define disease characteristics that predict disease course.

Conclusions: This new approach enables use of "hidden" information in generally available diagnostic medical reports for improved stratification of IBD patients.

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Postoperative complications, outcome, quality of life and self-image after ileal pouch-anal anastomosis in patients operated due to acute, severe or chronic, therapy refractory ulcerative colitis

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Background: Laparoscopic total proctocolectomy and ileal pouch anal-anastomosis (IPAA) is widely used surgical treatment in severe, therapy refractory ulcerative colitis (UC). Our aim was to assess influence of timing of IPAA surgery (urgent vs. elective procedure) on long-term functional outcome, early and late complication rates, patient reported outcome self-image and quality of life in UC patients who underwent IPAA surgery.

Methods: Demographic and clinical data was collected. Pouch function was established with the Öresland score. Body self-image after IPAA surgery was assessed with Dunker's body image questionnaire. Quality of life (physical, social, emotional status) was measured with Short Inflammatory Bowel Disease Questionnaire. Data were compared concerning the timing of surgical intervention.

Results: 30 patients were enrolled in this prospective study. 46.7%

of the patients underwent IPAA surgery due to the acute, severe UC and 53.3% of the cases because of chronic, therapy refractory UC or UC related colorectal carcinoma. The most common early complication was suture failure (23.3%) and subileus/ileus (30%) whereas the most frequent late complication was pouchitis (53.3%) and anastomosis stricture (23.3%). No difference was found between the urgent vs elective group regarding early complications and re-operation rate after IPAA procedure (p=0.3; p=0.7). Body mass index increased significantly after IPAA surgery (p=0.0003). Pouchitis was observed in 43.3% of patients and cuffitis was present in 20% of subjects during the follow-up. No significant difference was found between patients with and without pouchitis regarding to daily stool number and fecal incontinence. Rate of fecal incontinence was 26.6% at daytime and 53.3% at night. 59% of our patients think that they have some social disadvantage due to their health condition. However, self-image of the patients presented no significant difference before and after surgery independently of the timing. Patient reported outcome (PRO) was positive in more than three-quarter of the patients after IPAA procedure.

Conclusions: Our results shows that quality of life, PRO and self-image seems to be good among UC patients after IPAA surgery despite of frequent long-term functional abnormalities and complications independently of timing of surgery.

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Accuracy of magnetic resonance enterography for extraluminal complications of Crohn's disease

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Background: Crohn's disease (CD) can be associated with intraluminal and extraluminal complications like abscess and fistula. More than half of patients with Crohn's disease need surgery to treat these complications at least once in their life. Aiming to make an appropriate choice of intervention, the magnetic resonance enterography (MRE) is largely used to assess the type and severity of these complications. In a previous prospective study pre-operative MRE has been able to predict surgical approach in the most of symptomatic patients, showing low sensitivity and high specificity for the diagnosis of fistula or abscess and high sensitivity and low specificity for stenosis.

Methods: We reviewed a sample from a referral center of 42 consecutive symptomatic CD patients addressed to surgery who underwent preoperative MRE. All data were recorded in an electronic database (Excel Microsoft). We analyzed the concordance between MRI and surgical findings for presence of fistulas or abscesses and other stenosis-related characteristics (location, number and extent). We calculated the proportions of VP, FN, FP and VN with 95% confidence limits and the accuracy of the index test (MRE) compared to the reference test (surgery) for the diagnosis of stenosis, fistula or abscess.

Results: Fifty-two percent of patients were male, mean age was 40.5±13.6 years. Forty-one (98%) were symptomatic. The median time between MRE performance and surgery was 2 months (range

1–24); time was 3 months in 29 pts (69%). A laparoscopic approach was performed in 69% of patients. The prevalence of fistula at surgery was 24% and of abscess 17%. MRE failed in detecting fistulas in 2 patients and falsely identified abscess in one patient. Sensitivity and specificity of MRE were 40% and 99% for fistula and 67% and 94% for abscess, respectively. Accuracy of MRE for fistula was 76% (95% CI 60–88%) and for abscess 88% (95% CI 69–93). For detection of single and multiple stenosis the sensitivity of MRE was 93% and 88% respectively.

Conclusions: The MRE was a fairly accurate imaging test for the characterization of stenosis and for the diagnosis of fistula or abscess. Taking into account limitations due to retrospective data, MRE shows high specificity and low sensitivity for the diagnosis of fistula and abscess according to data from literature. Moreover, it appears more useful to identify the site and extension of stenosis and the single stenosis with respect to the multiple. Aiming to optimize the decision about surgery, there is still a need for development of shared criteria among radiologists and surgeons to further assess the reproducibility of MRE and its accuracy for the diagnosis of complications in prospective studies of patients with CD

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Accurate cut-offs for predicting endoscopic activity and mucosal healing in Crohn's disease with fecal calprotectin

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Background: The assessment of symptoms has not proved to be useful in accurately establishing endoscopic activity in Crohn's disease (CD). Fecal calprotectin (FC) has demonstrated high precision to detect endoscopic activity in CD. However, the clinical applicability of FC is limited as no consensus exists on the optimum cut-off point for establishing endoscopic activity and mucosal healing. The aim of this study is to analyze whether FC is a good tool for generating highly accurate scores for the prediction of the state of endoscopic activity and mucosal healing.

Methods: The simple endoscopic score for Crohn's disease (SES-CD) and the Crohn's disease activity index (CDAI) was calculated for 71 patients diagnosed with CD. FC was measured by the Enzyme-Linked Immunosorbent Assay test. An accuracy analysis was made by estimating ROC curve of FC with respect to the SES-CD. We calculate both FC cut-off point with greater accuracy to establish endoscopic activity and as values for sensitivity and specificity, as well as for predictive scores: positive and negative, global accuracy and likelihood ratios (LR). It was calculated that a cut-off with specificity >90% and LR+ ≥ 10 would present strong evidence to support the diagnostic hypothesis (endoscopic activity) and a cut-off point with sensitivity >90% and LR- ≤ 0.1 would offer strong enough for to reject the hypothesis. Finally, the Fagan nomogram was calculated to determine the probability of endoscopic activity or mucosal healing after obtaining the biomarker score and according to clinical symptoms.

Results: A FC cut-off of 170 $\mu\text{g/g}$ (Sensitivity 77.6%, Specificity 95.5% and LR+ 17.06) predicts a high probability of endoscopic activity, and a FC cut-off of 71 $\mu\text{g/g}$ (Sensitivity 95.9%, Specificity 52.3% and LR- 0.08) predicts a high probability of mucosal healing. In our sample, the prevalence of endoscopic activity was 69%, but if a patient shows FC $\geq 170 \mu\text{g/g}$ they have a 97% probability of presenting endoscopic activity; and if they have FC $\leq 71 \mu\text{g/g}$ the probability would be 84% for presenting mucosal healing. Clinical symptoms modified the probabilities of predicting endoscopic activity (100% if clinical activity vs 89% if clinical remission) or mucosal healing (75% if clinical activity vs 87% if clinical remission) in the diagnostic scores generated.

Conclusions: FC is a useful tool for generating highly accurate scores for predicting the state of endoscopic activity or mucosal healing in CD patients. Although, it is important to take into account the specific clinical context in order to interpret the probabilities of presenting endoscopic activity or mucosal healing according to the FC level.

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Utility of a semi-quantitative rapid test in diagnosis of ulcerative colitis

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Background: The aim of this study is to compare two methods for measuring the concentration of faecal Calprotectin (FC) and assess the possibility of distinguishing between ulcerative colitis (UC) and irritable bowel syndrome (IBS).

Methods: Fifty-three patients with UC and 46 patients with IBS were prospectively included in the study. All patients were performed colonoscopy to confirm the diagnosis. Faecal calprotectin levels were analyzed by semiquantitative rapid test (CalDetect[®]) and an enzyme-linked immunosorbent assay (ELISA). Sensitivity and specificity of both assays were calculated.

Results: The sensitivity of the test set for direct semiquantitative directly to a value of 15 $\mu\text{g/g}$ was 78% and specificity of 83% for diagnosis of ulcerative colitis. For the ELISA to a value of 50 mg/g sensitivity and specificity were 83% and, respectively 93% (p=0.068).

Conclusions: Although the ELISA test has a higher diagnostic accuracy, it is not significantly higher compared to the semi-quantitative test directly CalDetect[®]. In addition, direct semi-quantitative test has the advantage of having immediate results is much easier to use in ambulatory patients.

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Activity graph patterns recorded using a mobile monitoring system are associated with clinical outcomes of patients with Crohn's disease

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Background: Usefulness of a mobile monitoring system for Crohn's disease (CD) has not been evaluated. We aimed to determine whether activity graph patterns depicted at a web-based CD symptom diary (CSDS) could indicate disease clinical outcomes.

Methods: Patients with CD from 3 tertiary hospitals were prospectively invited to record their symptoms at CSDS site using a smart phone at least once a week. Activity patterns for at least 2 months were statistically classified into good (G) or poor (P) group based on two factors in two local windows; the first factor is the degree of score variation (maximum – minimum) at each window and the second factor is the trend (upward, stationary or downward) of patterns indicated by the difference of mean activity score between two windows. Clinical data regarding hospitalization, unscheduled hospital visit, and bowel surgery related with CD since study enrollment was retrospectively assessed by a medical personnel who blinded to results of CSDS. Association with outcomes was evaluated using logistic regression analysis.

Results: Among 309 patients invited, 266 who recorded their symptoms at least for 2 months were enrolled in the study (male 187; diagnosis age, mean yr, 23.6±8.7; follow-up, mean month, 39.9±10.1). Patient number of G and P group was 220 (82.7%) and 46 (17.3%), respectively. Baseline characteristics including sex, diagnosis age, location, and disease behavior were not different between groups. P group was significantly more associated with hospitalization (56.5% vs. 34.1%, p=0.004), unscheduled hospital visit (17.4% vs. 5.5%, p=0.011), and bowel surgery (19.6% vs. 1.8%, p<0.001) during follow-up period than G group. In multivariate analysis, P graph pattern (odds ratio (OR) 2.67, 95% confidence interval (CI) 1.36–5.27, p=0.005) complicating behavior (OR 2.92, 95% CI 1.69–5.04, p<0.001), and young diagnosis age (OR 1.05, 95% CI 1.02–1.09, p=0.003) were independently associated with hospitalization. P graph pattern (OR 4.06, 95% CI 1.50–10.99, p=0.006) and ileal location (OR 5.79, 95% CI 1.17–28.81, p=0.032) remained as independent risk factors for unscheduled visit. P graph pattern (OR 15.54, 95% CI 4.29–56.24, p<0.001) and complicating behavior (OR 6.13, 95% CI 1.49–25.17, p=0.012) were found to be independent risk factors for bowel surgery.

Conclusions: Activity graph pattern depicted at a web-based symptom diary is a useful indicator of poor clinical outcomes such as hospitalization, unscheduled hospital visit and bowel surgery in patients with CD.

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A change in ΔMCV predicts mucosal healing in patients with Crohn's disease under combination therapy

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Background: Higher tioguanine (6-TGN) levels have been associated with better clinical and endoscopic outcomes in patients with inflammatory bowel disease under thiopurine therapy. Unfortunately dosing of 6-TGN levels is not available in most centers. Previous studies have suggested that an elevated erythrocyte mean corpuscular volume (MCV) can be a valid surrogate of adequate 6-TGN levels.

Methods: This was a retrospective study using a cohort of patients

under combination therapy with Infliximab and azathioprine followed in a single center. We evaluated the influence of a ΔMCV in major endpoints including clinical and endoscopic response and remission at the end of the first year of treatment. Clinical response was defined as a decrease of 3 points in Harvey-Bradshaw Index and clinical remission as a Harvey-Bradshaw Index ≤4. Endoscopic response was defined as improvement in endoscopic appearance and endoscopic remission as the absent of ulcers. In a subgroup of patients anti-TNF pharmacokinetics (serum levels and antibodies) were also evaluated.

Results: 143 patients with Crohn's Disease (CD) were included, 76 patients (53.1%) male with mean age of 28±11.5 years. MCV at baseline and at week 48 of treatment was 88.2fL±15.8 and 89.7fL±4.7. At the end of the first year of combination therapy, 87.4% patients achieved clinical response, 74.1% clinical remission, 83.9% endoscopic response and 43.4% endoscopic remission.

Patients with higher variations in MCV were more likely to be in clinical remission (3.16±4.94 vs -0.95±6.44, p<0.001). There was no statistical significance between ΔMCV and clinical response. Patients with endoscopic response and remission had higher ΔMCV (2.57±3.70 vs -3.38±7.05, p<0.001 and 3.17±3.97 vs -0.27±5.74, p=0.006).

The area under the receiver-operating curve (auROC) for predicting endoscopic remission, endoscopic response and clinical remission according to the ΔMCV was 0.665 (95% CI 0.532–0.797, p=0.025), 0.714 (95% CI 0.545–0.883, p=0.011) and 0.711 (95% CI 0.616–0.806, p<0.001).

For each unit increase in MCV level there was a significant increase in the probability of achieving clinical remission- OR 1.17 (95% CI 1.07–1.27, p=0.001), endoscopic response- OR 1.29 (95% CI 1.10–1.50, p=0.001) and endoscopic remission- OR 1.17 (95% CI 1.027–1.326, p=0.018). There was a negative correlation between C-reactive protein (CRP) levels and ΔMCV (Spearman's ρ=-0.254, p=0.003); patients with a negative CRP at week 48 had higher ΔMCV (5.67±5.37 vs 3.45±4.71, p=0.012). We found no significant association between ΔMCV and Infliximab through levels and antibodies.

Conclusions: Our results suggest an association between ΔMCV and better outcomes in CD patients under combination therapy. Assessment of ΔMCV may be an alternative to 6-TGN dosing.

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Fatty liver assessment in inflammatory bowel disease patients using controlled attenuation parameter

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Background: It is well recognized that inflammatory bowel disease (IBD) patients are at risk of developing nonalcoholic fatty liver disease (NAFLD). Our aim was to assess the prevalence of fatty liver in IBD patients as quantified by controlled attenuation paramete-

ter (CAP), compared to conventional methods of detecting hepatic steatosis.

Methods: For this observational study, we prospectively evaluated all IBD patients presenting for a disease flare or follow-up visit in our clinic, during a 12 month period (Nov 1st 2015 – Oct 31st, 2016). Clinical characteristics and laboratory data were recorded. Hepatic steatosis was evaluated by abdominal ultrasound, hepatic steatosis index (HSI) and transient elastography with CAP (Fibroscan, Echo-sens, Paris). Significant steatosis ($S \geq 1$) was defined for a CAP value over 236 [1], and the cut-off of HSI for detecting NAFLD was set at ≥ 36 [2].

Results: Altogether 36 IBD patients (17 ulcerative colitis, UC and 19 Crohn's disease, CD), mean age 43 ± 13 years, 52.8% female, were included in the analysis. All patients denied alcohol use of more than 20 g/day. No significant difference in the two groups (UC, CD) was seen regarding disease activity (remission/flare – 52.9/47.1% in the UC group, 47.4/51.6% in the CD group), BMI (23.7 and 23.4 respectively), mean hemoglobin values (13.38 and 13.48 g/dl, respectively) or inflammatory markers (ESR 18 and 19.9 mm/h, fibrinogen 523 and 520 mg/dl, respectively). UC patients had higher mean cholesterol values (197.4 vs. 175 mg/dl) and 2 of them were diabetic (compared to none in the CD group). Mean CAP was similar among the two groups – 222 for UC and 223 dB/m for CD, as well as mean HSI, with values of 35 ± 6 and 34 ± 5 , respectively. Ultrasound and HIS both identified 8/36 (22.2%) patients with fatty liver, whereas CAP assessment detected 3 more patients (11/36, 30.5%) with significant steatosis ($S \geq 1$). NAFLD-IBD patients were more likely to have CD, history of resection, steroid use and longer disease duration – Table 1.

Table 1. Comparison of IBD patients with/without NAFLD using CAP assessment

	IBD with NAFLD	IBD without NAFLD
Age	44.8 \pm 13.4	42.3 \pm 13.2
IBD phenotype (CD%)	72.7	44
BMI	25.2 \pm 3.6	22.8 \pm 3.1
Disease duration (months)	35.6 \pm 32.6	26.5 \pm 40.1
History of resection (%)	27.3	0
Steroid use (%)	36.4	28
Cholesterol (mg/dl)	186 \pm 41	185 \pm 36
ESR (mm/h)	11.8 \pm 7	24.9 \pm 16
Fibrinogen (mg/dl)	454 \pm 139	564 \pm 139

Conclusions: CAP outperformed conventional ultrasound and HSI in detecting fatty liver in IBD patients. This result needs to be explored in larger cohorts.

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Evaluation of ability to predict mucosal healing by quantitative fecal immunochemical test in ulcerative colitis

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Background: Fecal biomarkers in inflammatory bowel disease is emerging as a non-invasive test to replace colonoscopy. The aim of our study was to evaluate the efficacy of quantitative fecal immunochemical test (FIT) as predictive biomarker of mucosal healing in UC.

Methods: Between February 2013 and November 2014, a total of 82 FIT results, obtained in conjunction with colonoscopies, were retrospectively evaluated for 63 patients with UC. The efficacy of FIT for evaluation of disease activity was compared to colonoscopic findings. Quantitative fecal blood with automated equipment examined from collected feces. Endoscopic disease severity were assessed using the Mayo endoscopic subscore (MES) classification.

Results: All of 21 patients with MES 0 had negative FIT (<7 ng/ml), but 22 patients with MES 2 or 3 had a mean FIT of >134.89 ng/ml. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of negative FIT about mucosal healing were 73.33%, 81.82%, 91.49%, 51.43% and 73.17%, respectively. Among patients with clinical remission, FIT was negative in 31 (81.6%) of 38 cases, with a mean fecal hemoglobin concentration of 6.12 ng/ml (range, negative to 80.9 ng/ml) for this group of patients. Among patients with clinical active disease, FIT was negative in 16 (36.4%) out of 44 cases, with a mean fecal hemoglobin concentration >167.4 ng/ml for this group of patients. FIT was positively correlated with endoscopic activity ($r=0.626$, $p<0.01$) and clinical activity ($r=0.496$, $p<0.01$).

Conclusions: Quantitative FIT can be a non-invasive and effective biomarker to predict mucosal healing and clinical activity in UC.

Clinical: Therapy and observation

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Combination therapy with adalimumab and immunomodulators decreases incidence of intestinal resection in Crohn's disease patients previously treated with infliximab: a large, multicentre cohort study

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Background: Few studies have reported factors associated with intestinal resection in patients with Crohn's disease (CD) treated with adalimumab (ADA). We investigated incidence of intestinal resection and the factors related to the requirement of intestinal resection in patients who participated in the Adalimumab Japanese Multicentre Cohort Study of Crohn's disease (ADJUST).

Methods: Data were retrospectively collected from all patients with CD who had received at least one induction dose of 160 mg of ADA between October 2010 and December 2013. Patients with active CD received ADA as induction of remission were included, while those with inactive CD started on ADA for prevention of postoperative recurrence were excluded. The cumulative rates of intestinal resection following the first administration of ADA were estimated by the Kaplan–Meier method. We also investigated the cumulative rate of intestinal resection and the related prognostic factors stratified by prior use of infliximab (IFX). Prognostic factors related to the cumulative rates of intestinal resection were evaluated by log-rank tests and multivariate Cox regression analysis.

Results: A total of 966 patients (median age, 33.6 years; female, 31%) were included in the study. The median duration of CD was 7.6 years. Forty-four percent of the patients with active CD who required induction of remission with ADA had undergone prior intestinal resection. Concomitant treatment with immunomodulators (IMs) and prednisolone (PSL) was administered to 38% and 16% of the patients, respectively. Forty-nine percent of the patients had been previously treated with IFX (IFX exposed group), and 51% were naïve to IFX (IFX naïve group). The 1-, 2-, 3- and 4-year cumulative rates of intestinal resection were 10%, 17%, 24% and 35%, respectively. The cumulative rates of intestinal resection were significantly higher in the IFX exposed group than in the IFX naïve group. In the IFX exposed group, the multivariate Cox regression analysis demonstrated stricturing or penetrating disease, ≤ 3.7 g/dL of serum albumin, without prior intestinal resection and concomitant treatment with PSL as independent predictors of high rates of intestinal resection, and the association between concomitant treatment with IMs and significant reduction of the incidence of intestinal resection. In IFX naïve patients, stricturing or penetrating disease was an independent predictor of high rates of intestinal resection. However, concomitant treatment with IMs was not associated with rates of intestinal resection in IFX naïve patients.

Conclusions: Our data suggested that combination therapy of ADA and IMs significantly decreased the rates of intestinal resection, particularly in CD patients previously treated with IFX.

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Efficacy of vedolizumab on patient-reported outcomes in ulcerative colitis patients: results from a prospective German observational study

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Background: Patient reported-outcomes [PROs] are becoming a major therapeutic goal in IBD, both in clinical trials and in daily clinical care. Moreover, it has recently been shown that in patients with UC the absence of rectal bleeding (Mayo Clinic endoscopic Score (MCSe)=0) shows high sensitivity for detecting mucosal healing. [1] We therefore investigated the efficacy of vedolizumab, a humanized monoclonal antibody against $\alpha 4 \beta 7$ -integrins, in achieving PROs, especially with regard to rectal bleeding (MCSe=0).

Methods: A consecutive cohort of 60 adult IBD patients with ulcerative colitis (partial Mayo score >4) receiving vedolizumab was prospectively recruited from 9 German tertiary IBD centers. Primary endpoint was the absence of rectal bleeding (MCSe=0) as determined at week 2, 6, 14, 30 and 54, resp. Secondary endpoints included a combined endpoint (absence of rectal bleeding and stool frequency of 1 or 2, respectively, according to the Mayo Clinic Scoring system (MCSsf)). Quality of life (QoL) was evaluated by use of a visual analogue scale (VAS; 0–100). This data represents a subgroup analysis from a larger prior observational study. [2] [3]

Results: 81.7% of patients had received prior treatment with anti-TNF-antibodies, 40% of patients had been hospitalized within one year prior to vedolizumab treatment initiation. 53.4% of patients received corticosteroids at week 0 (median 20 mg; range 0–60 mg). At week 54 20/60 patients (33.3%) reported absence of rectal bleeding, 17/60 patients (28.3%) achieved steroid-free cessation of rectal bleeding. A combined endpoint of MCSe=0 and normal stool frequency (MCSsf=0) was achieved by 16.7% of patients, while 26.7% of patients experienced absence of rectal bleeding (MCSe=0) and a mild increase in stool frequency (MCSsf=1) (Table 1). Quality of life increased from 47,5 at week 0 to 70 at week 14, 72.5 at week 30 and 70 at week 54, resp.

Table 1. Response to vedolizumab treatment

Week	2	6	14	30	54
MCSe=0	25%	36.7%	43.3%	36.7%	33.3%
MCSe=0, steroid-free	10%	23.3%	26.7%	30%	28.3%
MCSe=0 and MCSsf=0	5%	10%	21.7%	15%	16.7%
MCSe=0 and MCSsf=1	10%	16.7%	28.3%	26.7%	26.7%

Conclusions: In UC patients with a severe disease course vedolizumab treatment results in a rapid and persistent absence of rectal bleeding in one third of patients. Normalization of stool frequency occurs less frequently and may reflect chronic alterations/damages of the bowel that may not be reverted by anti-inflammatory treatment strategies in this severely ill patient population. Absence of rectal bleeding is associated with a substantial improvement in patients quality of life. However, a substantial percentage of patients still required steroid-treatment to achieve these endpoints.

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Evolution after a “de-intensification” strategy with anti-TNF therapy in patients with inflammatory bowel disease in clinical remission: multicenter study

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Background: The “de-intensification” of anti-TNF therapy in IBD patients with sustained remission may be considered for cost and safety reasons. Our aims were: 1) to evaluate the risk of relapse after anti-TNF “de-intensification” in clinical remission; 2) to identify predictive factors associated with relapse; 3) to assess the effectiveness of a second “re-intensification”; and 4) to analyze safety of this strategy.

Methods: An observational, retrospective and multicenter study was performed. Patients with Crohn's disease (CD) and ulcerative colitis (UC) who achieved remission on intensified anti-TNF therapy and then de-intensified a standard dose being in clinical remission were included. The follow-up after “de-intensification” was at least 6-months.

Results: 287 patients were included (50.9% male, mean age 43.1 years, 64.8% CD). Previous anti-TNF intensification was due to loss of response (58.9%) and partial response (35.6%). The reasons of “de-intensification” were: 87.7% medical decision following sustained clinical remission, 6.7% patient decision and 3.5% adverse events. 31.4% of patients relapsed with a median of 8 months (95% CI: 6.14–9.85). The cumulative rate of relapse was 11.5% at 6 months, 23.9% at 1 year, 33.4% at 2 years and 47.9% at 5 years; and the incidence rate of relapse was 18.9% patient-year. At time of “de-intensification”, endoscopy was performed in 32.2% of patients, out of them 66.3% had no activity and 31.5% mild activity. 48.4% continued combination with immunomodulators after “de-intensification”. In the multivariate analysis, the variables associated with a higher risk of relapse were: presence of extraintestinal manifestations (HR=1.72, 95% CI: 1.04–2.85, p=0.032), and previous surgery related to IBD (HR=2.30, 95% CI: 1.21–4.38, p=0.011). The factors associated with a lower risk of relapse: concomitant treatment with immunomodulator after “de-intensification” (HR=0.406; 95% CI: 0.23–0.70, p=0.001) and inflammatory behavior CD vs. structuring-fistulizing pattern (HR=0.385, 95% CI: 0.20–0.72, p=0.003). 74.2% of patients who relapsed were treated with a new anti-TNF intensification, 57.6% achieved remission in early 8 weeks, and 71.2% at the end of follow-up. After that, only 6% had adverse effects, most of them mild.

Conclusions: The incidence rate of inflammatory bowel disease relapse after “de-intensification” in patients with clinical remission was 18.9% patient-year. Extraintestinal manifestations and previous surgery for IBD were predictors of relapse; while concomitant treatment with immunomodulator and inflammatory behavior CD were associated with lower risk of relapse. The treatment of relapse with the new “re-intensification” was safe and effective in 3 out of 4 patients.

P328 Patient and physician perspectives on managing iron deficiency with or without anaemia in inflammatory bowel disease: findings from a European online survey

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Background: Iron deficiency (ID) and iron deficiency anaemia (IDA) are conditions frequently observed in patients with inflammatory bowel disease (IBD) and require appropriate treatment. This study investigated patient and physician perspectives on the management of these conditions.

Methods: Online surveys were conducted between July and September 2016 across France, Germany, Italy, Spain and the UK. Participating patients had to be diagnosed with IBD and have a history of oral or intravenous (IV) iron treatment for ID or IDA.

Results: In total, 1503 patients and 500 physicians (410 gastroenterologists, 90 internal medicine specialists) participated. According to physicians, approximately two-thirds (66%) of their patients with IBD were currently suffering from ID (33%) or IDA (33%), yet treatment was not thought necessary for 34% of patients with ID (versus 14% of patients with IDA). Only 71% of patients felt their treating physician was proactively checking for ID whereas 85% of physicians stated they monitor for it throughout IBD remission and flare. Of the patients surveyed, 60% waited >1 year from symptom onset to diagnosis. While patients tended to be less accurate than physicians in assigning symptoms, one-third (29%) of the participating physicians felt they cannot tell whether a symptom is caused by IBD or ID. Patients considered "weakness", "tiredness" and "paleness" as symptoms most clearly associated with ID, whereas physicians most frequently identified "paleness", "breathlessness" and "dizziness". Although there were differences between patient and physician perspectives on symptom assignment, survey responders agreed that ID severely impacts quality of life, with constant fatigue and

exhaustion impeding normal daily function. In terms of treatment, 67% of patients waited >3 months from diagnosis before receiving iron treatment. Distinct factors were found to influence the choice of iron therapy: "convenience" and "low cost" were the main reasons to choose oral iron treatment while "efficacy" and "speed of response" were key to choosing IV iron therapy. Overall, patients were satisfied with their iron therapy (mean score 7.0; range 0–10 where 10 is extremely satisfied) and treatment significantly improved patient daily wellbeing during both IBD remission and flare ($p < 0.05$), especially for patients who were severely affected by ID.

Conclusions: Our findings indicate gaps in patient and physician perspective and awareness of ID. Uncertainties in recognizing symptoms associated with ID may lead to undertreatment in the clinical setting. Patients and physicians agree that once ID or IDA is managed effectively with iron therapy, the quality of life for the IBD patient can significantly improve.

P329 Effect of adalimumab dose escalation on clinical, health-related quality of life, treatment satisfaction and work productivity outcomes among patients with ulcerative colitis in a clinical practice setting: results from INSPIRADA

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Background: Although adalimumab (ADA) has been shown to induce and maintain clinical remission in moderate to severe ulcerative colitis (UC), some patients (pts) may lose initial response and could benefit from dose escalation [1]. We assessed the effect of ADA dose escalation on various outcomes among pts with UC in clinical practice.

Methods: INSPIRADA was a single-arm, multi-country, open-label study that evaluated the effect of ADA on clinical outcomes, costs of care, treatment satisfaction, and work productivity in pts with UC treated according to usual clinical practice. Adults with active UC, Physician's Global Assessment (PGA) of ≥ 2 , and Short Inflammation

Abstract P329

Outcomes at Week 26	
SCCAI response, n/N (%)	82/129 (64%)
SCCAI remission, n/N (%)	43/129 (33%)
Change from BL to Week 26	
SIBDQ, mean \pm SD	14.4 \pm 14.6 ^a (N=128)
EQ-5D-5L: visual analogue scale, mean \pm SD	17.1 \pm 24.6 ^a (N=128)
TSQM, mean \pm SD	
Effectiveness	17.0 \pm 29.9 ^a (N=125)
Side effects	22.3 \pm 38.5 ^a (N=123)
Convenience	2.7 \pm 26.5 (N=124)
Global satisfaction	17.6 \pm 32.7 ^a (N=123)
WPAI, mean \pm SD	
Work time missed (%) ^b	-5.7 \pm 29.4 (N=65)
Impairment while working (%) ^b	-17.1 \pm 26.8 ^a (N=66)
Overall work impairment (%) ^b	-19.8 \pm 28.7 ^a (N=65)
Daily activity impairment (%)	-25.1 \pm 33.3 ^a (N=126)
^a P<0.001 compared with BL using paired t-test.	
^b Only patients who were employed were assessed.	

matory Bowel Disease Questionnaire (SIBDQ) ≤ 45 at baseline (BL) who failed conventional treatment and who had experienced rectal bleeding ≤ 7 days of BL were enrolled. Pts received ADA 160/80 mg at Wk 0/2 followed by ADA 40 mg every other week at Wk 4 through Wk 26. Pts who did not respond to ADA by Wk 8 were to discontinue ADA. Pts who lost response at or after Wk 8 could escalate to ADA 40 mg weekly. Outcomes were assessed for pts who dose escalated. Clinical outcomes included Simple Clinical Colitis Activity Index (SCCAI) response (SCCAI decrease ≥ 2) and remission (defined as an SCCAI ≤ 2). HRQoL was assessed using SIBDQ and the European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) questionnaire. Satisfaction with medication was measured using the Treatment Satisfaction Questionnaire for Medication (TSQM). Work Productivity and Activity Impairment (WPAI) outcomes were determined. Change from BL to Wk 26 in HRQoL, treatment satisfaction, and WPAI outcomes were calculated. Missing data were imputed using nonresponder imputation for response/remission and last observation carried forward for all other outcomes.

Results: Data from 129 pts who dose escalated were analysed. At Wk 26, 64% of pts who dose escalated achieved SCCAI response and 33% achieved SCCAI remission (Table 1). Except for work time missed and convenience in TSQM among pts who dose escalated, statistically significant ($p < 0.001$) improvements from BL to Wk 26 were seen in work productivity, performance of daily activities, SIBDQ, EQ-5D-5L, and treatment satisfaction. The safety profile of ADA among pts who dose escalated was consistent with that of pts who did not dose escalate.

Conclusions: In pts with UC who lost response, ADA dose escalation was an effective option to recapture response and remission. Significant improvements in HRQoL, treatment satisfaction, and work productivity were also observed.

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Discontinuation of corticosteroids among ulcerative colitis patients treated with vedolizumab in the United States

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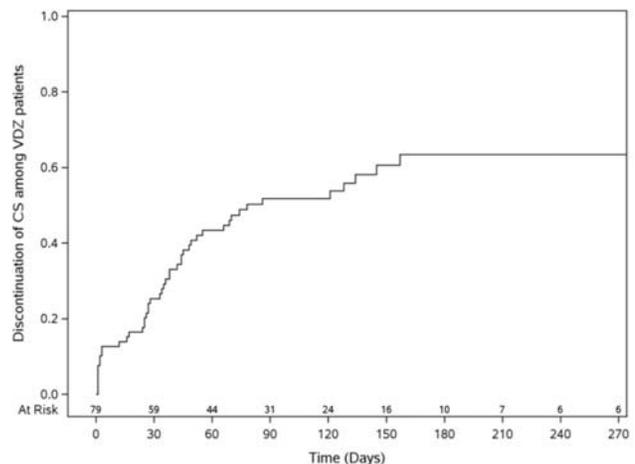
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Background: Corticosteroids (CS) are effective in the short-term induction of patients with moderate to severe ulcerative colitis (UC) but not for maintenance of remission, due to the associated risks. Vedolizumab (VDZ), a humanized monoclonal anti- $\alpha_4\beta_7$ integrin antibody, is approved for the treatment of adults with moderately-to-severely active UC. This study assessed VDZ treatment persistence and CS discontinuation among UC patients co-induced with CS.

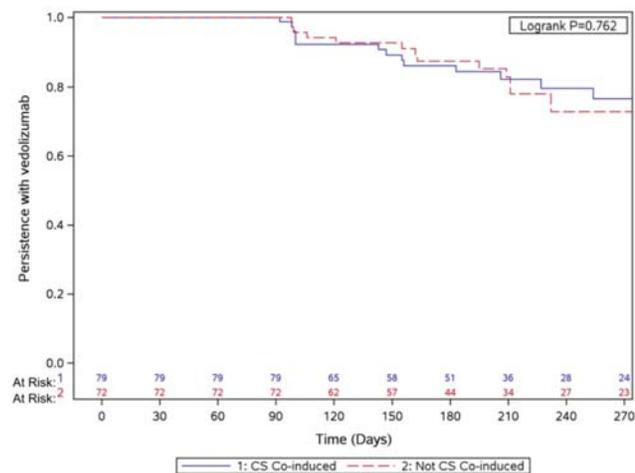
Methods: Adult (≥ 18 years) CD patients initiating VDZ between 1 May 2014 and 30 September 2016 were identified in the US Optum Research Database. Patients with ≥ 12 months history (baseline) before their first VDZ claim (index date) and who completed induction (defined as ≥ 3 infusions in ≥ 98 days post-index) were included. CS-related measures included: dependence ($\geq 80\%$ CS use during the 6 months immediately prior to index date), co-induction with CS (CS fill for ≥ 28 days during the induction phase), CS discontinuation (treatment gap ≥ 60 days between CS fills) while on VDZ therapy.

VDZ persistence was defined as no treatment gap ≥ 90 days between consecutive infusions. CS discontinuation and VDZ persistence were measured using the Kaplan-Meier method.

Results: A total of 151 VDZ patients were included with a mean (SD) age of 42.8 (16.6) years; 41% female, median follow-up period of 251 days. During baseline, 81%, 45% and 90% of patients were treated with aminosaliclates, immunomodulators, and CS, respectively; 68% of patients had received a biologic before initiating VDZ. Of UC VDZ patients, 52% ($n=79$) were co-induced with CS during the induction phase, of whom, 18% (14/79) were CS-dependent. Overall, 57% (45/79) of CS co-induced patients discontinued their CS and among CS-dependent patients, 36% (5/14) discontinued their CS. CS discontinuation and VDZ persistence are shown in Figures 1a & 1b.



Patients were censored at discontinuation of VDZ or the end of follow-up.



Patients were censored at the end of follow-up.

Figure 1. (A) Discontinuation of corticosteroids among patients with ulcerative colitis treated with VDZ. (B) Persistence with VDZ among patients co-induced with and without corticosteroids.

Conclusions: This real-world study, using a nationally representative US database, showed that nearly half of UC patients receiving VDZ were not co-induced with CS. Among VDZ patients co-induced with CS, over half discontinued during the follow-up period. Despite the treatment-refractory patients included in this study, the CS discontinuation rate at 26 weeks among VDZ patients was higher than what was reported from the GEMINI clinical trials. VDZ persistence was similar between CS co-induced patients versus those without CS co-induction. Future studies should examine CS-related outcomes over a longer follow-up period.

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Final results on efficacy and safety of biosimilar infliximab after one-year: results from a prospective nationwide cohort

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Background: Biosimilar infliximab CT-P13 received positive CHMP recommendation in June 2013 for all indications of the originator product. It has been previously shown that CT-P13 is effective and safe in inducing remission in inflammatory bowel diseases (IBD). We report here final results from a prospective nationwide IBD cohort.

Methods: A prospective, nationwide, multicentre, observational cohort was designed to examine the efficacy and safety of CT-P13 infliximab biosimilar in the induction and maintenance treatment of Crohn's disease (CD) and ulcerative colitis (UC). Demographic data were collected and a harmonized monitoring strategy was applied. Clinical remission, response and biochemical response was evaluated at week 14, 30 and 54. None of the patients had received infliximab within 12 months prior to initiation of the biosimilar infliximab. Safety data was registered.

Results: 353 consecutive IBD (209 CD and 144 UC) patients were included of which 229 patients reached the week 54 endpoint. The age at disease onset was 24/28 years (median, IQR: 19–34 and 22–39) in CD and UC patients, respectively. 31/41% of CD patients had colonic/ileocolonic disease location, 43.5% had complicated disease behaviour, 39% had perianal disease, while 56.2% of UC patients had extensive colitis. 23/19% of patients had received previous anti-TNF therapy in CD and UC, respectively. 60/51% of CD/UC patients received concomitant immunosuppressives at baseline.

49, 53, 48% and 86, 81 and 65% of CD patients reached clinical remission and response by week 14, 30 and 54, respectively. Remission and response rates were 56, 41, 43% and 74, 66 and 50% in UC patients. Previous anti-TNF exposure was associated with decreased clinical efficacy in both CD and UC. Mean CRP decreased significantly both in CD and UC by week 14, which was maintained throughout the 1-year follow-up. 31 (8.8%) patients had infusion reactions, 32 (9%) patients had infections and 1 death occurred.

Conclusions: Final results from this prospective nationwide cohort confirm that CT-P13 is effective and safe in inducing and maintaining remission in both CD and UC. Efficacy was influenced by previous anti-TNF exposure, no new safety signals were detected.

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Treat to target in Crohn's disease: ultrasonographic response is associated with better outcomes

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Background: Crohn's disease (CD) management targets mucosal healing on ileocolonoscopy as a treatment goal. We hypothesized that ultrasonographic response is also associated with better long-term outcomes.

Methods: Patients with CD treated with anti TNF agents who had serial small intestine contrast ultrasonography (SICUS) between January 2011 and October 2016 were identified. Disease site (based on bowel wall thickness), extent of lesions, and presence of complications (stenosis, prestenotic dilation, abscess, or fistulas) were evaluated using SICUS. Inclusion required pre-therapy SICUS with follow-up SICUS after 12 months, or 2 SICUS \geq 12 months apart while on maintenance therapy. At second SICUS, complete responders had all improved lesions, non-responders had worsening or new lesions, and partial responders had other scenarios. CD-related outcomes of corticosteroid need, hospitalization, and surgery were assessed at one year from the second SICUS.

Results: Seventy CD patients treated with anti-TNF alpha therapy (36% with Infliximab, 64% with Adalimumab) were identified. Most patients had ileal disease (67%) and stricturing phenotype (54%). Based on SICUS, thirty-five patients (50%) were complete sonographic responders, 24 partial (34%), and 11 non-responders (16%). Complete and partial responders at SICUS had a reduced risk for surgery in comparison with non responders [p=0.012 (0.11, CI: 0.021–0.60), p=0.04 (OR 0.17, CI: 0.031–0.93)]. Complete responders at SICUS had a reduced risk for need for rescue corticosteroids in comparison with non responders [p=0.012 (OR 0.17, CI: 0.031–0.93)].

Conclusions: Ultrasonographic response to medical therapy is associated with significant reductions in long-term risk of surgery and steroid usage among CD patients. These findings suggest the significance of response assessed by ultrasonography as a treatment target.

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Changing patterns of biological therapy use with the introduction of biosimilars in inflammatory bowel disease

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Background: Biosimilar infliximab (Inflectra™/Remsima™) has been available in the United Kingdom from 2015. We present data

from the UK Inflammatory Bowel Disease (IBD) audit programme demonstrating changing patterns of biological use, including the use of biosimilars.

Methods: Participating hospitals prospectively identified adult and paediatric patients who were newly started on biological therapies for the treatment of IBD between 1 March 2015 and 29 February 2016. Data was submitted by 138 adult trusts/health boards and 19 specialist paediatric sites. Demographics, disease and safety data were collected on 2722 adult and 278 paediatric patients. Of these patients 1977 had Crohn's disease (CD), 950 had ulcerative colitis (UC) and 73 had IBD unclassified (IBDU). In patients with CD, response to treatment was defined as a decrease of >3 in HBI for adults and a decrease of >15 in PCDAI for paediatrics.

Results: Median time from diagnosis to treatment in adult patients has fallen from 4.5 years in 2012 to 3.8 years in 2016 ($p=0.026$). 60% (1388/2308) adult and 47% (109/230) paediatric patients had complete pre-treatment screening for opportunistic infections. Over the last four rounds of audit median pre-treatment Harvey-Bradshaw Index (HBI) in adult patients has fallen from 9 to 7.

In 2016 800 (29%) adult and 175 (63%) paediatric patients were started on infliximab (Remicade[®]) compared with 596 (22%) adult and 82 (29%) paediatric patients started on biosimilar infliximab. Of the patients being treated with infliximab (Remicade[®]) 81% (651/800) of adults and 95% (167/175) of paediatrics were on any steroid or immunosuppressant therapy at time of initial treatment compared to 80% (474/596) adults and 95% (78/82) paediatrics being treated with biosimilar infliximab. A response was shown in 84% (59/70) of adult and 86% (19/22) of paediatric patients following 3 months of treatment with biosimilar infliximab (Inflectra/Remsuma) compared with 85% of adult (114/134) and 85% (28/33) of paediatric patients treated with infliximab (Remicade). 10% (82/855) adult patients and 5% (6/121) paediatric patients had an adverse reaction recorded at 3-month follow-up. The most common reaction was a rash. Infection was seen in 1% (9/855) of adult patients and there were no reported malignancies.

Conclusions: The pattern of use of biological therapies in IBD has changed over the course of the UK IBD audit with earlier use in milder disease. Short term safety and efficacy of biosimilar infliximab (Inflectra/Remsuma) appear equivalent to infliximab (Remicade). The adoption of these agents is clinically appropriate and their universal adoption will be reflected by a significant cost saving.

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Medication adherence in diverse inner city pediatric patients with inflammatory bowel disease and comparison to physician perception of adherence

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Background: Inflammatory bowel diseases (IBD) are chronic gastrointestinal diseases requiring medical therapy to maintain clinical remission. Adherence to medications is recognized to improve disease outcomes, yet it is a challenging task for patients, furthermore non-adherence is not well recognized by health care providers.

The aim of this study was to evaluate adherence in pediatric IBD patients using a recently validated adherence scale and to compare the results to physician perception of adherence.

Methods: IBD patients, ages 11 to 21 years were asked to fill 8-item Morisky Medication Adherence Scale (MMAS-8). Physicians

who were blinded to the instrument results completed a routine electronic medical note that included their perception of patient's adherence recorded as adherent or non adherent. We retrospectively reviewed charts and compared physician adherence evaluation vs. patient's MMAS-8 results.

Results: Out of 64 patients, 41 had a diagnosis of Crohn's disease and 23 had ulcerative colitis with mean disease duration of 28.9 months. The mean age was 16.7; 46.8% were female. Hispanics comprised 51.4% of our patients and African Americans comprised 25% of our patients. Fifty-six patients had both MMAS-8 and a physician adherence evaluation. Using the MMAS-8, 26/56 (46%) of IBD patients were identified to have low adherence, 21 (36%) had medium adherence and only 11 (18%) had high adherence. Physicians classified correctly all patients with high adherence but only 50% of patients with low adherence and 25% of patients with medium adherence.

Conclusions: Adherence to medications is challenging for IBD patients. Screening for medication adherence is important in identifying patients at risk of non-adherence, who might benefit from interventions that will improve patient care and outcome. Identifying non-adherence is challenging for physicians and using MMAS-8 is a reliable validated survey that can be incorporated into routine use.

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Prevalence and risk factors for non alcoholic fatty liver disease in inflammatory bowel disease

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Background: Non alcoholic fatty liver disease (NAFLD) is responsible for up to 40% of hepatic alterations diagnosed in inflammatory bowel diseases (IBD). We aimed to evaluate the prevalence and risk factors for NAFLD in a large cohort of IBD patients and the stage of liver fibrosis by transient elastography (TE).

Methods: This study included consecutive patients affected by Crohn's disease (CD) or ulcerative colitis (UC), referred to our tertiary centre for IBD from December 2015 to July 2016. Patients with previous diagnosis of chronic liver disease with different etiology from NAFLD, daily alcohol consumption higher than 20 g in women and 30 g in men or conditions affecting the execution of TE were excluded. Data regarding IBD characteristics and liver laboratory tests were collected. The markers of metabolic syndrome were analyzed. All subjects underwent an abdominal ultrasonography to estimate presence/degree of steatosis and TE to measure liver stiffness (LS). An age and sex-matched group of controls was recruited. Student's t or Chi-squared tests were used where indicated. For multivariate analysis, multinomial logistic regression was used to determine which factors could have influenced the presence of NAFLD.

Results: NAFLD was observed in 106 out of 378 (28%) patients with IBD and in 33 (20.1%) of 162 controls ($p=0.04$). The prevalence of diabetes and abdominal excessive adiposity was higher for IBD than controls. Patients with NAFLD were more frequently male, young and affected by diabetes, hypertension and insulin resistance. Their mean waist circumference and BMI were higher in NAFLD compared to non-NAFLD patients. Additionally, NAFLD subjects showed higher levels of transaminases and gamma-glutamyltranspeptidase, HDL cholesterol, triglycerides and fasting blood glucose. Finally, their mean LS was higher than in

Abstract P335 – Table 1. Comparison between controls and IBD

Variable	IBD (n=378)	Controls (n=162)	p value	OR (95% CI)
Age	46.3±15.6	43.8±17.8	0.10	NE
Alcohol intake	<10 g/day 10.8%, >10 g/day 0.7%	<10 g/day 28.0%, >10 g/day 0%	<0.0001	NE
Diabetes	7.4%	3.7%	0.01	2.91 (1.24–6.81)
Hypertension	17.7%	21.7%	0.26	0.78 (0.50–1.20)
Insulin resistance	1.6%	0%	0.08	6.61 (0.37–118.1)
Abdominal circumference (>102 for male, >88 for female)	15.6%	6.8%	0.003	2.50 (1.34–4.69)
Liver steatosis	28.0%	20.1%	0.04	1.55 (1.02–2.36)
Liver stiffness	5.1±1.7	4.9±1.7	0.42	NE
BMI	24.7±5.3	24.4±4.3	0.44	NE

non-NAFLD patients. At multivariate analysis the risk of NAFLD in IBD was directly correlated to insulin resistance (odd ratio OR=14.73 $p<0.0001$), high waist circumference (OR=4.85 $p=0.04$), high BMI (OR=1.6 $p=0.01$), high gamma-glutamyltranspeptidase level (OR=3.9 $p=0.04$) and high fasting blood glucose (OR=1.3 $p=0.04$). Detailed aspects of our analysis are reported in the table.

Conclusions: Despite NAFLD is an increasing problem in IBD, it seems to be correlated to the presence of metabolic syndrome rather than to IBD characteristics.

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Safety of anti-TNF treatment in older IBD patients: a systematic review and meta-analysis

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Background: Anti-tumour necrosis factor (Anti-TNF) therapy is effective for both inducing and maintaining remission in IBD patients. Recent meta-analyses have demonstrated their safety in the general IBD population. However, little is reported about the safety of these drugs in elderly patients.

Therefore, we aimed to investigate the safety of management of IBD in elderly patients using anti-TNF treatment by systematic review and meta-analysis of available data.

Methods: A literature search was conducted for papers and conference proceedings through November 2016 regarding elderly IBD patients and anti-TNF therapy. All studies were appraised using the adapted Newcastle-Ottawa Scale (NOS), which contains 9 criteria for cohort studies and is adapted to 6 criteria for case series and case reports. Three reviewers independently extracted data on anti TNF-exposed older and younger patients, with number of serious infections, dead during follow-up and cessation of therapy due to adverse events as outcomes of interest. Poisson regression was used to compare the occurrence of outcomes of interest per patient year follow up between older and younger IBD patients.

Results: From 454 found titles, four papers and 5 conference abstracts were included, totalling 1276 patients: 470 older and 806 younger patients. Data on combined steroid use was provided in 2 papers, data on IM combo-therapy in 5 papers. Papers used either 60 years or 65 years as cut off.

The rate ratio for serious infections was similar between older and younger IBD patients (2.1, $p=0.084$) and was not influenced by IM use (rate ratio 2.8, $p=0.054$). However, when steroid use was added to the model, the rate ratio for serious infections was 2.35 ($p<0.001$, 95% CI 2.3–2.4 and use of steroid increased the risk ($p<0.001$). Risk of death did not significantly differ between older and younger patients during follow (risk ratio 10.4, $p=0.19$) and was not affected by use of IM ($p=0.5$). When use of steroids was added to the model, there

was a trend towards an increased risk of death in older IBD patients during anti-TNF exposure ($p=0.06$, ratio 3.3, 95% CI 0.94–11.8)

Older patients were 3.1 x more likely to stop anti-TNF therapy due to AE ($p=0.008$, 95% CI 1.34–7.4) compared to younger patients, and this was not influenced by use of IM. Too few data were available on steroid use.

Conclusions: Although anti-TNF therapy is more often discontinued in older IBD patients due to adverse events, the use of anti-TNF was only associated with an increased risk for serious infections when combined with steroids. More data on safety of anti-TNF in elderly are needed, with special attention to indices of physical, frailty and mental and social impairment. This would enable a more personalised assessment of risk.

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Efficacy of intravenous cyclosporine in fulminant steroid-refractory ulcerative colitis with massive bleeding: a retrospective, observational study

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Background: Intravenous cyclosporine (ivCys) is used for rescue therapy for steroid-refractory ulcerative colitis (UC), as well as anti-TNF- α antibodies. For fulminant steroid-refractory UC with massive bleeding, colectomy is usually recommended. However, the efficacy and limitation of ivCys for these patients remains unclear. This study aimed to clarify the short- and long-term outcomes, limitations, and safety of ivCys for fulminant steroid-refractory UC with massive bleeding.

Methods: We retrospectively reviewed the outcome of patients with steroid-refractory fulminant UC with massive bleeding treated with ivCys between 2009 and 2015 in a single tertiary centre. At the starting of ivCys, the patients did not consent to colectomy, their vital signs were maintained, and they could not take medicine orally for severe abdominal pain. IBD surgeons waited for 24 hours for an emergency operation. Administration of ivCys was performed for 2 weeks (blood concentrations, 400–600 ng/ml), and was discontinued when symptoms were exacerbated or vital signs of shock that did not recover with transfusion were observed. In patients who were determined to be responsive on the 14th day, ivCys was discontinued at that time. The short-term outcome was evaluated by clinical efficacy (partial-Mayo score) and the long-term outcome was calculated using Kaplan–Meier method. Cox regression analysis was performed to identify predictors of colectomy.

Results: The study population comprised 51 patients with fulminant steroid-refractory ulcerative colitis with massive bleeding treated with ivCys. The median baseline partial-Mayo score was 8.6. Within 2 weeks of ivCys treatment, 11 (22%) patients achieved remission,

and nine (18%) partial response. Thirty-two (62%) patients underwent colectomy. Among 17 patients who responded to ivCys, the non-relapse rate was 45% at 1 year and 36% at 3 years. The non-hospitalisation rate was 67% at 1 year and 50% at 3 years, and the remaining free of colectomy rate was 79% at 1 year and 64% at 3 years. Adverse reactions, including hypomagnesemia (n=38, 72%), hyperkalaemia, (n=13, 25%), catheter infection (n=2, 4%), and renal dysfunction (n=1, 2%) occurred. No major reaction nor mortality occurred.

Conclusions: The short-term efficacy of ivCys for fulminant steroid-refractory UC with massive bleeding was limited in our patients because 60% underwent colectomy within 2 weeks. However, patients who improved with ivCys had a good long-term prognosis and remained colectomy-free. No serious adverse effects were observed with ivCys.

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Value of cross-sectional imaging in assessing active Crohn's disease before stoma reversal

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Background: There are currently no guidelines on the need to assess disease activity before stoma reversal in Crohn's disease (CD). We sought to determine the value of cross-sectional imaging for detecting active CD (i.e. the recurrence or persistence of lesions present after earlier surgery) before stoma reversal.

Methods: 38 CD patients underwent cross-sectional imaging before stoma reversal. CD activity was blindly evaluated by an independent radiologist. Postoperative outcomes were recorded.

Results: Before stoma reversal, cross-sectional imaging identified active CD in 20 of the 38 study participants (52.6%). CD recurrence was identified upstream of the stoma in 11 of the 38 patients (28.9%), including two with persistent lesions and one with divertive lesions downstream of the stoma. Five of the 38 patients (13.2%) had persistent lesions only (upstream only: n=1; downstream only: n=3; up- and downstream: n=1). Four of the 38 patients (10.5%) had divertive lesions only. In 9 out of 10 tested patients, radiologic and endoscopic assessments gave concordant findings with regard to CD recurrence before stoma reversal. Stoma reversal was delayed in half of the patients with active CD and in none of the patients without active CD. Before stoma reversal, tumor necrosis factor alpha antagonists or immunosuppressants were initiated in 45% of the patients with active CD and 5.6% of the patients without active CD. In the year following stoma reversal, the recurrence rate (in a radiologic assessment) was higher in patients with active CD than in patients without active CD (75.0% vs. 30.8%, respectively; p=0.04).

Conclusions: Cross-sectional imaging revealed postoperative recurrence in about a quarter of patients before stoma reversal; this finding may influence the postoperative treatment strategy and outcomes.

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MadCAM1 expression in intestinal lamina propria endothelium varies among inflammatory bowel disease patients

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Background: Vedolizumab, a monoclonal antibody against $\alpha4\beta7$ integrin has been shown to be effective in inducing and maintaining remission in inflammatory bowel disease (IBD). By blocking $\alpha4\beta7$, it is preventing the homing of lymphocytes through binding to mucosal vascular addressin cell adhesion molecule 1 (MadCAM1) localised on the intestinal endothelial cells. It is unclear to which extent the gut homing of lymphocytes is subject to redundant biological process involving other pathways than $\alpha4\beta7$ -MadCAM1 interaction. There are no data on the interindividual variability of MadCAM1 expression that might influence the effect of vedolizumab. The aim of our study was thus first, to determine the expression of MadCAM1 on the intestinal endothelial cells of IBD patients. Second, we aimed to assess the relationship of MadCAM1 expression with the clinical response to vedolizumab.

Methods: All IBD patients referred for the treatment with vedolizumab to one referral center were included. The biopsies or resection specimen from the inflamed intestinal tissue were stained by immunohistochemistry for MadCAM1 expression. Clinical response to vedolizumab was assessed in patients with the minimal treatment duration of 10 weeks and the differences in MadCAM1 expression between responders and non-responders were analyzed.

Results: In total, 34 IBD patients were referred for vedolizumab treatment; for 21 of them intestinal biopsies or surgical specimen could have been retrieved and stained for MadCAM1 expression. In three out of these 21 patients (14%) no MadCAM1 expression in intestinal endothelium was detected, remaining 18 patients expressed MadCAM1 to various extent (from 30 to 100% of all vessels).

Ten patients had the minimal follow-up of 10 weeks of treatment, 4 out of these 10 patients had clinical response to vedolizumab. The only two patients not expressing MadCAM1 in this group were both no responders with the respective follow-up of 16 and 14 weeks of treatment.

Conclusions: MadCAM1 expression in intestinal endothelium varies among IBD patients. Other gut homing mechanisms of lymphocytes might thus prevail in some IBD patients and limit the anti-inflammatory effect of vedolizumab.

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Prevalence and long-term effect of antiplatelet use in inflammatory bowel disease

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Background: Antiplatelet therapy is the cornerstone in the treatment of cardiovascular disease and atherosclerosis. Based on the role of platelets in inflammation and coagulation it has been suggested that antiplatelet treatment could be beneficial for patients with inflammatory bowel disease (IBD). Data on the prevalence of antiplatelet use as well as on safety and long-term effect of these agents in patients

with Ulcerative Colitis (UC) and Crohn Disease (CD) are limited. The aim of this study was to investigate the prevalence and the long term effect of antiplatelet use in IBD.

Methods: Records of 594 consecutive IBD patients that are regularly followed at the University Hospital of Heraklion were reviewed and patients on antiplatelet treatment were identified. Each one IBD patient on antiplatelet treatment was matched for age, sex, disease duration and extent with one IBD patient without any antiplatelet use. Side effects of antiplatelet therapy, as well as hospitalizations, emergency department (ED) visits, medications use, endoscopic findings and disease activity scores were analyzed.

Results: Forty patients (6.7%), 32 male, 18 CD- 22 UC, mean age 63.8 ± 11.8 years, with mean follow up period 121.8 ± 109.2 days receiving long term antiplatelet therapy (46.1% low dose aspirin, 35.9% clopidogrel, 10.2% on combination, 7.8% other antiplatelet agent) were identified. No difference was found between IBD patients on regular antiplatelet treatment comparing to those not receiving, regarding corticosteroid use (lifetime 62.5% vs 55%, $p=0.518$ or since the beginning of antiplatelet therapy 45% vs 25%, $p=0.171$), budesonide (35% vs 27.5%, $p=0.243$), biologic agents (27.5% vs 12.5%, $p=0.161$) or immunomodulators (52.4% vs 30%, $p=0.378$). IBD related ED visit frequency was not associated with antiplatelet use (65% vs 45%, $p=0.178$). IBD patients on antiplatelet treatment had more frequent and higher number of hospitalizations (85% vs 37.5%, $p<0.001$), more often clinically active disease during follow up (32.5% vs 20%, $p=0.027$), but there was no difference in endoscopic activity (35% vs 32.5%, $p=0.899$). No significant differences between UC and CD were found.

Conclusions: The prevalence of antiplatelet use in Greek patients with IBD is 6.7%. No beneficial effect of antiplatelet treatment in patients with IBD was observed. Long term antiplatelet use was found to be relatively safe in IBD patients but further larger prospective studies are needed.

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Combination of corticosteroids and 5-aminosalicylates or corticosteroids alone for patients with moderate-severe active ulcerative colitis: a global survey of physicians' practice

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Background: There are sparse data on whether 5-aminosalicylates (5ASA) confer additional benefit when combined with corticos-

teroids (CS) in active ulcerative colitis (UC). We examined gastroenterologists' approach toward this management decision

Methods: A cross-sectional questionnaire exploring physicians' attitude toward 5ASA+CS combination therapy versus CS alone was developed and validated. The questionnaire was distributed to gastroenterology experts in twelve countries in five continents. Respondents' agreement with stated treatment choices were assessed by standardized Likert scale. Background professional characteristics of respondents were analyzed for correlation with responses

Results: 664 questionnaires were distributed and 349 received (52.6% response rate). Of these, 340 were eligible respondents from 12 countries (Figure 1). In total, 221 (65%) would continue 5ASA in a patient hospitalized for intravenous CS treatment due to a moderate-severe UC flare, while 108 (32%) would stop the 5ASA ($p<0.001$), and 11 (3%) are undecided (Figure 2). Similarly, 62% would continue 5ASA in an out-patient starting oral CS. However, only 140/340 (41%) would proactively start 5ASA in a hospitalized patient not receiving 5ASA before admission. Most (97%) physicians consider the safety profile of 5ASA as very good. Only 52% consider them inexpensive, 35% perceive them to be expensive and 12% are undecided. On multi-variable analysis, less years of practice and perception of a plausible additive mechanistic effect of 5ASA+CS were positively associated with the decision to continue 5ASA with CS.

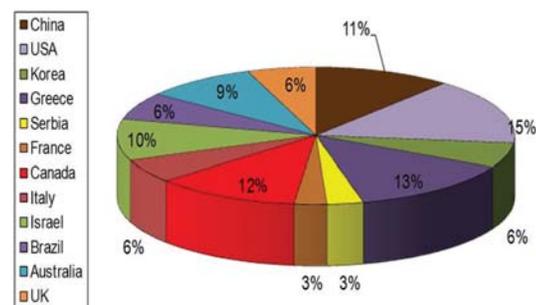


Figure 1. Distribution of countries of practice among the responding physicians.

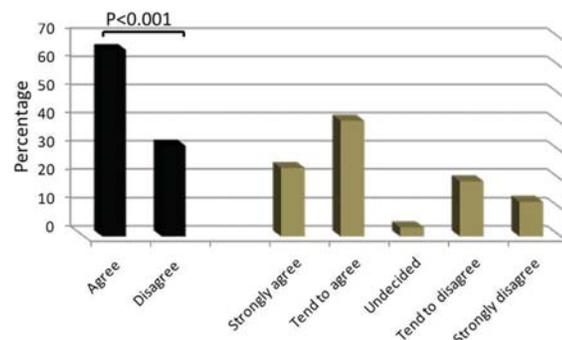


Figure 2. Continue 5ASA in a hospitalized steroid-treated patient.

Conclusions: Despite the absence of supporting evidence, the majority of gastroenterologists endorse combination of 5ASA + corticosteroids for patients with active moderate-to-severe UC, although practices vary greatly among clinicians. Randomized controlled trials are needed to assess if 5ASA confer any benefit for these patients.

P342

Maladaptive coping, self-efficacy and patient reported outcomes in inflammatory bowel disease

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Background: Patient reported outcomes (PRO), key aspects in the management of inflammatory bowel disease (IBD), are strongly influenced by biopsychosocial factors. Whereas self-efficacy and coping strategies are modifiable social constructs that may improve health outcomes following dedicated intervention. This study aims to evaluate the relationship of PRO and these constructs in addition to traditional biopsychosocial factors.

Methods: We conducted a cross-sectional study on patients with Crohn’s disease (CD) or ulcerative colitis (UC) at McGill IBD centre between September 2015 and March 2016. Patients were assessed for quality of life, disability and productivity using validated short IBD questionnaire (SIBDQ), IBD disability index (IBDDI) and work productivity assessment index respectively. Psychological assessment was performed using hospital anxiety and depression score (HADS). Brief COPE questionnaire were used for assessing coping strategies, and general self-efficacy scale was used for efficacy.

Results: 207 (144 CD/63 UC) patients, with median age of 39 (IQR 26) and 88 (42.5%) male, were included. 24.2% of patients had active disease (Harvey Bradshaw >4/Partial Mayo >2). Around one third of patients identified moderate to severe impairment on disability (31.3%), quality of life (33.3%) and productivity (29.1%); along with some degree of anxiety (32.9%) and depression (23.3%). Both poor quality of life (SIBDQ>47) and disability (IBDDI>33) were significantly associated with maladaptive coping (p=0.002 for both) and disease activity (p=0.001/p=0.002, respectively) in multivariate analysis (Table 1). Productivity loss was associated with female gender (p=0.023), active disease (p=0.003) and CD stricturing phenotype (p=0.03). In contrast, self-efficacy was protective of disability

(p<0.001) and productivity loss (p=0.016). Similarly, patients with active disease (p=0.005) and maladaptive coping (p=0.014) were at risk of anxiety (HADS ≥8), whereas the inverse relationship was found for self-efficacy (p=0.013) and older age (p=0.045). Finally, maladaptive coping (p=0.014), active disease (p=0.037) and stricturing phenotype (p=0.048) was associated with depression.

Conclusions: Unfavorable patient reported outcomes are significantly associated with maladaptive coping and disease activity while self-efficacy had a positive effect. These modifiable social constructs could assist with identifying high-risk patients, of whom may benefit from targeted intervention to improve health outcomes.

P343

Female gender, somatization and presence of IBS-type symptoms predicts Dyspareunia in patients with IBD

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Background: Sexual dysfunction is a well-recognized complication of chronic illness. In IBD factors such as age of diagnosis, increased bowel frequency, abdominal pain, fatigue, incontinence, perianal fistulas, abscesses, or skin tags, can lead to an accumulation of physical and psychosocial factors that can impair sexual function. Although 80% of IBD patients report sexual dysfunction only 40% will discuss it with their healthcare provider. Dyspareunia has been reported as occurring in unto 40% of patients with IBD.

Methods: We analyzed Rome III IBS symptoms, disease activity indices, and psychological, somatization, and quality of life data

Abstract P342 – Table 1. Patient reported outcomes: Regression analysis results.

PRO	Variable	Multivariate
Poor quality of life (SIBDQ < 47)	Disease activity	OR 12.08 (95% CI 2.75-53.01) p=0.001
	Maladaptive coping	OR 2.59 (95% CI 1.42-4.74) p=0.002
Disability (IBDDI > 33)	Disease activity	OR 45.7 (95% CI 4.30-486.62) p=0.002
	Self-efficacy	OR 0.7 (95% CI 0.57-0.85) p<0.001
	Maladaptive coping	OR 4.56 (95% CI 1.72-12.06) p=0.002
Productivity loss	Female	OR 4.31 (95% CI 1.23-15.13) p=0.023
	Stricturing CD	OR 3.87 (95% CI 1.14-13.16) p=0.03
	Disease activity	OR 6.56 (95% CI 1.90-22.68) p=0.003
	Self-efficacy	OR 0.83 (95% CI 0.71-0.97) p=0.016
Anxiety (HADS≥8)	Age	OR 0.935 (95% CI 0.876-0.999) p=0.045
	Disease activity	OR 15.29 (95% CI 2.26-103.4) p=0.005
	Self-efficacy	OR 0.84 (95% CI 0.72-0.96) p=0.013
	Maladaptive coping	OR 2.74 (95% CI 1.23-6.14) p=0.014
Depression (HADS≥8)	Stricturing CD	OR 14.75 (95% CI 1.02-129.21) p=0.048
	Disease activity	OR 14.75 (95% CI 1.18-185.21) p=0.037
	Maladaptive coping	OR 4.08 (95% CI 1.33-12.5) p=0.014

from 777 consecutive, unselected adult patients with IBD seen in clinics at St James's University Hospital in Leeds, United Kingdom from November 2012 through June 2015. Participants also provided a stool sample for fecal calprotectin (FC) analysis and serum for CRP.

Results: The overall prevalence of dyspareunia in our IBD cohort was 11.2%. 5.5% of males reported dyspareunia (19/348) compared to 18.2% of females (78/429) ($p < 0.0001$). 64.4% (55/87) of patients reporting dyspareunia were married compared to 60.4% (417/690) of patients without dyspareunia. The median age of patients with dyspareunia was 37 years compared to 42 years without. Median BMI was 25.58 in the group with dyspareunia and 24.53 in the group without. 11.5% of patients with Crohn's disease (51/444) reported dyspareunia compared to 10.8% of UC patients (36/333) ($p = 0.8186$). Prevalence of prior surgery was 25.3% (22/87) in the dyspareunia group compared to 25.8% of those without (178/690). Prevalence of perianal disease was 3.5% (3/87) in the dyspareunia group compared to 4.2% of those without (29/690). Median FC was 174.6 in the dyspareunia group compared to 150.1 of those without. CRP was elevated in 35.6% (31/87) of patients with dyspareunia group compared to 39.4% of those without (272/690). 54.0% (47/87) of patients with dyspareunia reported the presence of IBS-type symptoms compared to 34.8% (240/690) of those without ($p = 0.0006$). Median Somatic Symptom Scale - 8 (SSS-8) was 15 in the dyspareunia group compared to 9 in those without. Patient Health Questionnaire-12 (phq12) somatisation score was 11 in the dyspareunia group compared to 6 in those without.

Conclusions: The prevalence of dyspareunia in our centre is lower than some of the previously reported IBD cohorts. Dyspareunia was associated with IBS-type symptoms, female gender and higher somatisation scores but not with disease phenotype or other demographic factors.

P344 Vitamin D-Induced alterations in Cytokine levels lower the risk of clinical relapse in ulcerative colitis

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Background: Vitamin D has immunomodulatory effects *in vitro*, and we have previously associated serum levels with clinical outcomes in ulcerative colitis (UC). We sought to investigate a biological explanation for this link.

Methods: The effects of 1,25-hydroxyvitamin D on cytokine mRNA and protein levels were evaluated in human colonic epithelial cells (DLD1) challenged with lipopolysaccharide *in vitro*. Serum vitamin D and cytokine levels were measured at baseline in a prospective cohort of UC patients (N=70) in clinical remission, and correlated with risk of relapse within 12 months using logistic regression models.

Results: Vitamin D (10 nM) stimulated increased IL-10, and decreased TNF- α , levels in colonic epithelial cells *in vitro*. In patients, higher vitamin D positively correlated with the ratio of anti-inflammatory-to-pro-inflammatory cytokine levels in serum (IL-4+IL-10/IL-6+TNF- α , $r = 0.3249$, $p < 0.01$).

This ratio (IL-4+IL-10/IL-6+TNF- α) was higher at baseline among patients who remained in clinical remission over 12 months (mean 24 in remitters vs 13 in relapsers, $p < 0.05$).

This association with future risk of clinical relapse persisted when

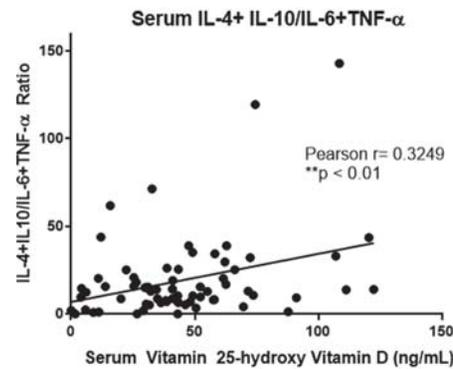


Figure 1

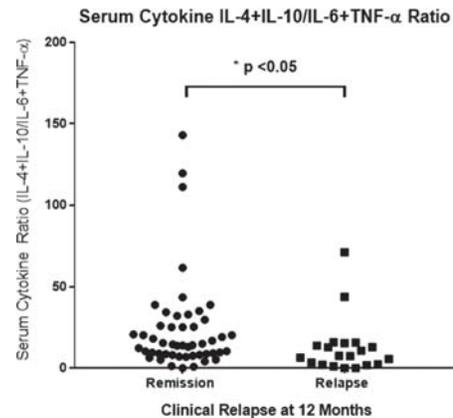


Figure 2

endoscopic and histological inflammation at baseline were controlled for in a multivariate model (O.R. 0.7, 95% CI 0.6–0.9, $p = 0.003$).

Conclusions: Vitamin D induces an anti-inflammatory cytokine profile that is more prevalent in patients with UC who exhibit sustained clinical remission. Such immunomodulatory properties warrant further examination for therapeutic potential.

P345 Inconsistency between electronic data of patient's adherence and self reported adherence score

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Background: Long term treatment adherence in chronic diseases is notably poor. In inflammatory bowel disease (IBD) adherence consists of compliance with diagnostic tests, endoscopies, laboratory workup, follow up appointments and adherence to long term medical treatment. There are several methods to evaluate adherence. Morisky score is a subjective questionnaire filled by the patient while electronic data collected by the physician provides an objective tool. This study aimed to compare adherence analyzed by the Morisky score

versus the gastroenterologists impression and medication purchase extracted from electronic data.

Methods: IBD patients were asked to fill a questionnaire including: demographic and disease parameters and the Morisky score to evaluate adherence. Physicians filled a questionnaire summarizing the impression of patient adherence as reflected from electronic patient files.

Results: Data from 214 IBD patients was available. Mean age was 37±14 years, 73 (34%) were males, 151 (70.6%) had Crohn's disease 50% received biologic treatment. The patients estimation of treatment efficacy was positive in 76%. Main reasons for non-adherence reported by the patients were: busy 19%, forget 36%, does not help 7% and side effects 13%. Electronic data regarding medications was only mildly correlated with the Morisky score ($r=-0.0302$, $p<0.001$). The doctor's comprehensive evaluation of patient's adherence was also only mildly correlated with the Morisky score ($r=-0.0334$, $p<0.001$). Compared with Morisky score, the adherence in 53% of patients was overestimated by the physician, while 12% were underestimated.

Conclusions: Current modes of adherence estimation are inaccurate and non-consistent. Mismatch between them emphasizes their limitation. An accurate estimation tool to evaluate patient adherence is needed.

P346

Dietary practices and beliefs among parents of children with inflammatory bowel disease: preliminary results

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Background: Patients with inflammatory bowel disease (IBD) often worry about a diet and they make links to certain foods in order to prevent disease flare. So far, dietary practices and beliefs were investigated in adult patients with IBD. The purpose of this study was to evaluate dietary beliefs and behaviors among parents of children and adolescents with IBD.

Methods: This prospective study was conducted in two University-affiliated hospitals for children in Poland (cities of Warsaw and Olsztyn) between March and November 2016. Parents of children with IBD diagnosed according to Porto criteria were asked to filled in questionnaire that consisted of two parts. The first part consisted of a few questions regarding age, sex and diagnosis of the patient. In the second part of the questionnaire, parents were asked about dietary beliefs and practices regarding their children.

Results: A total of 66 parents of children and adolescents with IBD participated in the survey. Mean age of children was 14.1±3.5 years, 52% girls, 45% Crohn's disease.

28% (n=19) of respondents believed that diet could initiate the disease, while 69% (n=46) believed that food could trigger a flare. About 72% (n=48) reported not eating foods that child usually like, in order to prevent relapse and around 38% (n=25) felt uncomfortable with outdoor dining because of the disease. 50% (n=33) of respondents reported that the disease had changed the pleasure of eating. 31% (n=21) of patients did not share the same menu as the other members of the family. Above 80% of respondents declared avoiding fast food, hot spices and soft and blue cheeses. 77% reported avoid-

ing soft drinks and salty snacks, and above 60% reported avoiding milk (boiled milk - 47%), legumes and fried foods. A half of respondents declared avoiding chocolate and other sweets. Majority of parents (65%; n=43) believed that their child with IBD requires nutritionist care and 47% (n=31) of them received nutrition advice by dietitian. 13% of patients has not received any nutrition advice ever. **Conclusions:** Preliminary results of our study showed that majority of parents of children with IBD hold beliefs concerning to the role of diet in IBD that result in avoidance of certain foods.

P347

Evaluation of step up therapy in patients with early ulcerative colitis: a prospective cohort study

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Background: The natural history of ulcerative colitis (UC) is unpredictable. The current approach is gradual step-up (SU) therapy in the majority of patients. Data on the need for and factors influencing SU therapy beyond 5ASA or steroids are understudied.

The aim of the study is to describe the first year SU therapy in patients with early UC failing on 5-ASA or steroids.

Methods: In this prospective multicentre observational trial patients with UC failing on 5-ASA and/or steroids where followed for 12 months. Patient characteristics, demographics, medical therapy, biomarkers, therapy adherence and quality of life were evaluated at every out-patient visit.

Results: A total of 103 patients (54% male, median age 40 years, median disease duration 17 months) were included. Only 2% were active smokers, while 51% were ex-smokers. Of the 103 patients 34%, 24% and 42% were 5-ASA-refractory, cortico-dependent and cortico-refractory respectively. After 1 year of follow up 81% of patients had mild or inactive UC based on the Mayo score. Sixty percent of patients had been treated with immunomodulators and 30% with biological therapy. Eighteen percent used combination therapy, representing only 54% of patients on anti-TNF therapy. The median time to initiation of immunomodulators and anti-TNF was 1 day and 55 days respectively, with a quicker initiation of anti-TNF treatment in cortico-dependent (34 days; 95% CI: 0–148) and cortico-refractory (57 days; 95% CI: 2–181) patients as compared to 5-ASA-refractory patients (97 days; 95% CI: 17–262). In total, 24/43 (56%) cortico-refractory patients started anti-TNF treatment. This was a significantly higher number compared to 4/25 (16%) of the cortico-dependent group ($p=0.002$) and 7/35 (20%) of the 5-ASA-refractory group ($p=0.002$). Biomarkers (CRP and platelet count) and clinical scores were numerically higher at initiation of anti-TNF

therapy compared to immunomodulators. Whereas the use of faecal calprotectin was negligible (7%) in therapeutic decision making. Two patients underwent colectomy. Based on the results of the MMAS-8 questionnaire, patients with severe disease at baseline presented a lower median MMAS-8 score throughout the study period and thus were less adherent to therapy.

Conclusions: In patients with early UC a step up approach leads to good clinical outcomes at 1 year. Immunomodulators are initiated very early in patient flaring on 5-ASA or steroids, and up to 30% will be on anti-TNF treatment within 1 year, with cortico-refractory patients having the highest risk. Surprisingly, combination therapy is not used very often in daily clinical practice. The gradual SU and the acceleration of the therapy are based on sanguine biomarkers and clinical scores, not on faecal calprotectin levels.

P348 Persistent hyperCKemia during infliximab therapy in patients with inflammatory bowel disease

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Background: Both muscle-related complaints and elevated serum creatine kinase (CK) levels have been reported in patients with inflammatory bowel disease (IBD) treated with infliximab (IFX), mainly as case reports. The aim of this study was to investigate the effect of IFX therapy on serum CK levels in a cohort of Greek IBD patients.

Methods: Demographic, clinical and laboratory data of consecutive IBD patients on maintenance treatment with IFX and a matched control group of IBD patients without any use of biological treatment were retrospectively analyzed. All patients and controls had at least 3 CK measurements, with at least 10 days interval among them and we used the mean CK value for the analysis. Data of all patients with elevated mean CK were reviewed for persistent muscle complaints not associated with exercise and for the existence of other causes of persistent hyperCKemia (muscular damage, use of statins or thyroxine, coronary heart disease and kidney disease).

Results: The IFX-treated IBD patient group included 88 individuals [65 Crohn's Disease (CD), 23 ulcerative colitis (UC), mean age 42.5±14.7 years, 62.5% men, median (IQR) duration of IFX treatment 26 (13–71) months]. Eighty-eight patients without treatment with any biological agents formed the control group (54 CD, 34 UC, mean age of 49.7±16.1 years, 61.2% men). Twenty-seven IFX-treated patients (30.7%) had elevated mean serum CK levels (>180 U/L) compared to 9 (10.2%) in the control group (p=0.0002). Other possible causes of persistent hyperCKemia were identified in 7 of the 27 (25.9%) patients of the IFX group compared to 2 of the 9 (22.2%) of the control group. When those patients were excluded, the difference among the two groups remained significant (p=0.01). The median (range) CK value in the IFX group was 123 U/L (40–1145), which was significantly higher than that of the control group (81 U/L, 14–1034, p<0.0001). There were no correlations between elevated CK and the disease type (CD vs UC) or the clinical characteristics of the disease. In the logistic regression analysis the presence of hyperCKemia after adjustment for age, disease type and existence of other causes of elevated CK was independently associated with the use of IFX [OR 2.92 (1.63–9.45) p=0.002]. No patient with hyperCKemia in both groups reported any persistent symptoms of myopathy.

Conclusions: More than 30% of IBD patients under maintenance treatment with IFX present asymptomatic persistent and treatment related hyperCKemia. Serum CK levels are significantly higher in IFX treated patients compared to patients without any biological treatment. Further relevant prospective investigation is needed.

P349 The therapies influencing postoperative surgical recurrence in Crohn's disease

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Background: Postoperative recurrence is inevitable in most Crohn's disease patients. In result, multiple bowel resections may lead to short bowel syndrome, which may affect the patients' life. Therefore, we need to seek for optimal strategies to prevent progression of the disease postoperatively. Lately, anti-tumor necrosis factor alpha (TNF α) agents and endoscopic balloon dilatation have been used widely, and treatment strategy has been changing. This study was aimed to clarify which therapy was the most efficient to suspend the postoperative surgical recurrence in Crohn's disease in the era of these novel therapies.

Methods: Seventy operations were undergone in 46 Crohn's disease patients. There were 32 males and 14 females. Clinical data were obtained with retrospective chart review. The age at surgery was 19–74 (median: 34.5), and the duration of Crohn's disease was 0–30 (median: 8.5) years. The observation period ranged 100 to 7758 (mean: 1671) days. The therapies analysed were aminosalicylates, immunomodulators (azathiopurine, 6-mercaptopurine), anti-TNF α agents (infliximab, adalimumab), nutritional therapy including elemental diet, and endoscopic balloon dilatation. Survival curves were drawn, and log-rank tests were employed to evaluate statistically for univariate analysis. We ran proportional hazard model for multivariate analysis. A p value of <0.05 was considered to be significant.

Results: The patients who underwent anti-TNF α therapy had statistically better prognosis than those without (p=0.0276). Balloon dilatation seemed to be useful, because the prognosis of the patients who received dilatation technique had better prognosis (p=0.0167). Immunomodulators were effective to prevent surgical recurrence with statistical significance (p=0.0460). Patients who maintained elemental diet (more than 900 kcal/day) had statistically better prognosis than those without or with lower quantity (p=0.0010). By multivariate analysis, the only significant factor was the nutritional therapy (p=0.0186), followed by endoscopic balloon dilatation therapy (p=0.0572).

Conclusions: Anti-TNF α therapy, immunomodulators, endoscopic balloon dilatation therapy, and elemental diet therapy were effective to suspend postoperative recurrence in Crohn's disease by univariate analyses. Elemental diet therapy was significantly associated with surgical recurrence by multivariate analysis, and there was a trend of advantage for endoscopic dilatation.

P350 Induction of antiphospholipid antibodies in patients with inflammatory bowel disease treated with anti-TNF α agents

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Background: Anti-tumor necrosis factor alpha drugs (antiTNF α) can induce the production of autoantibodies, mainly anti-nuclear antibodies (ANAs) and anti-dsDNA. There are limited data on the induction of other antibodies such as antiphospholipid antibodies (APLs) or the development of antiphospholipid syndrome in patients receiving such agents. Our aim was to determine the presence of antiphospholipid antibodies in a cohort of Inflammatory Bowel Disease (IBD) patients receiving treatment with an antiTNF α .

Methods: We performed a longitudinal study in IBD patients that were scheduled to start treatment with an antiTNF α agent. Coagulation tests were determined prior to drug initiation and at each monitoring visit (every 8 to 12 weeks). If activated partial thromboplastin time (aPTT) without prolongation of prothrombin time was identified, the result was confirmed in a second analysis. If prolongation of aPTT was established, then lupus anticoagulant (LAC), anticardiolipin antibodies (aCL) and anti- β 2-glycoprotein (a β 2GPI) were determined. Time from start of antiTNF α to the first prolonged aPTT was recorded. Clinical data including a history of thrombosis and abortions were collected. Results were expressed as medians, percentages and percentiles. Fisher's exact test was used for categorical variables, and Mann-Whitney U for quantitative variables. Statistical significance was determined with a double-tailed p-value of <0.05.

Results: Two-hundred and eighty-eight patients with IBD were included. Age at inclusion was 40 years [32–50], 48% were women and 75% had a diagnosis of Crohn's disease. Out of the cohort, we identified 23 patients (8%) with prolongation of aPTT, with a median of 63 months [35–84] from the start of the antiTNF α until the alteration was found. Seventy percent of these patients were women (p=0.048, OR: 2.66, 95% CI: 1.09–6.5), 68% (n=15) had positive LAC, 22% (n=5) were aCL positive and 17% (n=4) had a positive a β 2GPI. Additionally, 80% had positive ANAs and 43% anti-dsDNA. No patient fulfilled criteria for antiphospholipid syndrome. There were no differences in type of IBD, duration, location or behavior of the disease, concomitant treatment and type of antiTNF α agent between patients with or without aPTT prolongation.

Conclusions: Antiphospholipid antibodies can be induced in IBD patients that are receiving treatment with antiTNF α drugs. It would be reasonable to include coagulation studies at the start and follow-up of patients receiving antiTNF α treatment and to evaluate for the presence of antiphospholipid antibodies.

P351 Do self-selected "Non-Transitioned" referrals from paediatric services have lower treatment requirements?

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Background: Best practice guidelines stipulate children with long term health problems should have their care transitioned between paediatric services and adult health services. Our paediatric IBD patients are offered an appointment in a transition clinic, however non-attendance is high. The aim of this study is to compare treatment requirement (as a surrogate marker of disease severity) and service engagement between patients choosing to attend transition clinic (transitioned) and those not (non-transitioned patients).

Methods: All known IBD referrals from Birmingham Children's Hospital to University Hospital Birmingham aged 16–18 years from

2010–13 were collected. Baseline demographics, disease status and treatment history were collected from both adult and paediatric settings. Post referral procedures, changes in treatment and clinic attendance data were collected.

Results: 57 patients were identified of which 33 were transitioned. Data regarding treatment prior to referral to adult services and changes post-referral are presented below. Data is also presented for clinic attendance and follow-up length.

Table 1. Patient baseline demographics and pre-referral therapy

	Non-transitioned patients	Transitioned patients	p value
Number	24	33	–
Male:Female ratio	13:11	14:19	0.385
Ethnicity (Cauc/Black/South Asian/ Unknown or mixed ethnicity)	14/1/1/8	14/1/7/11	–
Crohn's disease	17 (70.9%)	25 (75.8%)	0.789
Ulcerative colitis	7 (29.1%)	8 (24.2%)	–
Pre-referral azathioprine/ methotrexate use	10 (41.7%)	22 (66.7%)	0.063
Pre-referral anti-TNF use	4 (16.7%)	8 (24.2%)	0.492
Pre-referral IBD surgery [^]	5 (20.8%)	12 (36.4%)	0.210

[^]Small bowel resection, stricturoplasty, and drainage of perianal abscesses.

Table 2. Post-referral therapy and engagement with adult services

	Non-transitioned patients	Transitioned patients	p value
New anti-TNF use	5 (20.8%)	7 (21.2%)	0.963
New course of steroids	6 (25%)	10 (30.3%)	0.927
Surgical procedure	4 (16.7%)	7 (21.2%)	0.670
Endoscopic procedure	11 (45.8%)	15 (45.5%)	0.978
Mean days follow-up per patient (months)	1361 (44.7)	1351 (44.4)	–
Total attended clinic appointments (per patient)	233 (9.7)	356 (10.8)	0.051
Number of non-attendances (percentage of appointments)*	32 (13.7%)	16 (4.5%)	0.031

*Hospital baseline 2015 DNA rate was 11.1% for new patients and 8.7% for IBD follow-up clinic patients overall.

Conclusions: Fifty-eight percent of IBD patients referred from paediatric services chose to attend a transition clinic. Patients attending transition clinic are a self-selecting group in our cohort, as all are offered such a clinic appointment. Following referral both groups continue to have high therapy demands. A new course of steroids, starting Anti TNF therapy or surgical procedure was considered a surrogate for increased disease activity. Our data suggests that those attending a transition clinic are not less likely to flare, compared to those who did not attend. This is in contrast to other datasets which suggest that transition reduces disease flares. An assumption that patients choosing not to attend transition clinic have milder disease and need less intensive follow-up, is not supported by our data.

P352 Assessment of the use of therapeutic drug monitoring of Adalimumab during maintenance therapy in children with inflammatory bowel disease

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Background: Adalimumab (ADA) is effective in the induction and maintenance of remission in pediatric Crohn's disease (CD). Phar-

macokinetics analysis of the IMAGINE-1 study demonstrated that a higher ADA concentration is associated with greater rates of remission. Data remains scarce in terms of which level is predictive of clinical remission in pediatric patients. Moreover, few study, have established the rate of anti-adalimumab antibody (AAA) in this population.

Methods: Aims: To review our experience with therapeutic drug monitoring (TDM) in children with CD and Ulcerative colitis (UC) treated with ADA. The primary objective was to assess the serum levels of ADA in children aged 5–18 years during maintenance. We also aim to 1) establish the rate of AAA in our population and 2) correlate the levels of ADA with clinical response.

Methods: This was a single-center retrospective cohort study. Patients were included if they had at least one serum level of ADA/AAA drawn between June 2014 and November 2016. ADA and AAA analysis were performed in a central lab using a classic ELISA technique. We collected biochemical inflammatory markers drawn the same day or, if missing, at a maximum of two weeks prior to the ADA level. The physician global assessment (PGA) was also recorded if it was done within 4 weeks of the ADA level.

Results: In our database, we identified 95 patients treated with ADA during the study period. Fifty-eight (61%) had at least 1 ADA level drawn (47 with CD, 9 patients with UC and 2 with Indeterminate colitis (IBD-U)). The 2 patients with IBD-U were excluded. Eleven CD patients (19%) had not received infliximab prior to initiating ADA. We collected 97 ADA levels (84% in CD). The overall median ADA level was 12 ug/mL, with a median dose of 0.74 mg/Kg/injection and at a median frequency of every 14 days. Four patients, all with CD, developed AAA (7.14%). A weekly administration was associated with a higher drug level (14.8 vs 10.1ug/mL, p-value 0.0011). A PGA of remission was linked to 47 (55.3%) levels. An ADA level above 10 correlated with remission according to PGA with a sensitivity of 76% and a specificity of 47.4% (p-value 0.0205). AAA and previous infliximab exposure correlated with a lower in ADA level (p=0.0016 and 0.0448 respectively). Combination therapy improved ADA levels in all patients, but more significantly in patients previously exposed to infliximab (p=0.0369).

Conclusions: ADA measurement is a useful tool in monitoring therapy in children with CD or UC. Aiming for levels above 10 ug/mL could be a target, as it correlates with clinical remission. Combination therapy helps to improve ADA levels. Prospective studies are required to better assess the role of TDM with ADA therapy.

P353

Long-term safety of adalimumab in patients with Crohn's disease: final data from PYRAMID registry

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Background: The final top-line results of the long-term safety of ADA assessed in patients (pts) with moderately and severely active Crohn's disease (CD) treated in routine clinical practice and enrolled in the global postmarketing observational registry PYRAMID are presented. The primary objective was to rule out a doubled risk of lymphoma for pts treated with ADA compared with the expected background lymphoma rate.

Methods: Pts who were newly prescribed ADA or currently receiving ADA according to the local product label were enrolled in the registry and followed for up to 6 years. Adverse events (AEs), serious AEs (SAEs), AEs of special interest, and AEs leading to drug discontinuation were collected. Registry treatment-emergent AEs (TEAE; any event with onset on/after first dose of ADA until 70 days after last ADA injection) and observational AEs (any event occurring from first dose of ADA until last contact) were collected. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 and reported as events/100 patient-years (PY).

Results: A total of 5025 pts were evaluated in this analysis (57.1% female, mean age 37.8 years at enrollment), representing 16680.4 PYs of ADA exposure over 6 years. The mean (SD) duration of ADA exposure during the registry was 1212.4 (835.4) days. A total of 2852 pts (56.8%) had prior biologic use, 1798 (35.8%) used immunomodulators (IMM), and 1463 (29.1%) used corticosteroids (CS) at registry baseline (BL). Overall, 3478 (69.2%) pts discontinued ADA or the registry. A total of 1853 pts (36.9%) reported 4129 treatment-emergent SAEs (24.8/100 PY) (Table). A total of 556 pts reported 792 treatment-emergent serious infections (SI) (4.7/100 PY). The only treatment-emergent SI reported by ≥1% of pts was perianal abscess (0.7/100 PY). The SI rate was higher for pts with concomitant medication at BL (ADA+CS, ADA+IMM, ADA+CS+IMM)

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Table. Registry TEAEs.

Adverse Event	Adalimumab	
	N=5025 n (%)	PYs=16680.4 Events (E/100 PY)
Any AE	2392 (47.6)	6124 (36.7)
Serious AE	1853 (36.9)	4129 (24.8)
Serious AE at least possibly related to ADA*	422 (8.4)	627 (3.8)
AE leading to drug discontinuation	596 (11.9)	766 (4.6)
AE leading to death	43 (0.9)	52 (0.3)
Any infection	855 (17.0)	1333 (8.0)
Serious infection	556 (11.1)	792 (4.7)
Opportunistic infection (excluding oral candidiasis and TB)	19 (0.4)	21 (0.1)
Active TB	10 (0.2)	10 (<0.1)
Latent TB	7 (0.1)	7 (<0.1)
Any malignancy	116 (2.3)	134 (0.8)
Non-melanoma skin cancer	36 (0.7)	49 (0.3)
Lymphoma	10 (0.2)	10 (<0.1)
Demyelinating disorder	8 (0.2)	8 (<0.1)

* As assessed by the investigator.

vs ADA monotherapy (6.4, 4.8, 5.0 vs 4.2/100PY, respectively). A total of 116 pts experienced 134 treatment-emergent malignancy events (0.8/100 PY), of which 10 were lymphomas. No non-treatment-emergent lymphoma events were reported. The registry exposure-adjusted rate of lymphoma was 0.060/100 PY. The upper bound of the 1-sided 95% CI of this rate was 0.102/100 PYs and fell below 0.168/100 PYs (double the expected rate of 0.084/100 PYs). TEAEs leading to death were reported in 43 pts (0.3/100 PY).

Conclusions: The registry achieved the goal of ruling out a doubling of lymphoma risk in pts with CD treated with ADA. No new safety signals were identified.

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The effect of value based health care delivery for inflammatory bowel diseases on outcomes of patients

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Background: Innovative approaches in the transitioning landscape of healthcare, such as value-based healthcare (VBHC), are widely examined and defined but data on effects of these methods is lacking. VBHC is defined by continuous measurement of health & cost outcomes and precisely timed care coordination and deemed by healthcare pioneers as the way forward to battle the rising costs. The UCLA Center for Inflammatory Bowel Diseases (IBD) started with a VBHC program in 2012. This study aimed to look at readmission rates, flares and hospitalization rates in IBD patients.

Methods: The implementation of the VBHC program consisted of designing the program, training of physicians, care coordinators, administrators and patients, and introducing IBD specific technology applications. Data on IBD patients enrolled at the UCLA Center for Inflammatory Bowel Diseases were collected from the electronic medical health record system (EPIC). IBD patients were selected and identified by using ICD-9 codes that correlate with Crohn's disease or ulcerative colitis. We aimed to directly extract data from the UCLA EMR system, and assess the impact of VBHC delivery on IBD-related emergency department visits, IBD-related admissions (any hospitalization or surgery related to IBD) and IBD flares.

Results: Out of 4053 IBD patients currently treated by the UCLA health system, 829 were enrolled in the VBHC program. Care providers included 2 IBD physicians, 2 IBD nurses and 2 dedicated IBD administrators. The patient facing application was made available on iOS and Android platforms. Educational material for patients consisted of videos and hands-on training in the clinic. Pre-existing IBD care pathways were used to guide disease management. Data on the 829 patients was collected from May 2013 until May 2016. Stunningly, the results show that there was a decrease of 79,4% in IBD related hospitalizations within the study period. Regarding ED visits a reduction of 69,5% was observed and the overall relapse rate decreased by 46,6% during this period.

Conclusions: The implementation of a VBHC program has led to significant reduction in care utilization and associated decrease in medical costs. Shifting away from the fee-for-services model to new value-based approaches can optimally prepare health practices for value-based contracting.

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A structured care pathway improves quality of care for acute severe ulcerative colitis

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Background: The UK IBD Audit 2014 identified important deficiencies in the care of hospitalised patients with Acute Severe Ulcerative Colitis (ASUC). Our aim was to assess whether the introduction of a structured inpatient care pathway improves adherence to the UK IBD Audit guidelines and improves patient care.

Methods: A retrospective review of all patients admitted with ASUC between January 2010-November 2011 identified areas for improvement of inpatient care. As a result, a structured pathway was introduced to be used for all admissions for ASUC. A further review of admissions with ASUC was conducted following the introduction of an integrated care pathway from July 2015-September 2016. A comparison was made of key outcomes and quality measures at baseline and following introduction of the care pathway. Comparison was also made with the UK IBD Audit, 2014. Key outcomes measured included length of stay, time till seen by GI team, stool C&S and C Difficile being sent, endoscopy during admission, steroid prescription, bone protection, VTE prophylaxis, dietician referral, IBD nurse referral, weight recording, stool chart recorded, PFA on admission and investigation of anaemia

Results: A total of 67 patients with a primary discharge diagnosis of colitis were identified. 26 patients were excluded (elective admission for surgery or endoscopy). 41 patients were considered eligible for further study. The outcomes in this cohort were compared to those in the January 2010-November 2011 study and later to the UK IBD Audit 2014 (Fig. 1).

M:F ratio 25:16 (61%:39% vs 68%:32%). Median age was 32 (± 13.8) vs 47 (± 17.68). Notable results included a statistically sig-

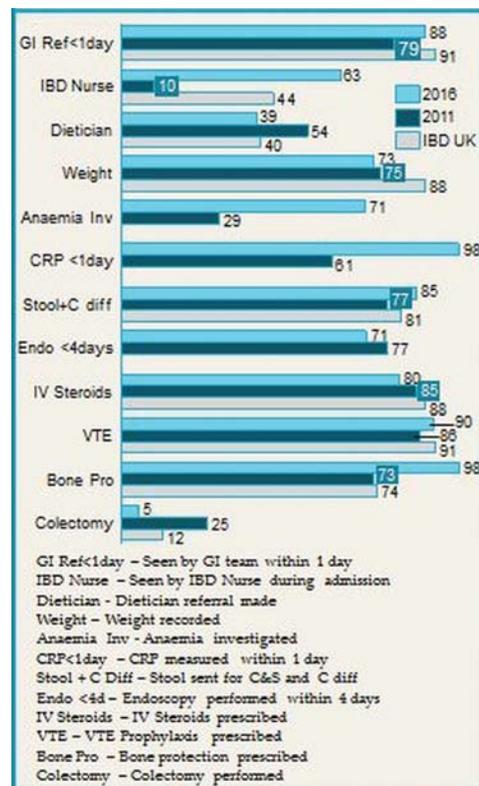


Figure 1

nificant reduction in hospital length of stay (mean 7 days vs 13 days, log rank $p < 0.001$). There was also a significant reduction in time to administration of VTE prophylaxis (log rank $p < 0.0001$). Otherwise, there were improvements in patients who:

1. Were seen by a specialist gastrointestinal team within 1 day (87.8% vs 78.9%)
2. Had stool samples sent for culture, sensitivity and C Difficile (85.4% vs 76.9%).
3. Were prescribed bone protection (97.6% vs 73%).
4. Were seen by an IBD specialist nurse during admission (63% vs 10%).
5. Had anaemia evaluated (70.6% vs 28.6%).
6. Had a CRP measured on admission (98% vs 61%).

Conclusions: The introduction of a structured care pathway for ASUC resulted in an overall improvement in inpatient care and adherence to UK IBD Audit recommendations, with a significant reduction in hospital length of stay.

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Treatment with anakinra induces T cell production of IL22 and GI mucosal healing in an IL-10RA mutation patient

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Background: IL10 is an immune-regulatory cytokine that plays an important role in the maintenance of intestinal homeostasis. Loss-of-function mutations in IL10, IL10RA or IL10RB cause severe intestinal inflammation and is refractory to conventional immunosuppressive medications. We have recently shown that IL1 β is highly upregulated in IL10R deficiency and blocking IL1 attenuated colitis in an IL10R-deficient mouse model. Thus, we elected to treat one patient with medical-refractory severe inflammatory bowel disease secondary to IL10RA mutation with anakinra, an IL1 receptor antagonist to evaluate its potential as the bridge to the allogeneic hematopoietic stem cell transplantation.

Methods: The intestinal inflammation was evaluated by endoscopy and histology. Lamina propria mononuclear cells (LPMC) were isolated from both biopsy terminal ileum samples pre-and post-anakinra treatment of the IL10R-deficient patient and surgical terminal ileum samples of Crohn's disease (CD) patients by mechanically disassociation and enzyme digestion. Peripheral blood mononuclear cells were isolated by Ficoll-Pague density gradient centrifugation. For flow cytometry analysis, lymphocytes were stimulated with 200ng/ml PMA, 1 μ g/ml Ionomycin and 1 \times Monensin for 4.5 hours, stained with antibodies (anti-Human Lineage Cocktail 3

or anti-CD3, anti-CD45/CD56/CD117/CD127/NKp44/IL22/IL17A and IFN γ).

Results: Anakinra therapy led to marked clinical, endoscopic, and histological improvement within a few weeks for the IL10R deficient patient. The frequency of IL22-producing lymphocytes among Lineage (+) CD45 (+) LPMC greatly increased from 2.17% pre-anakinra to 50.9% post-anakinra. Analysis of an additional ileal biopsy 3 months later demonstrated that the number further increased to 53.9%. Additionally, we detected a trend towards reduction of the IL22-producing lymphocytes ($p=0.07$) among Lineage (+) CD45 (+) LPMC in the inflamed tissue (2.89%, $n=9$) compared to unaffected tissue (5.75%, $n=3$) of those CD patients. Furthermore, we observed a significant increase in blood-borne TH22 and TH17 cells, both single producers and IL22/IFN γ , IL17A/IFN γ double producers, in the patient, as well as in CD subjects.

Conclusions: Herein, we present a case of a patient with severe IBD due to an IL10RA mutation whose intestine showed signs of mucosal healing accompanied by increased frequency of IL22-producing lymphocytes in the lamina propria of the terminal ileum after anakinra treatment. The increase in IL22, which promoted tissue repair, might have had an important role in the recovery of this patient and suggests an additional important mechanistic mode of action of anakinra in the gut.

P357

A multi-institutional report of postoperative outcomes in Vedolizumab-Treated patients undergoing major abdominal operations for inflammatory bowel disease

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Background: Vedolizumab, a gut specific monoclonal antibody targeting the $\alpha 4\beta 7$ integrin, was recently approved for treatment of moderate to severe ulcerative colitis (UC) and Crohn's disease (CD). We combined data from four institutions to investigate the 30-day postoperative complication rate among IBD patients who received

Abstract P357 – Table 1. 30 day post-operative complications

	No biologic Therapy (n=194)	TNF α inhibitors (n=130)	Vedolizumab (n=142)	P-value
Death	0	0	2 (1.4%)	P=0.101
Any postoperative SSI	16 (8%)	7 (5%)	38 (27%)	P<0.001
sSSI	12 (6%)	5 (4%)	23 (16%)	P<0.001
dSSI	3 (2%)	2 (2%)	12 (8%)	P=0.001
Anastomotic leak	0 (0%)	2 (2%)	5 (4%)	P=0.032
MCS	2 (1%)	0 (0%)	6 (4%)	P=0.017
SBO/ileus	4 (2%)	4 (3%)	4 (3%)	P=0.832
Readmission	11 (6%)	8 (6%)	26 (18%)	P<0.001
Return to OR	7 (4%)	5 (4%)	10 (7%)	P=0.293

SSI = Surgical Site Infection (superficial, deep, anastomotic leak, mucocutaneous separation), sSSI = superficial surgical site infection, dSSI= deep space surgical site infection, MCS= mucocutaneous separation, Return to OR = return to the operating room, SBO=small bowel obstruction

Abstract P357 – Table 2. Multivariable predictors of surgical site infection (SSI) among all IBD patients

	Odds ratio	95% Confidence Interval	P value
Group			P<0.001
Vedolizumab versus TNF α inhibitors	6.026	2.687, 15.439	P<0.001
Vedolizumab versus No biologic	3.816	2.025, 7.456	P<0.001
TNF α inhibitors Versus No biologic	0.633	0.236, 1.541	P=0.321
BMI	0.942	0.899, 0.987	0.013
Steroids at time of operation, n (%)	1.755	0.980, 3.132	0.058

*Univariate predictors with p values <0.10 were added to the multivariable model

vedolizumab within 12 weeks of an abdominal operation as compared to patients who received TNF α inhibitors or no biologic therapy.

Methods: A multicenter retrospective review of adult IBD patients who underwent an abdominal operation between 5/20/2014 and 12/31/2015 was performed. The study cohort was comprised of patients who received vedolizumab within 12 weeks of their abdominal operation and the control cohorts were patients who received TNF α inhibitors or no biologic therapy.

Results: 142 patients received vedolizumab within 12 weeks prior to an abdominal operation. Vedolizumab treated patients were younger (p<0.001) and were more likely to have taken steroids and/or immunomodulators (IMM) within the 12 weeks prior to surgery (p<0.001). Fewer vedolizumab treated patients had a primary anastomosis (p=0.001), but more underwent laparoscopic surgery (p=0.003) and had an ostomy formed at the time of their operation (p=0.029). Vedolizumab treated patients had a significantly increased risk of any postoperative Surgical Site Infection (SSI) (p<0.001), superficial SSI (p<0.001), deep space SSI (p=0.001), anastomotic leak (p=0.032), and mucocutaneous separation of the diverting stoma (p=0.017).

On univariate and multivariate analysis, exposure to vedolizumab remained a significant predictor of postoperative SSI (p<0.001).

There were no significant differences found across the four institutions in the SSI rate.

Conclusions: We found vedolizumab treated patients are at significantly increased risk of postoperative SSIs and anastomotic leaks following a major abdominal operation. Consideration to be given to delaying surgery in elective settings and diverting anastomoses with a protective stoma.

P358

Efficacy of golimumab for the treatment of ulcerative colitis patients in clinical practice: a retrospective cohort study

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Background: Golimumab is the third anti-TNF agent which received marketing authorization for the treatment of ulcerative colitis (UC) patients who are refractory to conventional therapies. To date, only few data are available regarding its efficacy in UC patients in clinical practice. The aim of our study was to evaluate the efficacy of golimumab for the treatment of UC patients in two tertiary French referral centers.

Methods: This was a retrospective cohort study including all consecutive UC patients treated with golimumab for induction of clinical

remission in two French tertiary referral centers from August 2014 to April 2016. Clinical response and clinical remission during the induction phase was defined according to physician judgment. Previous treatments, duration, optimization and withdrawal of golimumab were also collected.

Results: Twenty-four UC patients (13 Female and 11 Male) were included in the study. Montreal classification in UC patients at the time of golimumab introduction was a proctitis in 4% (1/24) of the patients, a left-sided colitis in 38% (9/24) and a pancolitis in 58% (14/24). Median delay between UC diagnosis and golimumab introduction was 81.7 months (IQR 1–3: 45–158). Golimumab was started in 7 (29%) patients who were naïve from biotherapies, in 4 (17%) patients who already received another anti-TNF and in 13 (54%) who already received more than one anti-TNF. Golimumab was associated with a concomitant immunosuppressant in 25% (6/24) of the cases. Short-term clinical response was achieved in 60% (13/22) of the patients. Clinical remission evaluated after a median treatment duration of 5 months (IQR 1–3: 3–5.3) was achieved in 29% (7/24) of the patients. A secondary loss of response was observed in 28% (2/7) of the UC patients who achieved clinical remission. Among UC patients with primary non-response to golimumab, 4 (24%) patients had an optimization of golimumab therapy with a clinical efficacy in 25% of the cases (1/4). Cumulative probability of golimumab withdrawal free survival was 27.4% \pm 9.9 at one year. In univariate analysis, there was no association between failure of golimumab (withdrawal and/or optimization) and previous exposure to anti-TNF or disease extent. However, there was a trend regarding the association between the concomitant use of an immunosuppressant and the maintenance of golimumab therapy without optimization (RR=0.4; CI 95%: 0.12–1.4, p=0.163).

Conclusions: In our cohort, golimumab was maintained with clinical efficacy in about 30% of the UC patients at one year. Previous exposure to anti-TNF seems to have non influence on treatment efficacy. Use of concomitant immunosuppressant may increase the efficacy of golimumab in the treatment of UC in clinical practice.

P359

Correlation between physician and patient disease assessments in ulcerative colitis: baseline data from the ICONIC study of 1816 patients in 33 countries

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Background: ICONIC is the largest prospective multi-country (n=33) observational study, assessing burden in adult ulcerative colitis (UC)

Table 1. Baseline clinical & demographic characteristics of UC patients in ICONIC*

Characteristic	All patients N=1816
Sex, n (%)	
Female	833 (45.9)
Age, years	
Mean \pm SD	38.5 \pm 14.6
Current smoker, n (%)	212 (11.7)
Time since UC diagnosis, days	
Median (25% Q, 75% Q)	171 (59, 317)
Disease Duration, n (%)	
0 – 6 months	873 (48.1)
6 months – 1 year	584 (32.2)
1-3 years	278 (15.3)
Duration of symptoms prior to UC diagnosis, n (%)	
< 1 year	1296 (71.4)
1-3 years	380 (20.9)
> 3 years	134 (7.4)
Disease severity since diagnosis, n (%)	
Improved	1278 (70.4)
Worsened (flare)	157 (8.6)
Remains similar	330 (18.2)
Endoscopic finding, n (%)	
Normal/Inactive	93 (5.1)
Mild	390 (21.5)
Moderate	550 (30.3)
Severe	209 (11.5)
Physician assessment of UC severity, n%	
Mild	672 (37.0)
Moderate	668 (36.8)
Severe	234 (12.9)
In remission	230 (12.7)
SIBDQ	
Mean \pm SD	48.4 \pm 13.2
PHQ-9	
Mean \pm SD	6.3 \pm 5.4
PHQ-9 depression severity, n (%)	
None-minimal	822 (45.3)
Mild	556 (30.6)
Moderate	256 (14.1)
Moderately severe	109 (6.0)
Severe	51 (2.8)
EIMs, n (%)	186 (10.2)
Any treatment since UC diagnosis, n (%)	1724 (94.9)
Response to current UC treatment, n (%)	
Not applicable/no current treatment	63 (3.5)
Too early to assess	187 (10.3)
Complete response	757 (41.7)
Partial response	712 (39.2)
No response	70 (3.9)

* Only available observed data are shown.

patients (pts) under routine care. Both pt & physician assessments of disease severity, activity & life impact will be captured at 6 month intervals through 2 years. This analysis will evaluate baseline (BL) demographics, clinical characteristics & the extent of agreement between pts & physicians in measures of disease activity.

Methods: Adult pts with early UC (diagnosed \leq 36 months) were enrolled irrespective of disease severity or treatment. Pt self-assessments include: disease severity, Pictorial Representation of Illness & Self-Measure (PRISM, [a tool assessing perception of disease-associated suffering]), Patient Health Questionnaire-9 (PHQ-9), Short Inflammatory Bowel Disease Questionnaire (SIBDQ) & pt-modified Sim-

ple Clinical Colitis Activity Index (P-SCCAI). Physician assessments include: clinical parameters, PRISM, & SCCAI. Correlation between PRISM & SIBDQ, PHQ-9, & SCCAI were evaluated. BL characteristics were obtained from observed data by calculating means. Mean differences between pt & physician measures were calculated using a one-sample t-test. Correlation analyses were performed by kappa statistics & Pearson correlation.

Results: BL demographic & clinical characteristics of 1816 UC pts enrolled in ICONIC are summarized in Table 1. At BL, pt/physician PRISM was moderately correlated with SIBDQ, PHQ-9, P-SCCAI, or SCCAI (Table 2). For 1796 pts with self & physician assessments, most showed agreement on disease severity (concordant pairs: mild 60.3%, moderate 60.6%, severe 56.0%) ($\kappa=0.43$, 95% CI 0.40–0.47, $p<0.0001$). Although P-SCCAI & physician SCCAI mean values \pm SD differed (4.2 \pm 3.6 & 3.0 \pm 3.0 [$p<0.0001$]), the measures were highly correlated (Table 2). For pt/physician PRISM assessments, mean scores (4.0 \pm 2.5 & 4.3 \pm 2.4, respectively) differed ($p<0.0001$) & were moderately correlated (Table 2).

Conclusions: Although the majority of pts received therapy & reported improved disease activity since diagnosis, nearly half had moderate-to-severe UC. PRISM, used for the first time in UC, was moderately correlated with disease-specific measures (SIBDQ & SCCAI) & a general depression assessment (PHQ-9). Alignment between pts & physicians on disease activity/severity may depend on the instrument used.

P360

Trough levels and antibodies to ustekinumab are not correlated to response to ustekinumab treatment in Crohn's disease patients

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Background: Ustekinumab (UST) has been shown to be effective in refractory Crohn's disease (CD) in phase III trials. The aim of the present study was to prospectively evaluate the association between UST trough levels and anti-ustekinumab antibodies, with the response and the remission to induction and maintenance UST treatment in CD patients.

Methods: We performed a prospective study including all CD patients refractory to anti-TNF who received subcutaneous UST from September 2015 to October 2016 in the tertiary French referral center of Gastroenterology in Claude Huriez hospital in Lille. During induction, patients received 90mg of SC UST at week 0, 4 and 12. During the maintenance phase, patients received 90mg of SC UST every 8 weeks that could be optimized by shortening injection interval to every 4 weeks in case of loss of response. Clinical response was defined by a decreased Harvey Bradshaw Index (HBI) by 3 points, clinical remission by HBI <5, loss of response by new increase of HBI. UST trough levels and antibodies were dosed at 12 weeks, and at a single time-point for patients who had received more than 3 months of UST.

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Table 2. Pearson correlation coefficients between selected instruments.

	SIBDQ	PHQ-9	PRISM (Physician)	P-SCCAI
PRISM (Patient), r (P-value)	0.5 (<0.0001)	-0.4 (<0.0001)	0.59 (<0.0001)	-0.4 (<0.0001)
SCCAI (Physician), r (P-value)	ND*	ND	-0.44 (<0.0001)	0.75 (<0.0001)

*not determined.

The results of dosage were obtained by enzyme-Linked ImmunoSorbent Assay technique. We evaluated the correlation between clinical and biological response and remission to UST, and UST through levels and antibodies concentrations. Differences between independent groups were traced with the use of the Mann–Whitney exact test.

Results: Forty-two patients with active disease received at least three UST injections and were prospectively included. At time of ustekinumab introduction, 62% of patients received concomitant immunosuppressant and 43% received corticosteroids. At the end of the induction phase (week 12), clinical response was observed in 57% patients. There was no significant difference in mean UST trough levels in patients who responded to UST induction (median 1160ng/ml; IQR: 603–1644) as compared to patients who did not respond (median 1556ng/ml; IQR: 494–2758, $p=0.24$). Thirty-two (76%) patients received at least 4 injections of UST, with 11 patients who were optimized at the time of dosages. Clinical response was observed in 23/32 (72%) patients. Median UST concentration in clinical responder was 1398ng/ml (IQR: 477–1979) and 1548ng/ml in non-responder (IQR: 453–2392), with no significant difference between the two groups of patients ($p=0.77$). UST antibodies were undetectable for the 42 patients.

Conclusions: We confirmed that UST treatment is effective in the majority of CD patients refractory to anti-TNF agents. Median trough levels to UST are not correlated to response and remission to UST induction and maintenance treatment, with no antibodies developed against UST.

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Machine learning models at week 6 of vedolizumab therapy for ulcerative colitis can predict week 52 corticosteroid free endoscopic remission

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Background: Vedolizumab is an effective therapy for ulcerative colitis (UC), but costly and slow to produce remission. New clinical responses continue to accumulate even after 30 weeks of therapy. Physicians, patients, and insurers want to know whether a given patient with UC will respond to vedolizumab when starting therapy, or at an early time point after starting therapy.

Methods: Through the Clinical Study Data Request Site, we obtained access to the phase 3 clinical trial data for the induction and maintenance of ulcerative colitis using vedolizumab. Random forest modeling was applied to 70% training sets and tested on 30% test sets to predict the outcome of corticosteroid-free endoscopic remission with vedolizumab at week 52. Models were constructed using baseline data, or data through week 6 of vedolizumab therapy.

Results: The original study included 895 subjects that were enrolled and included in the analysis. Subjects assigned to placebo (N=275), with missing predictor variables (N=125), or missing outcome data (N=4), were excluded. The AuROC for prediction of corticosteroid-free endoscopic remission at week 52 using baseline data was only 0.63, but was 0.73 when using data through week 6 of vedolizumab therapy. The sensitivity of this model was 72%, with a specificity of 68%. The most important predictors included fecal calprotectin at week 6, the slope of the vedolizumab level, slope of FCP, albumin, and vedolizumab level at week 6. Patients predicted to be in CS-free

endoscopic remission at week 52 by the model achieved this endpoint 55% of the time, while patients predicted to fail only succeeded 19% of the time.

Conclusions: A machine learning algorithm using laboratory data through week 6 of vedolizumab therapy was able to accurately identify which UC patients would achieve corticosteroid-free endoscopic remission on vedolizumab at week 52. Application of this algorithm could have significant implications for clinical decisions on whether to continue this costly medication, whether to consider adding a co-therapy, or to change to an alternative therapy for ulcerative colitis at week 6.

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Magnetic resonance healing predicts long-term outcomes in patients with Crohn's disease

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Background: Crohn's disease (CD) is a chronic transmural inflammatory condition usually involving the small bowel. While endoscopic mucosal healing is the currently accepted therapy target, in most patients and adequate evaluation of the small bowel is not possible. Magnetic resonance enterography (MRE) is a noninvasive modality commonly performed to assess the small bowel in CD. However, long-term outcomes associated with MRE improvement are still to be assessed. The purpose of this study was to determine whether MRE remission predicts long-term outcomes in patients with CD.

Methods: Using a prospectively maintained database of patients with inflammatory bowel disease, we retrospectively analyzed patients with CD restricted to the small bowel, and with MRE examinations. Outcomes included surgery and need to start or change immunosuppressive therapy.

Results: We included 246 patients, median age at MRE examination of 37.0 (8–78) years. The median time from diagnosis to MRE was 7 (0–40) years with a median follow-up of 4 (1–9) years following MRE. MRE showed active inflammation in 175 studies (71.1%). Patients demonstrating MRE-active inflammation were more likely to require a change in anti-TNF (45.3% versus 18.3%, $p<0.001$), thiopurines (34.1% versus 14.9%, $p=0.002$), any medication (60.0% versus 26.8%, $p<0.001$), and also more likely to undergo surgery (18.9% versus 2.8%, $p<0.001$). A compound unfavorable outcome including change in medication or surgery was also more likely in patients with active MRE (65.1% versus 28.2%, $p<0.000$). In logistic regression analysis, MRE-activity (OR 5.85 95% CI 1.32–25.91, $p=0.02$) and the presence of a stricture (OR 2.75 95% CI 1.24–6.12, $p=0.01$) were independently associated with surgery.

Conclusions: In this study, MRE remission was associated with significantly improved long-term outcomes. Obtaining MRE remission may be a potential therapy target in patients with CD.

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The impact of transition to adult gastroenterology services on health-related quality of life in young adult patients with IBD: the UK TRANSIT study

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Background: Paediatric patients with IBD move from family-oriented paediatric to individual-oriented adult gastroenterology services at a time of significant physical and psychological change. There is some evidence that coordinated transition programmes may improve outcomes in IBD when transferring to adult services. The health-related quality of life (HRQoL) of adolescent/young adults following transfer to adult services has not been described.

Methods: An observational, multi-centre, mixed methodology study of adolescent/young adult patients (age ≥ 16 years) with a confirmed diagnosis of IBD before age 16 who had been under the care of adult services for ≥ 12 months at recruitment was conducted in 11 UK centres. Transition visits were defined as those involving clinical staff from both paediatric and adult services; transition patients had attended ≥ 2 transition visits and non-transition patients attended none. Patients completed the following questionnaires at recruitment: Short Inflammatory Bowel Disease Questionnaire (SIBDQ), Inflammatory Bowel Disease Control Questionnaire (IBDCQ-8 and IBDCQ-VAS [visual analogue scale]), Hospital Anxiety and Depression Scale (HADS), Work Productivity and Activity Index (WPAI) and self-reported days of education lost due to IBD. Socioeconomic status was measured using the English Index of Multiple Deprivation (IMD).

Results: Transition (n=95) and non-transition (n=34) patients were similar in terms of demographic and clinical characteristics at recruitment (transition: median age 19.6 years; 47% female; 78% CD; median 2.1 years since index visit) and non-transition patients (n=34; median age 19.3 years; 41% female; 74% CD; median 2.3 years since index visit; all $p > 0.05$). Overall, patient-reported quality of life and perceived IBD control were similar in transition and non-transition patients (all $p > 0.05$; see table). Significant symptoms of anxiety and depression were reported by 20% and 2%, respectively, of transition patients and by 13% and 0%, respectively, of non-transition patients ($p > 0.05$; see table). Of those in employment, 16% of transition and 27% of non-transition patients had time off work in the previous

week. Time lost from education and socioeconomic status were similar in transition and non-transition patients (both $p > 0.05$; see table). **Conclusions:** Surveys collected from at least 120 adolescent/young adult patients with IBD taking part in this study describe health related quality of life at this time point.

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A Swedish observational study (SVEAH) on vedolizumab assessing effectiveness and healthcare resource utilization in patients with inflammatory bowel disease

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Background: Clinical trials may not reflect real world clinical practice. We aim to assess long-term effectiveness of vedolizumab in patients with inflammatory bowel disease (IBD), in a variety of care context, by implementing a national study integrated with the national Swedish quality registry for IBD (SWIBREG).

Methods: Patients with active IBD disease (defined by endoscopy, MRI and biochemical activity) initiating vedolizumab from 1/6/2015

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Table. Health-related quality of life and socioeconomic status of adolescent/young adult patients with IBD following transfer to adult services

Questionnaire	Transition patients (n=95)	Non-transition patients (n=34)
SIBDQ ^a	52.0 (12.7), n=87	52.1 (11.1), n=33
IBDCQ ^a	10.9 (4.7), n=89	11.7 (4.4), n=33
IBDCQ-VAS ^a	76.4 (23.6), n=89	75.8 (25.9), n=33
HADS anxiety	n=86	n=30
Mean score ^a	6.2 (4.6)	6.3 (3.9)
Patients with score ≥ 11 ^{b,c}	17 (20%)	4 (13%)
HADS depression	n=85	n=29
Mean score ^a	2.8 (3.0)	3.2 (2.4)
Patients with score ≥ 11 ^{b,c}	2 (2%)	0 (0%)
WPAI: % working time missed in past 7 days ^b	n=43	n=15
0%	36 (84%)	11 (73%)
1-50%	7 (16%)	4 (27%)
>50%	0 (0%)	0 (0%)
Days of education missed/patient/year ^d	n=76	n=29
	14.5 (7.6–26.9)	13.3 (5.0–20.0)
IMD decile ^d	5.0 (3.0–8.0), n=85	7.0 (5.0–8.0), n=33

Data presented as ^amean (standard deviation), ^bn (%) or ^cmedian (interquartile range); VAS: visual analogue scale; ^dScores ≥ 11 indicate significant symptoms of anxiety or depression

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Table 1. Clinical Characteristics of patients with inflammatory bowel disease		
	Crohn's disease n=120	Ulcerative Colitis n=80
Median age yr. (IQR)	42 (19-79)	41.5 (19-80)
Sex female no. (%)	60 (50)	37 (41)
Location – no. (%)*		
Ileum (L1)	20 (17)	
Colon (L2)	32 (27)	
Ileocolonic (L3)	57 (48)	
Upper GI (L4)	1 (1)	
Extent –no. (%)**		
Proctitis		1 (1)
Left-sided colitis		17 (21)
Extensive colitis		55 (69)

*Final report on disease location not confirmed yet (n=10)

**Final report on disease extent not confirmed yet (n=7)

have consented to participate in a prospective, observational, multi-centre cohort study in Sweden. Exclusion criteria were concurrent participation in a clinical trial in which IBD treatment is dictated by a study protocol, contraindications to vedolizumab and planned discontinuation of vedolizumab treatment within <12 months from baseline. Information on clinical characteristics, treatment (previous and ongoing), clinical-, biochemical-, endoscopic activity, quality of life measures, health-care resource use is recorded at baseline and prospectively, using an electronic Case Record Form, integrated with SWIBREG. Data from other national registries that is the Patient Registry, the Cancer Registry, Statistics Sweden's LISA registry on occupational details, the Social Insurance register on long-term sick leave and the Prescription registry are linked to the dataset. Outcomes, including clinical effectiveness, defined by Harvey Bradshaw index and Mayo score, are assessed at 12 and 52 weeks.

Results: 120 Crohn's disease (CD) and 80 ulcerative colitis (UC) patients were included, by 1/11/2016 (Table 1) At this time, 24 CD and 19 UC patients had completed the 12 month study period, of whom 21 (88%) and 14 (73%), respectively, were still on treatment with vedolizumab. Interim analyses are ongoing and further results will be reported.

Conclusions: Our national implementation of a prospective observational study, where data are electronically integrated with the national Swedish quality registry for IBD and additional data retrieved from other national registries, illustrates next generation of prospective real world cohort studies, aiming to generate robust long-term data on effectiveness, safety, and used health care resources in vedolizumab treated IBD patients.

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Serum adalimumab levels predict successful remission and safe de-intensification in inflammatory bowel disease patients in clinical practice

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Background: Little is known about the association between the pharmacokinetic features of adalimumab (ADL) and disease outcome in patients with inflammatory bowel disease (IBD). Aims: To assess the association between random serum ADL levels and clinical and biochemical remission and between ADL levels and clinical decision making in daily practice. To determine the cut-off value for successful dose reduction in IBD patients treated with ADL.

Methods: We conducted a prospective cohort study (18 months) of IBD patients who received maintenance therapy with ADA (at least 12 weeks).

Results: Data were available for 157 serum samples from 87 patients. Serum ADL levels were associated with clinical remission: median 9.2 µg/ml vs 6.0 µg/ml for Crohn's disease patients with active disease (p=0.009) and 14.4 µg/ml vs 5.2 µg/ml for ulcerative colitis patients with active disease (p=0.002) (Fig. 1).

Serum ADL levels were 9.2 µg/ml for patients with a normal C-reactive protein (CRP) value (<5mg/l) and 5.2 µg/ml for patients with a high CRP value (p=0.002) (Fig. 2).

ADL levels were significantly associated with normal fecal calprotectin values (<80 ng/g) (10.8 µg/ml vs 7.6, respectively, p=0.038) (Fig. 3).

We analyzed the clinical decisions taken on the basis of serum ADA levels according to the cut-off values described in previous studies (8 µg/ml).

Figure 4 describes patients' drug levels according to the clinical decision taken. Serum ADL levels were significantly associated with

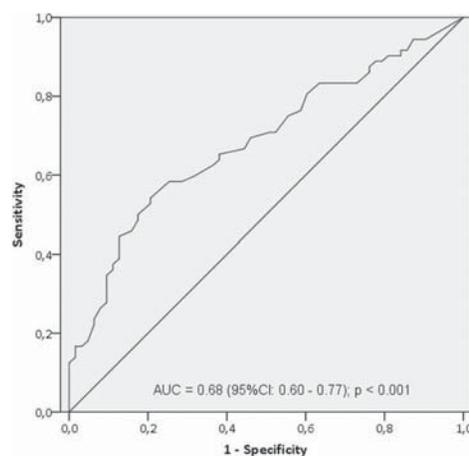


Figure 1. Receiver operating characteristic (ROC) curve. Serum ADA levels and remission of disease.

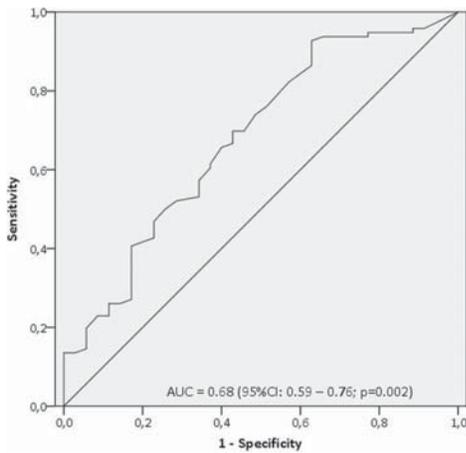


Figure 2. Receiver operating characteristic (ROC) curve. Serum ADA levels and normalization of C-reactive protein levels.

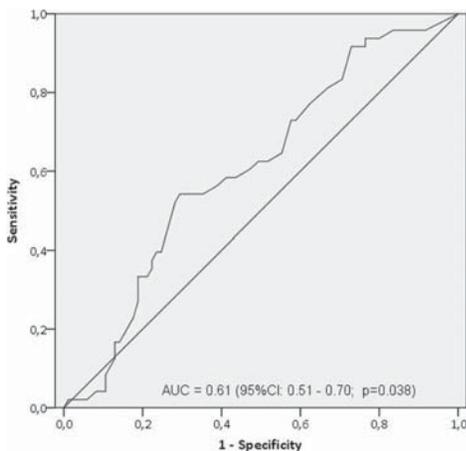


Figure 3. Receiver operating characteristic (ROC) curve. Serum ADA levels and fecal calprotectin <math>< 80 \mu\text{g/g}</math>.

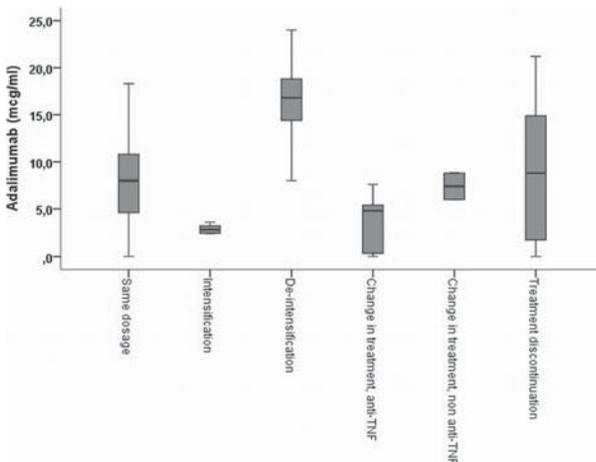


Figure 4. Decisions taken in clinical practice based on serum ADA levels: median serum ADA level for each decision group.

successful de-intensification compared with the group in which doses remained unchanged (AUC 0.88; 95% CI: 0.81–0.95; $p < 0.001$). The cut-off value for successful de-intensification was 12.2 $\mu\text{g/ml}$.

Conclusions: Higher ADA levels were significantly associated with clinical and biochemical remission. Our results, which were obtained under conditions of daily clinical practice, suggest that an ADA cut-off of 12.2 $\mu\text{g/ml}$ is appropriate for successful dose reduction in IBD patients treated with ADA.

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The efficacy of vedolizumab for induction of clinical response and remission in anti-TNF naïve patients with inflammatory bowel disease – a multicenter European real world experience

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Background: Vedolizumab (VDZ) is a humanized anti- $\alpha 4\beta 7$ integrin monoclonal antibody that is effective and approved for treatment of ulcerative colitis (UC) and Crohn's disease (CD). In the GEMINI trials, anti-TNF naïve patients had a superior response compared to previously anti-TNF exposed patients. Several real world experience (RWE) series were published so far, with response rates ranging between 40–60%; however very few patients in those series were anti-TNF naïve. The aim of our study was to describe the outcome of VDZ treatment in anti-TNF naïve patients in a real-world setting.

Methods: This was a retrospective multicenter European pooled cohort analysis that focused on anti-TNF naïve patients who received VDZ and were prospectively followed for 14 weeks. Patients who completed the induction protocol or discontinued the treatment before week 14 for adverse events or primary non-response were included. Clinical, laboratory and endoscopic data were collected. The primary endpoint was induction of clinical remission at week 14; secondary endpoints included clinical response and CRP decrease.

Results: Fifty seven anti-TNF naïve patients treated with VDZ from 10 centers (3 – Italy, 3 – Israel, 1 – Germany, 1 – France, 1 – UK, 1 – Finland) were included in the study (26 (45.6%) male).

Forty seven (82.4%) patients received VDZ 300 mg at week 0, 2, 6 and 14; 10 (20%) received and additional dose at week 10. Thirteen (22.8%) patients had CD and 44 (77.2%) UC. For CD patients: 8/13 (61.5%) had elevated CRP, 2 (15.4%) received concomitant methotrexate and 2 (15.4%) received systemic corticosteroids at treatment onset. At week 14, 11 (84.6%) responded to treatment, of them 5 (38.5%) achieved clinical remission; CRP levels decreased in 7/8 (87.5%) of the patients. For UC, 25 (56.8%) patients had elevated CRP, 11 (25%) received concomitant immunomodulators and 17 (38.6%) received systemic corticosteroids at treatment onset. At week 14, 38 (86.4%) responded to treatment, of them 25 (56.8%) achieved clinical remission. CRP levels decreased in 23/25 (92%) patients with elevated baseline CRP.

At week 14, VDZ was continued in 50 (87.7%) of the patients; in 6 patients (5 – UC, 1 – CD) VDZ was discontinued for primary non-response and in 1 patient (UC) for an adverse effect (tinnitus). Three patients required hospitalization during the induction, of them 2 were referred to colectomy and one was treated for *Clostridium difficile* infection

Conclusions: VDZ was effective for induction of clinical response in anti-TNF naïve patients with both UC and CD. CRP was reduced by week 14 in a vast majority of patients. Response and remission rate in anti-TNF naïve patients were substantially higher than the rates reported for anti-TNF experienced patients in current RWE series.

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The availability of infliximab trough levels in IBD patients on maintenance therapy deeply impacts therapeutic decision-making

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Background: Infliximab (IFX) trough levels (ITL) have emerged as a promising tool for the management of inflammatory bowel disease (IBD) patients. However, its real usefulness in clinical practice is still controversial.

Methods: Observational study where IBD patients on maintenance IFX therapy were prospectively included from June 2015 to June 2016. At each IFX infusion, patients were visited by their physician and the actual clinical decision (ACD) was taken regarding clinical and biological data (C-reactive protein (CRP) levels). At this time, blood samples for ITL were collected. Our aim was to compare the ACD with the decisions of 3 experts' based on the same data plus the results of ITL (ITL-guided decision –TLGD-). The decisions between experts were also compared. Both comparisons were calculated by the linear Cohen's Kappa (κ) index.

Results: A total of 235 infusions were analyzed among 77 IBD patients. Concordance between ACD and TLGD was poor ($\kappa=0.10$ [95% CI: 0.01–0.20]/ $\kappa=0.11$ [95% CI: 0.01–0.21]/ $\kappa=0.10$ [95% CI: 0–0.21]) for experts A/B/C, respectively. This “disagreement” was mainly due to a higher proportion of dose-escalations according to the TLGD as compared to the ACD. Among the 215 infusions where no action was taken according to the TD, 85 (40%), 43 (20%) and 59 (28%) patients would have been dose-escalated according to the TLGD for experts A, B and C, respectively. Despite this “disagreement”, most patients remained in clinical and biological remission during the follow up, since only 28% of events were recorded as loss of response defined as clinical relapse and/or CRP ≥ 5 mg/L. Moreover, concordance between experts was moderate ($\kappa=0.55$ [95% CI: 0.41–0.71]/ $\kappa=0.40$ [95% CI: 0.26–0.55]/ $\kappa=0.30$ [95% CI: 0.21–0.40]) for experts A-B/B-C/A-C respectively).

Conclusions: ITLs significantly change the therapeutic decision making on IBD patients treated with IFX, mainly towards dose-escalation of IFX. Both the clinical and economical impact of such a potential change in the management of IBD patients needs to be evaluated in future cohorts.

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Treatment of inflammatory bowel disease in the elderly

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Background: Data on efficacy and safety of inflammatory bowel disease (IBD) treatment in the elderly is sparse as they are often excluded from clinical trials. We aimed to analyse treatment options and adverse events in elderly IBD patients.

Methods: Retrospective study including 345 IBD patients followed in our outpatient clinic from January 2008 to October 2016. Demographic and clinical data was analysed. Elderly was defined as patients over 60 years of age.

Results: 173 (50.1%) Crohn's disease, 168 (48.7%) Ulcerative colitis and 4 (1.2%) Indetermined colitis patients were included, 56.2% were female and the median follow-up was 13 years (IQR 8–19). Mean age at diagnosis was 33.0 years (IQR 23.0–45.5), 36 (10.4%) patients had elderly-onset IBD and 106 (30.7) were ≥ 60 years at the time of the study analysis. Charlson comorbidity index (4.1 ± 1.4 vs. 0.8 ± 1.3 , $p < 0.001$) and total number of daily medications (4.3 ± 3.5 vs. 1.6 ± 1.6 , $p < 0.001$) were significantly higher in patients ≥ 60 years. This group received more frequently sulfasalazine or 5-aminosalicylates (84.6% vs. 72.0%, $p = 0.001$) and less frequently azathioprine (19.8% vs. 51.5%, $p = 0.000$) or tumor necrosis factor inhibitors (13.2% vs. 36.0%, $p = 0.000$). There was no significant difference concerning the use of metotrexate or surgery. When comparing elderly with non-elderly, global incidence of adverse events was not significantly different (16.0% vs. 21.3%, $p = 0.253$), neither was the sub-analysis of patients under sulfasalazine or 5-aminosalicylates ($p = 0.233$), azathioprine or 6-mercaptopurine ($p = 0.786$) or tumor necrosis factor inhibitors ($p = 0.549$). Infection was not more frequently diagnosed in the elderly ($p = 0.784$).

Conclusions: One in each 10 patients has elderly-onset IBD. Although immunosuppression was used less frequently in this population, there was no significant differences in its safety profile.

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Safety and lymphocyte-lowering properties of etrasimod (APD334), an oral, potent, next-generation, selective S1P receptor modulator, after dose escalation in healthy volunteers

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Background: Etrasimod is an oral, potent, next-generation S1P modulator with an optimized S1P receptor activity profile that is in Phase 2 clinical development for ulcerative colitis.

Methods: Two randomised, double-blind studies evaluated safety and pharmacodynamics of etrasimod, administered orally as single dose (Study 001; dose-escalation design) or repeat once daily (QD) dosing (Study 002; multiple ascending-dose design) in healthy adults. In Study 001, up to 8 subjects per cohort were randomised to etrasimod

mod (n=6) or placebo (n=2), starting at 0.1mg. Following screening (21 days), single doses were administered on Day 1 and observations undertaken until at least Day 7. In Study 002, up to 12 subjects in each of 3 cohorts (0.7, 1.35 and 2.0mg) received etrasimod (n=10) or placebo (n=2) for 21 days. Dosing in Cohorts 4 and 5 started at 0.35 and 0.5mg for 7 days with titration to 2.0 and 3.0mg, respectively.

Results: In single doses, etrasimod was well tolerated at 0.1, 0.35, 1 and 3mg. Mild-to-moderate headache (1/6–3/6 of subjects) and contact dermatitis (1/6–2/6) were the most commonly reported AEs, occurring with similar/lower frequency to placebo (2/3 each). In the 5mg cohort, 4 events of first or second degree AV block, with and without bradycardia, occurred in 3/6 subjects; although asymptomatic, further dose escalation was stopped. Dose-related declines in blood pressure and heart rate from baseline (vs placebo) were statistically significant with 3.0 and 5.0mg doses only ($p<0.05$); all resolved without intervention. With multiple dosing, common AEs with etrasimod versus placebo included contact dermatitis (1/10–7/10 of subjects vs. 6/10), constipation (2/10–3/10% vs. 0), headache (1/10–3/10% vs. 4/10) and diarrhoea (2/10–3/10% vs. 1/10). These were mild-to-moderate, and not dose related. Small asymptomatic declines in blood pressure and heart rate were noted. 3 subjects developed first degree AV block (placebo: 1; 2mg: 1; 0.5/3mg: 1). No serious AEs or deaths were reported. Single etrasimod doses of 3mg and 5mg decreased total peripheral blood lymphocyte counts to 52.5% and 35.9% of baseline and with time to nadir of ~15 hours and ~11 hours post-dose, respectively. With multiple dosing, etrasimod had a dose-dependent effect on lymphocyte lowering, plateauing at 2mg QD. Median reduction in lymphocyte counts was ~67% for the higher doses (2 and 3mg QD for 21 days). For both studies, mean counts returned to baseline levels within 7 days of dosing discontinuation.

Conclusions: In Phase I studies, etrasimod was well tolerated and modulated lymphocyte levels when administered orally at dose levels ≤ 3 mg in healthy volunteers. These findings support further evaluation of this S1P modulator in clinical studies.

P370

A randomised controlled trial of acceptance and commitment therapy for the treatment of stress in inflammatory bowel disease

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Background: The inflammatory bowel diseases are associated with high levels of psychological stress. Acceptance and commitment therapy (ACT) is a psychological intervention that comprises acceptance and mindfulness procedures along with commitment and behaviour-change strategies to increase psychological flexibility and reduce stress. The aim of this study was to determine the effect of ACT on stress in IBD patients.

Methods: Ninety five patients (mean age 40 years; 42 male) with quiescent or mildly active IBD were randomly assigned to an eight week ACT course (n=47) or to a control group (n=48) stratified by disease type and gender. Clinical, demographic, disease activity, biochemical (including CRP and faecal calprotectin) and psychological data were collected at i) baseline, ii) post-intervention (8 weeks) and iii) 20 weeks. Patients on antidepressants, those with psychiatric disorders or those who had received steroids over the previous three

months were excluded from study. Stress symptoms and reaction to stress was measured using the DASS-21 and perceived stress using the stressometer. Intervention and control groups were well matched for age, gender, social variables, disease activity, CRP and calprotectin levels.

Results: ACT was associated with a 42% and 37% reduction in DASS-21 stress scores at 8 and 20 weeks respectively, in comparison with control patients whose DASS-21 stress scores remained stable over the study period (ANOVA, $p<0.05$) (see Figure 1).

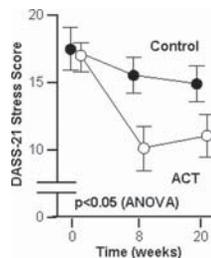


Figure 1. DASS stress scores in ACT and control groups.

ACT was also associated with a reduction in perceived stress scores at 8 and 20 weeks when compared with control patients ($p<0.05$). No changes were found in clinical or biochemical disease activity, nor in other psychological parameters, in either group over the 20 week study period.

Conclusions: An 8 week course of ACT is an effective treatment for reducing stress in IBD patients. If it is true that stress is causally associated with subsequent IBD activity, future therapeutic paradigms may include appropriate psychological treatments to favourably impact on stress and, perhaps, long term disease activity.

ClinicalTrials.gov Registration No: NCT02350920

P371

Healthcare maintenance in inflammatory bowel disease patients: need for a top down approach

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Background: Patients with inflammatory bowel disease (IBD) often depend on their gastroenterologist for IBD related healthcare maintenance. In our institution, we provide verbal advice to the patient and written guidance to the primary care physician on issues including vaccinations, bone health and cancer/dysplasia surveillance. Furthermore, we hold quarterly education days for newly diagnosed IBD patients and offer chronic disease self-management courses.

Aims: To capture adherence to ECCO healthcare maintenance guidelines and to identify factors contributing to poor compliance.

Methods: We administered an anonymous written survey to patients attending the IBD clinic and the infliximab infusion suite. The survey contained fourteen questions pertaining to the IBD diagnosis, medications, duration of disease, influenza and pneumonia vaccination status, smoking status, sun avoidance and sunscreen use and bone density scanning.

Results: One hundred and twenty-seven patients completed our survey, 59 (46%) were male, ages ranged from 17 to 78. Sixty-five patients had Crohn's, 51 ulcerative colitis, 1 indeterminate colitis and 9 patients did not know their diagnosis. Duration of disease, gender or age were not significantly associated with knowledge of disease. Patients who did not know their disease were more likely not to know what medications they took ($p=0.002$) but it did not influence smok-

ing status, vaccination uptake, use of sunscreen, regular attendance for laboratory investigations or measurement of bone density ($p=ns$). We found no significant difference in vaccination uptake and sunscreen use between patients taking biologic and immunosuppressant medications compared to patients treated with mesalamine products or on no therapy. Female patients were mostly up to date with cervical smear tests, likely a reflection of the Irish Cervical Screening programme. Seventeen percent of patients with Crohn's continue to smoke and half the smokers claim cessation was never recommended. **Conclusions:** Despite verbal and written advice to patients and primary care physician's vaccination uptake in patients on immunomodulatory and biologic therapy was poor. We provide structured education sessions but still 7% of patients had limited knowledge of their disease or of their medications. We propose that our patients attend an IBD nurse led annual review and education clinic to address ongoing healthcare issues to minimise adverse events associated with immunomodulatory and biologic therapy.

P372

The long term course of patients undergoing ileal pouch-anal anastomosis for ulcerative colitis

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Background: Proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for patients with ulcerative colitis who require colectomy for medically refractory disease or other complications such as dysplasia. The aim of this study was to evaluate the long term course of patients undergoing IPAA for ulcerative colitis, and to assess the occurrence of pouchitis and other complications.

Methods: A retrospective analysis of all records of patients admitted at "Villa Sofia-Cervello" Hospital from 1988 to 2016 who underwent proctocolectomy with IPAA for ulcerative colitis was performed. At least one endoscopic evaluation during follow-up was available for all patients.

Results: Among 1,490 patients with ulcerative colitis admitted at "Villa Sofia-Cervello" Hospital during the study period, the records of 71 patients (4.8%) undergoing IPAA were analyzed. The surgical procedure was performed in two stages in the majority of cases (76.0%), and the median time to recanalization was 6 months (I.Q.I. 6.5). The mean duration of follow-up after IPAA procedure was 110±77 months. The occurrence of pouchitis was reported in 48 (67.6%) patients. The time between IPAA and the diagnosis of pouchitis ranged from 1 to 120 months, with a median of 12 months. In addition, 33 out of 48 patients (68.8%) developed chronic pouchitis, while Crohn's disease of the pouch was diagnosed in four patients (8.3%). The stenosis of the anastomosis was reported in 18 patients (37.5%), and the presence of abscesses/fistula in 11 (22.9%). The occurrence of pouch failure was observed in 6 patients (12.5%), all of them suffering from chronic pouchitis complicated by fistulizing disease. No dysplasia nor Cytomegalovirus infection of the pouch were reported. Subgroup analysis of patients developing pouchitis

revealed that only the chronic form of this condition was associated with the stenosis of the anastomosis, which conversely was rarely observed when the pouchitis was episodic and did not become chronic (88.9% vs. 11.1%, $p=0.04$).

Conclusions: Our cohort with long term follow-up showed that pouchitis and chronic pouchitis are very frequent events. Conversely, Crohn's disease of the pouch is rare, and no cases of Cytomegalovirus infection of the pouch were reported.

P373

Real-life prospective experience with adalimumab in inducing remission in ulcerative colitis in Italian primary inflammatory bowel diseases centres

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Background: Moderate-to-severe active ulcerative colitis (UC) may be treated with anti-TNF α . Since the Adalimumab (ADA) distribution in Italy by National Health System (April 2014), its use in UC patients follows rigid entry criteria and a standard schedule of evaluation of clinical outcomes. Aim of this study was to assess the efficacy and safety of Adalimumab in inducing remission or clinical response in outpatients UC patients treated in Italian primary Inflammatory Bowel Diseases centres.

Methods: Fifty-seven consecutive UC patients with at least 12-week follow-up were enrolled. The primary endpoint was clinical remission reaching, defined as Mayo score or partial Mayo score ≤ 2 after 12 weeks.

The secondary endpoints included: (1) clinical response to treatment, defined as partial Mayo score reduction of at least 2 points; (2) safety of the drug, defined as occurrence of adverse events during treatment.

Results: Demographic characteristics of the enrolled population are reported in table 1. At 8-week follow-up, clinical response was obtained in 36/57 (63.2%) patients and clinical remission was achieved in 22/57 (38.6%) patients. At 12-week follow-up, clinical response was obtained in 35/55 (63.6%) patients and clinical remission was achieved in 21/55 (38.2%) patients. Significantly, no adverse events neither colectomy were recorded during the 12-week trial.

Conclusions: Real-life effectiveness of adalimumab in inducing UC remission is promising, also in patients had already been exposed to infliximab beforehand. Larger groups of patients, with longer follow-up, are warranted to confirm such results.

P374 Home or hospital-based analysis of stool calprotectin: assessing two methods for monitoring inflammatory bowel disease

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Background: For 8 years we have been following patients with inflammatory bowel disease by periodically measuring calprotectin levels in their sent-in stool samples with an enzyme-linked immunosorbent assay (ELISA). Levels below 250 µg/g confirmed disease remission, levels above 500 µg/g indicated a disease flare, and indecisive values between 250 and 500 µg/g required retesting after 1 month. Physicians and patients found repeated testing of calprotectin helpful to guide therapy, but both wished to receive the results without delay. BÜHLMANN Laboratories recently developed a lateral flow-based calprotectin test and a software application (IBDoc[®]) that turns an ordinary smartphone camera into a reader for quantitative measurements at home. We compared this new method with the established ELISA method to see whether they agreed sufficiently for the new to replace the old, or to use the two interchangeably.

Methods: Eligible teenagers and adults, who had a smartphone validated for the IBDoc[®] app, received an instruction manual to perform the calprotectin stool test at home. The residual of the stool specimen was sent to the hospital for ELISA measurement of calprotectin. Agreement between methods was assessed, as well as critical misclassifications of disease activity (leading to over- or undertreatment). Predefined acceptable limits of agreement were ± 100 µg/g in the lower ranges of calprotectin and ± 200 µg/g in the higher ranges.

Results: 85 participants produced 152 paired calprotectin measurements. In the lower ranges (i.e., between 40 and 400 µg/g) 99 of 117 pairs (85%) were within acceptable limits of agreement, and in the higher ranges (>400 µg/g) 20 of 35 pairs (57%). Eighty percent of all paired measurements were concordant (Figure 1). Critical misclassification (disease remission with one method and disease flare with the other) was observed in 4% of pairs. Two critical misclassifications leading to undertreatment (low IBDoc[®], high ELISA) were in fact invalid measurements by a single patient who continued the analytical step before the indicated incubation period.

Conclusions: We found acceptable agreement between IBDoc[®] home test and hospital-based ELISA in the critical lower ranges of calprotectin and therefore the new method can be used to monitor patients

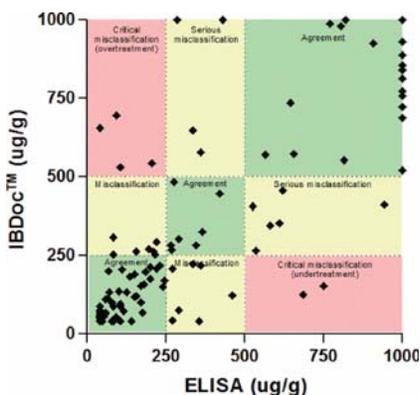


Figure 1

in remission. Results in the higher range need to be confirmed before therapy adjustment. Misclassification can probably be further reduced with a face-to-face training of the patients.

P375 Intraoperative endoscopy is safe and helps to determine the resection extent in Crohn's disease

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Background: The majority of Crohn's disease (CD) patients will undergo surgery because of CD complications. To determine the extent of the resection, endoscopy and cross-sectional imaging prior surgery, as well as intraoperative assessment by surgeon might not be sufficient. Intraoperative endoscopy can be of value in guiding the extent of resection but the data on its safety and usefulness in this setting are scarce.

The aim of our study was thus first, to analyze the safety of intraoperative endoscopy. Second, we aimed to determine its impact on the extent of the resection.

Methods: All CD patients operated on in one referral center from January 2015 till October 2016 were included. Intraoperative endoscopy was performed in case of unclear disease extent based on cross-sectional imaging and/or endoscopy prior surgery. Duration of surgery and hospital stay, C-reactive protein, procalcitonin, white blood cells count and rate of complications (anastomotic leak, abscess, re-admission) were noted. The differences between endoscopy and no endoscopy group were analyzed statistically. In addition, the impact of intraoperative endoscopy findings on the extent of the resection was determined.

Results: In total, 41 CD patients underwent surgery (25 laparotomies, 9 laparoscopic and 7 single port laparoscopic surgeries) because of stricturing (25pts), penetrating (14pts) disease complications or treatment failure (2pts). Nineteen intraoperative endoscopies were performed in 17 pts (8 enteroscopies, 1 gastroscopy, 10 colonoscopies).

The endoscopy group had significantly longer median hospital stay compared with the group without endoscopy (respective medians of 6 vs. 5 days, $p=0.03$). There were no significant differences between the two groups with regards to the duration of the surgery (respective medians 160 vs 135 minutes - endoscopy vs no endoscopy group, $p=0.15$). C-reactive protein, procalcitonine levels and white blood cells were numerically higher in the endoscopy group during the first five postoperative days but the difference was not statistically significant.

Complications occurred in one out of 17 patients in the endoscopy group (intraabdominal abscess) and in one out of 24 patients in the non-endoscopy group (bleeding from the anastomosis) ($p=n.s.$).

Twelve out of 19 intra-operative endoscopies provided the information that led to change in the extent of resection (5 reductions and 7 extensions of the to be resected segment) compared with the extent planned based on the cross-sectional imaging and the intraoperative judgment by surgeon.

Conclusions: Intraoperative endoscopy is a safe and useful tool helping to tailor the extent of surgery in complicated Crohn's disease.

P376**Assessment of nutritional status and food related experience of adult inflammatory bowel disease inpatients**K. Keetaru^{*1}, S. Bloom², X. Qu³, G. Grimble³¹University college london hospital, Nutrition and dietetics, London, United Kingdom; ²University College Hospital, Department of Gastroenterology, London, United Kingdom; ³University College London, Department of Gastroenterology and Nutrition, London, United Kingdom**Background:** Ulcerative colitis (UC) and Crohn's disease (CD) are types of inflammatory bowel disease (IBD). Significant abnormalities in body composition including muscle mass depletion have been found in IBD patients, despite a healthy Body mass index (BMI). It is proposed that more complete nutritional assessments of IBD patients needs to be incorporated into routine clinical practice.

The objectives of this study were to

1. Assess nutritional status of IBD inpatients
2. Compare two methods for body composition Tricep Skinfold thickness (TSF) and the Bioelectrical Impedence (BIA)
3. Audit inpatient experience of food and nutrition.

Methods: This pilot prospective study was conducted over 6 weeks (June-July 2016). Patients admitted to the gastroenterology ward for >24 hours with a confirmed diagnosis of IBD were approached. Anthropometric measurements including: weight, height, hand grip and pinch strength, TSF, Mid-upper arm circumference (MUAC), mid-upper arm muscle circumference (MAMC), clinical and demographic data was collected. Patients were also screened using the Malnutrition Universal Screening Tool. All measurements were taken at one time point at the patients' bed side. Additionally patients were asked to complete a diet and nutrition questionnaire.**Results:** 23 IBD patients (13 males, 10 females) participated in the study. All four nutritional parameters (TSF, MAC, MAMC and grip strength) were lower than published population norms. UC patients had higher BMI, Fat mass percentage (FM%) and Lean body mass percentage (LBM%) than CD patients (BMI: 24.33±6.92 vs 21.84±4.13, FM%: 25.11±8.59 vs 24.04±15.09, LBM%: 76.73±16.26 vs 74.89±8.59) respectively.

The FM%, FM and LBM measured by BIA and TSF agreed well (correlation p>0.05).

Most patients were satisfied with hospital food (70%) and food portion size (86%). Patients' dissatisfaction was due to unappetising food (54%) and unmatched provision as per individual requirement (37.5%).

Conclusions: Both BIA and TSF correlated well and to some extent were interchangeable. BMI in CD patients was lower than population norms, but no obvious impairment was observed in UC. Both FM% and LBM% of CD patients were lower than UC patients.

It is recommended that grip strength is incorporated into routine nutritional assessment of IBD patients in addition to BMI to help detect LBM deficit as it is a fast, convenient and non-invasive measurement. Further research requires larger patient numbers and further validation of body composition assessment measures requires comparison to the DXA method. Improvements in food and nutritional support of IBD inpatients are required.

P377**Evaluation of the pharmacokinetic profiles of SB5 and reference adalimumab**D. Shin¹, J.W. Kang², S. Park², S.Y. Cheong¹, E. Hong^{*1}¹Samsung Bioepis Co., Ltd, Medical Team, Incheon, South Korea; ²Samsung Bioepis Co., Ltd, Quality Evaluation Team, Incheon, South Korea**Background:** SB5 has been developed as a biosimilar of the reference adalimumab (ADL) which is a TNF- α inhibitor indicated for the treatment of arthritis, plaque psoriasis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, etc. Analytical studies showed that SB5 was highly similar to ADL in structural properties. Pharmacokinetic (PK) results comparing SB5 and ADL in cynomolgus monkeys, healthy subjects, and patients with rheumatoid arthritis (RA) are reported here.**Methods:** The pre-clinical PK profiles were evaluated in cynomolgus monkeys following subcutaneous administrations of 32 mg/kg of SB5 or US-ADL every week for 4 weeks. In healthy subjects, the PK equivalence between SB5 vs. EU-ADL, between SB5 vs. US-ADL, and between EU-ADL vs. US-ADL were assessed in a phase I, 40 mg single dose study. [1] Equivalence was to be concluded if the 90% confidence interval (CI) for the ratio of geometric least squares means (LSMeans) of the primary PK parameters (area under the concentration-time curve [AUC] from time zero to infinity [AUC_{inf}], maximum concentration [C_{max}], AUC from time zero to the last quantifiable concentration [AUC_{last}]) were within the standard margins of 0.8 to 1.25. The steady state PK were evaluated in a phase III study in patients with RA where patients received 40 mg of either SB5 or EU-ADL every other week for 24 weeks. [2] Serum concentration was measured through electrochemiluminescence for the pre-clinical study and enzyme-linked immunosorbent assay for the clinical studies.**Results:** C_{max}, time to reach C_{max} (T_{max}), and the area under the concentration-time curve from time zero to 168 hour (AUC₀₋₁₆₈) were similar in cynomolgus monkeys treated with SB5 or US-ADL. In healthy subjects, the 90% CIs for the primary PK parameters for all pairwise comparisons (SB5 vs. EU-ADL, SB5 vs. US-ADL, EU-ADL vs. US-ADL) were within the margin of 0.8 to 1.25, indicating PK equivalence. In patients with RA, the mean trough concentrations were similar at each time point between SB5 (ranging from 3.850 to 6.761 μ g/mL) and EU-ADL (ranging from 3.892 to 6.773 μ g/mL). Furthermore, in both phase I and phase III studies, the PK profiles were similar between SB5 and the reference products when analysed by the presence of anti-drug antibody, substantiating the similar PK profile.**Conclusions:** In addition to the pre-clinical study in cynomolgus monkeys, similar PK profiles were demonstrated between SB5 and ADL in healthy subjects and in patients with RA. Together with the analytical similarity, a similar PK profile could be expected between SB5 and ADL in indications that were not directly studied in the SB5 program.**References:**

- [1] D Shin et al. (2015), A Phase I Pharmacokinetic Study Comparing SB5, an Adalimumab Biosimilar, and Adalimumab Reference Product (Humira[®]) in Healthy Subjects, *Ann Rheum Dis*, 74(Suppl 2): 459
- [2] M Weinblatt et al. (2015), A Phase III, Randomized, Double-Blind Clinical Study Comparing SB5, an Adalimumab Biosimilar, with Adalimumab Reference Product (Humira[®]) in Patients with Moderate to Severe Rheumatoid Arthritis Despite Methotrexate Therapy (24-week Results), *Arthritis Rheumatol*, 67(Suppl 10).

P378 Renal AA amyloidosis associated with Crohn's disease

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Background: Renal AA amyloidosis is a rare but severe complication of Crohn's disease (CD), with high prognostic impact, even more important than the underlying disease itself.

Methods: We described the cases of 3 patients with renal AA amyloidosis associated with CD.

Results: Case 1: A 29-year-old patient had a paucisymptomatic stricturing ileal CD with ankylosing spondylitis, followed for 9 years and treated by salazopyrin. A severe hypoalbuminemia was discovered, with a limited ileal disease and without exsudative enteropathy, a nephrotic syndrome (NS) was diagnosed. Labial and rectal biopsies were performed but negative, the diagnosis of amyloidosis was confirmed on a percutaneous renal biopsy. The patient was put on colchicine and anticoagulants seeing the severe hypoalbuminemia. He is now stable on both digestive and renal plans.

Case 2: A 48-year-old patient has been followed for 12 years for an ileal penetrating CD, inaugurated by an appendicular plastron, operated, then put on azathioprine. During follow-up, we noticed ascites and renal feet oedema, a NS was diagnosed. A renal amyloidosis was confirmed on labial biopsy. Creatinine clearance was 14ml/min. The patient was put on Colchicine and anticoagulants seeing the major hypoalbuminemia. The evolution was marked by the occurrence of an intra-abdominal abscess in the right iliac fossa, treated by antibiotics and exclusive parenteral nutrition during 21 days. On the renal plan, there was a worsening of the renal function with a creatinine clearance of 11ml/min, despite the treatment by azathioprine. The patient underwent hemodialysis but was deceased after 15 days.

Case 3: A 41-year-old patient has been followed for 22 years for an ileal penetrating CD, inaugurated by an enterocutaneous fistula and a right psoas abscess, operated twice; then put on azathioprine, but the patient did not take the treatment. After 12 years, a NS was diagnosed, it was associated with renal failure. A renal AA amyloidosis was confirmed by a labial biopsy. On the digestive plan, the patient had a stricture of the ileo-colonic anastomosis, with an extensive inflammatory stenosis of the terminal ileon. According to nephrologists, the treatment of amyloidosis is based on treating the underlying disease. The patient has been put on Infliximab therapy seeing the multiplicity of post-operative recurrence risk factors. A further follow-up is needed to evaluate the renal response to anti-TNF therapy.

Conclusions: In CD, amyloidosis is a rare complication, predominant in men with ileal and penetrating disease. It usually manifests in a nephrotic syndrome with renal failure. Its treatment is based on colchicine and the underlying disease must be controlled, so the progression of both diseases could be prevented. New therapies are still in study and under evaluation.

P379 Is febusostat the solution for patients who develop side effects to low dose azathioprine and allopurinol co-therapy?

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Background: We and others have previously reported the utility of

low dose azathioprine and allopurinol co-therapy in patients who develop side effects to standard dose azathioprine. This practice allows patients the convenience of continuing an oral drug and leads to health care savings by avoiding biologic drugs. In our practice we have identified that a small number of patients are intolerant to allopurinol. In these patients we substitute allopurinol for the alternative xanthine oxidase inhibitor febusostat. We report our experience at one year.

Methods: We maintain a prospective database of all IBD patients treated with immunosuppressive therapy. We searched our database for all patients who were intolerant of allopurinol and were treated with febusostat. Data on disease type, age, duration of treatment, tolerability, week 4–6 azathioprine metabolite levels and steroid free remission were reviewed.

Results: 6 patients were identified 1 (16.7%) was female. Mean age; 48 years, (range 38–65). Disease type was Crohn's disease; 3 (50%), ulcerative colitis; 3 (50%).

In 5 patients side effects developed after starting allopurinol for treatment of IBD; side effects reported were; fatigue, nausea, diarrhoea, pruritus, arthralgia and paraesthesia. 1 patient started febusostat in primary care for treatment of gout prior to commencing thiopurine therapy. All 6 (100%) tolerated febusostat. 6-thioguanine levels (taken at week 4–6) were available in 5 (83%), mean TGN; 532 (range 196–1130). Mean 6-MMPN; 182 (range <100–224).

5 (83%) patients were in a steroid free remission at 1 year and continue on low dose thiopurine and febusostat. 1 patient stopped 1 month after commencing low dose mercaptopurine and febusostat due to developing lichen sclerosis.

Conclusions: In this small case series febusostat when combined with low dose azathioprine was efficacious and well tolerated in patients who were previously intolerant of allopurinol.

We recommend a trial of febusostat in patients intolerant of allopurinol. This strategy could reduce the need for biologic drugs and lead to cost savings in clinical practice.

P380 Assessment of the awareness and education of vaccination in our IBD cohort: an observational study

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Background: Inflammatory Bowel Disease (IBD) confers an increased risk of opportunistic infection. Chronic inflammation and the use of steroids, thiopurines and biologic medications contribute to immunosuppression state. ECCO guidelines recommend checking the vaccination status before starting immunosuppressive agents and actively vaccinate them. However many studies have shown poor uptake of recommended vaccinations despite the guidelines and education provided to them by GI health care providers.

In our department we have a dedicated IBD nurse specialist and we provide individual and quarterly group education sessions about different aspects of IBD for our patients. We provide written recommendations to the general practitioner and expect vaccines to be administered in the community.

The aim of this study was to assess patient awareness regarding importance of vaccination and their vaccination status

Methods: This is single centre observational study performed at a tertiary care centre in Dublin Ireland. A written questionnaire based on ECCO guidelines was developed with simple Yes/No answers.

This was given to IBD patients at the outpatient clinics, Infusion suite and in the community. The data was analysed using microsoft excel

Results: A total of eighty nine patients completed the survey, 45 (51%) were male. Fifty two percent (47) had Crohn's. Average duration of the disease was 11 years (range 6ms to 46 years). At least 64% of them were exposed to steroids and similar numbers were on thiopurines. Sixty six percent had been or were being treated with an anti-tnf. One patient was on a combination of anti-tnf and of methotrexate.

Only 20% of patients responded that they knew about the vaccination recommendations and 18% responded that they were educated about the vaccination at some point in their disease course.

Fifteen percent have their up-to-date Pneumococcal vaccination while influenza vaccination was approximately 48%. Twenty one percent have been vaccinated against their hepatitis B. Regular cervical smear check was significantly better as compared to the vaccination which was around 64% of females

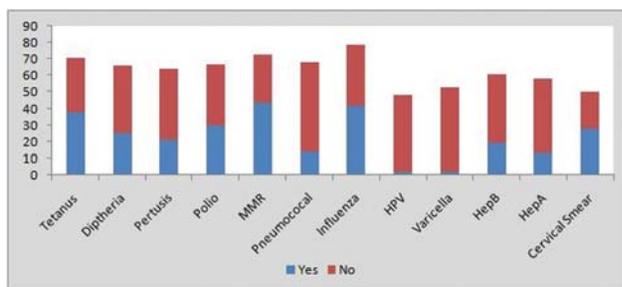


Figure 1. Vaccination status of the study group.

Conclusions: Despite having regular education sessions about the awareness and the importance of vaccination, the uptake of vaccination is very poor.

Our findings would suggest that despite education sessions and recommendations to GPs that uptake remains poor, therefore GI providers should take a more pro-active approach and offer vaccination as part of the ambulatory care management of our IBD patients

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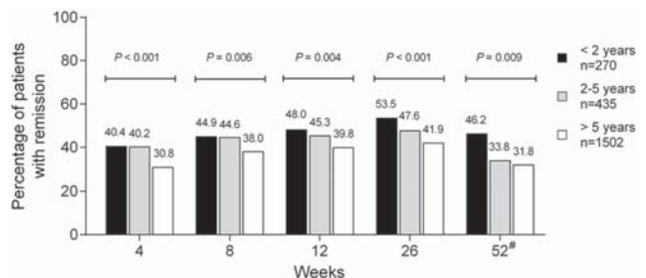
Adalimumab efficacy and safety by disease duration: analysis of pooled studies of Crohn's disease

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Background: Adalimumab (ADA) has been shown in one *post hoc* analysis to be effective in pts with moderately to severely active Crohn's disease (CD) with <2 yrs disease duration [1]. In this analysis, we pooled data from 9 CD clinical studies of ADA to assess the impact of disease duration on clinical outcomes in ADA-treated pts. **Methods:** Pts receiving double blind (DB) or open label (OL) ADA induction (80/40mg or 160/80mg ADA at week [wk] 0/2) followed by DB ADA 40mg every other wk (EOW)/every wk (EW) or OL ADA 40mg EOW/EW were included in the analysis. Pts random-

ized to PBO were excluded. Pts were analysed by <2, 2–5, >5 years disease duration at BL. Remission (CDAI <150 or HBI<5) rates were analysed within disease duration groups from 4–52 wks using Cochran-Armitage test. A modified non-responder imputation was used whereby pts who moved to OL EOW or EW ADA for flare/non-response were reported according to their observed response. AE rates were reported by BL disease duration.

Results: Of 2207 pts included in this analysis, approximately 60% were female. BL disease duration groups included 270 (<2 yrs), 435 (2–5 yrs), and 1502 (>5 yrs) pts. Mean CDAI and HBI ranged from 292.3–304.3 and 10.7–11, respectively, across disease duration groups. Significant differences in BL fistula presence, BL corticosteroid (CS) use and prior α -TNF use were observed between disease duration groups (fistula: 27 [10.0%], 73 [16.8%], 278 [18.5%], [p=0.003]; CS: 84 [31.1%], 86 [19.8%], 332 [22.1%], [p=0.001]; α -TNF use: 33 [12.2%], 108 [24.8%], 389 [25.9%], [p<0.001] for <2, 2–5, >5 yrs disease duration groups, respectively). Significant differences between disease duration groups in remission rates occurred as early as wk 4 and sustained for up to wk 52 (Figure 1). Overall rate of AEs, SAEs, AEs leading to discontinuation and malignancies were similar between disease duration groups. Serious infection rate was lower in the <2 yrs disease duration group vs 2–5 yrs and >5 yrs groups (4.2 vs 8.7 and 8.3/100PY). In the >5 yrs BL disease duration group, 2 deaths occurred that have been previously reported [2].



P values are from Cochran-Armitage exact test across disease duration groups
[#]Week 52 data from CDAI studies only, as studies using HBI were only 20-26 weeks in duration; number of patients in <2, 2-5, and >5 groups were 104, 160, and 638, respectively

Figure 1. Proportion of patients with remission (CDAI <150 or HBI <5) by BL disease duration.

Conclusions: In 9 CD clinical studies, ADA-treated pts with shorter disease duration achieved a better clinical benefit than pts with longer disease duration. Overall safety of ADA was consistent between disease duration groups.

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P382

A panel of serum markers for early detection of endoscopic healing with infliximab in patients with ulcerative colitis

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Background: The need for surrogate markers to detect endoscopic healing in inflammatory bowel disease (IBD) is imminent. Previously, neutrophil gelatinase B-associated lipocalin and matrix metalloproteinase-9 (NGAL-MMP-9) complex was found to be superior to CRP for detection of endoscopic healing with infliximab (IFX) in patients with ulcerative colitis (UC)[1]. Both cathelicidin LL-37 and chitinase 3-like 1 (CHI3L1) are secreted by neutrophils and were previously associated with IBD [2,3]. The aim of this study was to investigate whether LL-37 and/or CHI3L1 could improve detection of endoscopic healing with IFX in UC patients.

Methods: Serum samples were obtained from 145 UC patients (41% female, median [IQR] age 41.3 [30.8–51.9] years) who underwent endoscopy following IFX initiation and from 75 controls (56% female, median [IQR] age 33.6 [29.2–51.8] years). Endoscopic healing with IFX was defined as a Mayo endoscopic subscore of 0 or 1. CRP, NGAL-MMP-9 and neutrophils were previously determined [1], and LL-37 and CHI3L1 were measured with ELISA (Hycult Biotech and R&D systems, respectively). For all markers, optimal cut-offs were determined with ROC analysis and binary variables were entered in a logistic regression model to generate the Ulcerative Colitis Response Index (UCRI). Non-parametric tests were performed and p-values <0.05 were considered significant.

Results: Median (IQR) time to serum sampling after IFX was 8.2 (6.0–14.0) weeks. 83 patients (57%) had endoscopic healing, whereas 62 patients (43%) did not. Median [IQR] LL-37 levels (ng/ml) were significantly lower in healers (24.3 [16.1–41.4]) compared to non-healers (37.3 [24.0–53.8], p=0.002), but remained elevated compared to controls (16.7 [10.2–27.1]; p<0.001). Median [IQR] CHI3L1 levels (ng/ml) were significantly lower in healers (20.9 [14.3–34.4]) compared to both non-healers (30.0 [22.7–53.9], p<0.001) and controls (31.9 [19.6–48.6], p=0.003). UCRI consisted of CRP (Odds ratio [95% CI] 3.3 [1.4–7.5]), CHI3L1 (3.1 [1.3–7.7]), neutrophils (4.9 [2.1–11.2]) and LL-37 (2.5 [1.0–6.4]). The AUC of UCRI was 0.83 and Q1 (0.0–2.6) was able to discriminate healing with 54% sensitivity, 92% specificity, 60% NPV and 90% PPV, whereas Q4 (7.2–9.8) was able to discriminate non-healing with 37% sensitivity, 95% specificity, 67% NPV and 85% PPV. Finally, UCRI could detect endoscopic healing as early as 3 weeks after IFX initiation (Hazard ratio [95% CI] 4.1 [2.6–6.5]).

Conclusions: In the search for surrogate markers of endoscopic healing, UCRI was shown to accurately identify UC patients who fail to achieve healing with IFX and may help in early decision making to therapy switch.

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P383

Increasing treatment time on REMICADE® (infliximab) predicts subsequent long-term retention in stable infliximab inflammatory bowel disease patients in Canada

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Background: A high percentage of patients treated with anti-TNF agents discontinue therapy. The objective of this analysis was to determine the long-term retention patterns of stable Canadian IBD patients treated with REMICADE® (infliximab [IFX]).

Methods: Using IMS Brogan's™ database of Canadian private and public insurance claims data, our analysis included IBD patients with: (1) first IFX claim between Jan 2008-May 2015; (2) no IFX claims 12 months prior to the initial claim; (3) ≥1 claim for any drug 12 months after the initial IFX claim; and (4) ≥1 claim for any non-IFX drug 4 months after May 2015. Retention was measured at 12-month intervals and unadjusted odds ratios were determined. Within-group analyses compared 12 month retention by number of years on IFX and considered cohorts of patients according to age group, gender and previous biologic experience.

Results: 4,360 patients had ≥2 years of claims history and had been on IFX for ≥1 year. Within-group comparisons showed that the probability of being retained on IFX in subsequent 12 month periods increased with cumulative prior time on IFX. Patients on IFX for 2 to 5 years showed significantly higher retention in the subsequent 12 months compared to patients on IFX for only 1 year (p<0.05). Similar trends were observed across both genders, in patients 19–64 years of age, and for patients who were biologic-naïve.

Conclusions: Real world patients treated with IFX have excellent

Abstract P383 – Table 1. Patients retained 12 months later (%)

# Years on IFX	IBD patients N=4,360	Male N=2,055	Female N=2,288	Bio-naïve N=4,147	Bio-exposed N=221	0–18 years N=419	19–64 years N=3,561	65+ years N=361
1	80.3	82.1	78.5	80.5	76.9	81.4	79.8	83.9
2	84.4	84.7	84.0	84.2	86.3	87.7	83.9	86.8
3	86.9	87.5	86.4	87.0	89.8	87.8	86.3	92.1
4	88.0	89.9	86.0	88.2	70.0	87.0	87.9	90.3
5	90.9	90.9	91.0	90.7	100	76.9	92.5	88.0

Abstract P383 – Table 2. Odds ratio of being retained (p<0.05 unless noted otherwise)

Year vs year	IBD patients N=4,360	Male N=2,055	Female N=2,288	Bio-naïve N=4,147	Bio-exposed N=221	0–18 years N=419	19–64 years N=3,561	65+ years N=361
2 vs 1	1.3	1.2 (p=0.06)	1.4	1.3	1.9	1.6	1.2	1.3 (p=0.36)
3 vs 1	1.6	1.5	1.7	1.6	2.7	1.6 (p=0.08)	1.4	2.2
4 vs 1	1.8	1.9	1.7	1.8	0.7 (p=0.40)	1.5 (p=0.26)	1.7	1.8 (p=0.12)
5 vs 1	2.5	2.2	2.8	2.4	N/A	0.8 (p=0.57)	2.8	1.4 (p=0.46)

long-term retention. Previous duration of IFX treatment appears to predict better future retention, becoming statistically significant after 2 years. The results were robust and consistent amongst various subgroups of stable Canadian IBD patients.

P384

Long-term outcome and endoscopic healing rates following long modified side-to-side stricturoplasties

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Background: A long modified side-to-side isoperistaltic stricturoplasty (SSIS) is an option in patients undergoing surgery for extensive stricturing Crohn's disease (CD) to avoid extensive small-bowel resections. The aim of this study was to assess the endoscopic healing rates six months following SSIS, and to analyse the long-term outcome of these patients including need for re-intervention and/or re-introducing medical therapy.

Methods: The electronic medical records of all 40 patients (16 men and 24 women; median age 39 years; range 16–73 years) who underwent a long modified SSIS between 2010 and 2015 at our tertiary referral centre, were reviewed. In all patients, SSIS was performed because of extensive stenotic CD (>20 cm) of the (neo-) terminal ileum. Each patient received the same standardized follow up (FU) with clinical and endoscopic evaluation after median time of 6 months (interquartile range, IQR, 6–8 months). We also analysed disease recurrence during follow up necessitating medical or surgical re-intervention.

Results: Median FU period was 33 months (IQR, 15–47 months). Only 10 patients (25%) continued medical treatment immediately after surgery because of remaining disease activity in the colon or systemic disease activity with a high risk of clinical relapse. At month 6, 24/40 patients (60%) showed important mucosal improvement of the stricturoplasty side, with increasing healing observed from distal to more proximal. At the end of FU, the cumulative clinical relapse rate was 62.5% (25 patients), median time to relapse was 13 months (IQR 6.7–16.5 months). Two patients necessitated endoscopic balloon dilatation of the most proximal anastomosis side of the SSIS for symptoms related to subobstruction. Only 2 patients (5%) so far needed surgical re-intervention; one patient developed recurrent stenosis at the inlet of the SSIS, another patient needed revision due to adhesions. No resection of any stricturoplasty was required. Of the 25 patients with clinical relapse, 18 patients (72%) were started on anti-TNF antibodies or vedolizumab, 4 patients received budesonide and 2 patients azathioprine. At the last FU, 27/40 patients (67.5%) patients had durable response including 10 patients in clinical remission (no treatment). 13 patients failed medical therapy and changed treatment and/or 2 received surgery.

Conclusions: The long modified SSIS is a safe procedure with good long-term outcome. Postoperative ileocolonoscopy after six months showed a remarkable tendency for mucosal healing. The exact mechanism needs further investigation. With a median follow up of 2.5 years, surgical reintervention rates were very low and two thirds of patients showed durable response or were in remission on (very often) previously-failed treatments.

P385

Assessment of long-term outcomes of patients with ulcerative colitis and mucosal healing under different therapies: Is all mucosal healing the same?

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Background: Mucosal healing (MH) has been associated with improved outcomes in patients with Ulcerative Colitis (UC) including lower requirement of steroids, hospitalization, and surgery. Most studies have been limited by the analysis of small cohorts of patients over a short follow-up time. Furthermore, the difference in obtaining MH with different therapies has seldom been assessed. The aim of this study was to compare the long-term outcomes of patients with UC and MH in relation to the degree of endoscopic remission (endoscopic Mayo score of 0 or 1) and according to therapeutic regimen used (aminosalicylates, thiopurines or anti-TNFs).

Methods: Observational study including patients with UC and MH. Patients were followed from the baseline endoscopy showing MH until recurrence. Recurrence was defined as the need for hospitalization, surgery, change in therapy and endoscopic recurrence (defined as endoscopic Mayo subscore >1). Patients with a follow-up under 12 months were excluded from analysis.

Results: From a cohort of 453 patients with UC, 212 were studied from the time of MH. The mean time from diagnosis to MH was 72.2±101.6 months and the mean follow-up time was 91.1±59.4 months. MH was achieved with in 161 patients under 5-ASA (75.9%), in 41 patients under thiopurines (19.3%), and in 10 patients under anti-TNF (4.7%). The time until recurrence was significantly longer in patients with Mayo 0 (80.0±60.5 months versus 61.0±49.6 months, p=0.019). While there was no significant difference in 12-month recurrence (log-rank p=0.236), 5-year (log-rank p=0.005), and 10-year (log-rank p=0.045) recurrence rates were significantly higher in patients with Mayo 1. The percentage of patients achieving Mayo 0 was not influenced by the drug used (p=0.7), nor were recurrence rates (log-rank p=0.144) or time until recurrence (p=0.120). Patients not reaching MH were more likely to need surgery (12.4% versus 1.4%, p<0.001). Disease extension (OR 11.5 95% CI 4.1–32.2, p<0.001), male gender (OR 2.3 95% CI 1.04–5.25, p=0.039) and not obtaining MH (OR 13.4 95% CI 3.6–42.7, p<0.001) were significant associated with the need for surgery.

Conclusions: MH was an achievable target associated with long-standing remission irrespective of the drug used.

P386

A target 6-thioguanine nucleotide ≥ 125 is associated with a higher rate and longer durability of response in infliximab–thiopurine combination therapy: a retrospective study in Crohn's disease patients

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Background: Recent data suggest that lower doses of thiopurines are as effective as higher doses in combination with infliximab (IFX) in

Crohn's disease (CD), and that 6-thioguanine nucleotide (TGN) levels ≥ 125 pmol/ 8×10^8 RBC positively influence IFX pharmacokinetics. We aim to assess clinical outcomes after induction and during maintenance in CD patients treated with IFX and a thiopurine with respect to TGN and IFX levels.

Methods: CD patients commenced on IFX between 2010–15 with or without concomitant thiopurines were retrospectively identified. "Response" to induction (CRP < 5 mg/L and absence of activity on physician global assessment) or "non response" (lack of clinical improvement during induction or flare requiring CD therapy adjustment or surgery during first 6 months) were assessed at week 14. Maintenance outcomes were assessed in 6-month semesters and classed as "response", "flare" or "failure" (IFX cessation due to active disease or intolerance). TGN and IFX trough levels were recorded during induction and maintenance.

Results: Of 89 patients (49 male, mean age 35y, range 18–61), combination therapy (n=73) had a higher response than IFX monotherapy (n=16) on induction (78% vs 50%, $p=0.02$). Median TGN was similar between responders and non-responders (314 vs 254, $p=0.12$), with TGN ≥ 125 patients more likely to respond (76% vs 47%, $p=0.018$). On multivariable analysis, TGN ≥ 125 was associated with response (OR 5.7; 95% CI: 1.6–20.1; $p=0.006$). Mean time to IFX failure was 26 months for monotherapy vs 53 months for combination therapy ($p=0.55$); a significant difference was observed when re-stratified by TGN ≥ 125 , $p=0.043$ (Fig. 1).

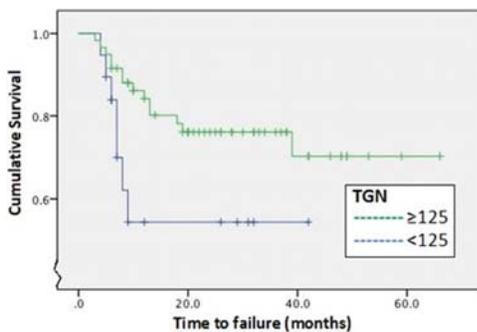


Figure 1. Kaplan-Meier survival analysis of time to failure, TGN ≥ 125 vs < 125 .

Of 395 maintenance semesters, 323 (82%) were classified remission, 61 (15%) flare, and 11 (3%) fail. There was no difference in number of remission semesters between combination and monotherapy (79% vs 79%). Median TGN was similar in remission and non-remission semesters ($p=0.44$), with no difference observed when stratified by TGN ≥ 125 . Median IFX levels were higher in remission vs non-remission semesters (4.5 vs 3 μ g/mL; $p=0.01$), and higher IFX levels were independent predictors of response to maintenance therapy on multivariable analysis (OR 1.3 [1.05–1.5], $p=0.014$).

Conclusions: Combination therapy was superior to monotherapy for induction, with a target TGN ≥ 125 associated with a higher response rate and longer durability of response. Continuing combination therapy during maintenance was not associated with better clinical outcomes, suggesting a role for thiopurine withdrawal.

P387

The addition of an immunosuppressant is an effective optimization strategy after loss of response to anti-TNF-alpha monotherapy in patients with inflammatory bowel disease: a two-year experience

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Background: In patients with inflammatory bowel disease (IBD) the addition of an immunosuppressant (IM) after loss of response to anti-TNF alpha monotherapy is regarded as an emerging strategy of therapeutic optimization. However, few clinical data have been reported to date. The aim of this study was to evaluate efficacy and tolerability of this selective combination therapy in patients with IBD.

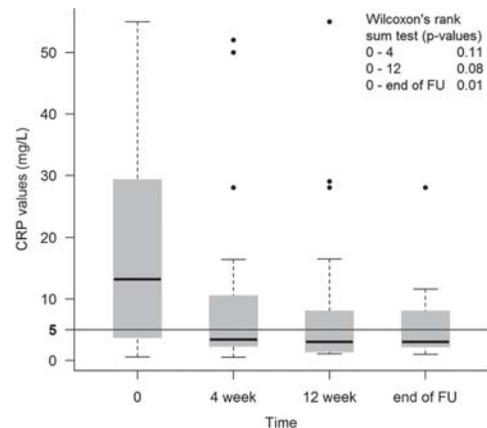


Figure 1. C-reactive protein values among patients with response to combination therapy (normal values < 5 mg/L).

Methods: All consecutive patients with loss of response to anti-TNF alpha monotherapy despite an intensive dose optimization who added an IM from October 2014 to October 2016 were entered in a prospectively maintained database. The steroid-free remission and the clinical response, this latter defined as a clinical improvement (reduction of Harvey-Bradshaw Index ≥ 3 for Crohn's disease and of Mayo Partial Score ≥ 2 for ulcerative colitis compared with baseline) with a concomitant reduction of steroid dosage compared with baseline and discontinuation within twelve weeks, were set as clinical end points.

Results: Among 630 patients treated with biologics during the study period, 46 (33 Crohn's disease and 13 ulcerative colitis) were included. A total of 31 patients (67.4%) were treated with an intravenous anti-TNF α (infliximab, as originator product or biosimilar), while 15 (32.6%) with a subcutaneous anti-TNF α agent (10 adalimumab and 5 golimumab). The mean doses of thiopurines used in combination therapy were below those regarded as therapeutic in IBD, methotrexate was mostly employed at a dose of 15 mg/week, and all patients treated with mycophenolate mofetil were able to tolerate the target dose of 1500 mg/day. The mean duration of total follow-up was 12.8 ± 7.3 months. Twenty-one patients (45.7%) remained on combination therapy at the end of follow-up: 15 (32.6%) maintained a steroid-free remission, and 6 patients (13.0%) achieved a clinical response. In patients who experienced a treatment success, mean value of C-reactive protein sharply decreased from the baseline (16.6 ± 25.6 mg/L, normal values < 5 mg/L) to the following months and at the end of follow-up (5.6 ± 6.1 mg/L, $p=0.01$ compared with baseline; figure 1). Adverse events leading to treatment discontinuation were reported in 7 out of 46 (15.2%) patients.

Conclusions: In patients with IBD the addition of an immunosuppressant is an effective and safe optimization strategy after loss of response to anti-TNF alpha monotherapy. Low doses of IM are sufficient to achieve a clinical response in this setting.

P388 Risk of relapse in ulcerative colitis patients in clinical remission with combination therapy (anti-TNF and azathioprine) after immunomodulator discontinuation

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Background: In patients with inflammatory bowel disease in remission the de-escalating treatment strategy is controversial. Because of safety and economic issues, stopping one therapy in ulcerative colitis (UC) patients in remission might be an option, but there are no recommendation regarding this question. The aim of our study was to assess the risk factors for relapse in UC patients in remission for at least 6 months with combination therapy (anti-TNF and azathioprine – AZA) after AZA discontinuation.

Methods: Between January 2013 and June 2015 we prospective enrolled in a single tertiary center the UC patients who were in clinical remission for at least 6 months with combo therapy (anti-TNF and AZA) and stopped AZA. All patients were evaluated 1 year after AZA withdrawal. Demographics, clinical, endoscopic and therapeutic data were collected.

Results: The study included 56 patients with UC, 32 female and 22 male, with a mean age of 44.6 years (range 18–73 years). All patients were treated with AZA and infliximab (38 patients) or adalimumab (18 patients). 1 year after AZA withdrawal the relapse appeared in 13 patients (23.21%). On multivariate analysis, predictors of relapse were: fecal calprotectin (>50 $\mu\text{g/g}$, $p=0.039$), endoscopic Mayo score (>1 vs 0 or 1, $p=0.042$), and the duration of remission <1 year ($p=0.04$). There were no statistical differences between the patients who relapsed and those who maintained remission regarding sex, age, smoking habit, extension of the disease, type of anti-TNF. **Conclusions:** The azathioprine can be safely withdrawn in patients with combo therapy who are in clinical remission for more than 1 year, have fecal calprotectin <50 $\mu\text{g/g}$ and endoscopic Mayo score 0 or 1.

P389 Low-dose metronidazole is associated with a decreased rate of endoscopic recurrence of Crohn's disease after ileal resection

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Background: Recurrence of Crohn's disease (CD) after surgical resection and primary anastomosis is an important clinical challenge. Previous studies have demonstrated the benefit of imidazole antibiotics, but have been limited by adverse events and medication intolerance. We evaluated whether administration of low-dose (LD) metronidazole (250 mg three times a day) for three months reduces endoscopic postoperative recurrence rates.

Methods: We performed a retrospective cohort study of patients with Crohn's disease who underwent ileal resection with a primary anastomosis and subsequently received care at our center. We compared the cases who received LD metronidazole (primarily from one clini-

cian, DTR) to control patients (DTR and others) who did not receive this therapy. Data collected included demographics, risk factors for recurrence, and medications before and after surgery. The primary endpoint was the number of patients with ≥ 2 (Rutgeerts) endoscopic recurrence by 12 months. Variables found to be predictive in univariate analysis at $p<0.10$ were introduced in the Cox model for multivariate analysis.

Results: 70 Crohn's patients (35 cases) met inclusion criteria. Risk factors for Crohn's recurrence were similar between groups (Table 1).

Table 1. Patient characteristics

	All	Control	Low Dose Metronidazole	P-Value
Total number of patients	70	35	35	
Age at surgery (mean \pm SD)	37.79 \pm 13.95	36.22 \pm 14.20	39.36 \pm 13.71	0.343
Race				0.038
Caucasian	60	30	30	
Hispanic	2	0	2	
Black	3	1	2	
Asian	1	0	1	
Unknown, not Hispanic	4	4	0	
Sex				0.227
Male	41	23	18	
Female	29	12	17	
Time to surgery (years)	10	9	10	0.204
Smoking status at surgery				1
Never	54	27	27	
Former	12	6	6	
Current	4	2	2	
Number of previous resections				0.903
0	44	26	18	
1	13	4	9	
2	8	4	4	
≥ 3	5	1	4	
Phenotype				0.558
Penetrating	32	17	15	
Non-penetrating	33	18	20	
Days on metronidazole (median)	-	-	90	

Median time to endoscopic follow-up for both groups was similar (cases: 184 days, IQR 178–246; controls: 192 days, IQR 166–250). The number of patients with ≥ 2 endoscopic recurrence following ileal resection was significantly lower in the LD metronidazole group (7 of 35 patients; 20%) compared to the control group (19 of 35 patients; 54.3%) ($p=0.0058$) (Figure 1).

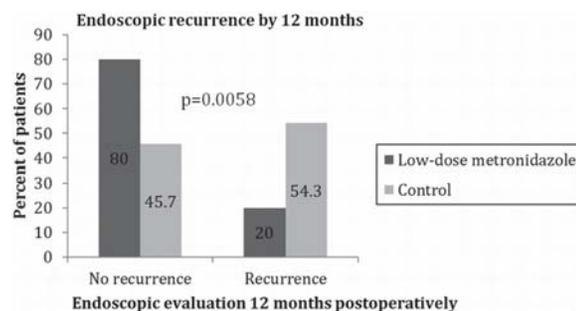


Figure 1. Percent of patients without endoscopic recurrence (Rutgeerts score <2) and with endoscopic recurrence (Rutgeerts score ≥ 2) after ileal resection with primary anastomosis (95% CI: 0.065–0.610; $p=0.0058$).

Eight participants (22.86%) in the LD metronidazole group experienced adverse events, and 3 of these patients (8.57%) discontinued the therapy.

Conclusions: Low-dose metronidazole for 3 months postoperatively significantly reduces endoscopic recurrence of CD and is safe and well-tolerated. This intervention should be considered as a bridge to other therapies after ileocectomy.

P390
Open-label study to evaluate the pharmacokinetics of fidaxomicin in inflammatory bowel disease patients with *Clostridium difficile* infection (the PROFILE study): pharmacokinetics analysis

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Background: *Clostridium difficile* infection (CDI) causes a substantial healthcare burden in hospitalised and community-based inflammatory bowel disease (IBD) patients. Fidaxomicin (FDX), a non-absorbable antibiotic, is approved for CDI treatment in adults, but FDX data in IBD patients are lacking. Whether FDX absorption differs in these patients owing to IBD-associated intestinal inflammation is unknown.

Methods: The PROFILE study aimed to investigate plasma pharmacokinetics (PK) of FDX and primary metabolite OP-1118 in patients with IBD and CDI in the EU. This open-label, multicentre, single-arm study enrolled patients ≥ 18 years diagnosed with active IBD and a positive local standard CDI test ≤ 48 h prior to enrolment (with subsequent central laboratory testing). Patients received 10 days' FDX treatment (200 mg, twice daily). Blood samples to assess PK were taken on days 1, 5 and 10 (pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5 and 12 h post-dose).

Results: PK data were obtained from 24 patients (54% male; mean [standard deviation, SD] age 38.9 [16.9] years); 14 with Crohn's disease (CD) and 10 with ulcerative colitis (UC). Median (range) baseline Harvey Bradshaw Index score was 8 (5–20) and partial Mayo score was 5 (3–8). E3 UC (pancolitis) was present in 8 patients. Baseline CDI severity (ESCMID criteria) was severe for 5 patients and non-severe for 19 patients. PK findings are shown in Table 1. No difference was observed in FDX or OP-1118 levels between CD and UC patients and there was no apparent correlation between FDX exposure and the extent of intestinal inflammation. Tmax values were similar to those in healthy volunteers for both FDX and OP-1118 (range 0.5–11.5 h). Cmax values for FDX (1.2–154 ng/mL) and OP-1118 (4.7–555 ng/mL) were within the measured range of concentration values found in CDI patients without IBD 3–5 h post-dose on days 1 and 10 of FDX Phase III studies (FDX, 0.4–197 ng/mL; OP-1118, 0.3–871 ng/mL; n=97–309) [1]. The Cmax values were well below the human equivalent no-observed-adverse-effect levels in 3-month dog toxicology studies (3000 ng/mL). Treatment-emergent adverse events were reported in 15 (60.0%) patients. These were pos-

sibly or probably drug related in 10 (40.0%) and serious in 2 (8.0%) patients (hypoxia and skin ulcer). There were no deaths.

Conclusions: FDX plasma PK parameters fell within historical PK ranges observed in patients without IBD, suggesting no increase in FDX absorption in this patient population with IBD.

References:

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P391
Differential use of vedolizumab in ulcerative colitis and Crohn's disease. Real life results from 2 tertiary referral centres in the United Kingdom

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Background: Vedolizumab (VDZ) is an anti- $\alpha 4\beta 7$ integrin antibody efficient for the treatment of ulcerative colitis (UC) [1] and Crohn's disease (CD) [2]. As patient population in clinical trials may not be reflective of real life practice, we describe our experience with VDZ in two tertiary UK centres.

Methods: We identified all patients receiving VDZ from infusion clinic and reviewed their electronic and written case notes. Disease activity was recorded using clinical (Simple Clinical Colitis Activity Index for UC and Harvey Bradshaw Index for CD) and biochemical indices (Calprotectin). Continuous variables are expressed as mean (SD) and compared with paired student's t-test.

Results: 22 UC and 15 CD patients were included. All received VDZ at weeks 0, 2, 6 (induction) and then 8 weekly. Their age was 39.8 (14.1) and 36.6 (13.3) years respectively.

In the UC group, 14 (64%) had extensive disease. All were previously exposed to thiopurines (TPs), 12 (55%) to anti-TNFs, 8 (36%) were on corticosteroids (CS) at baseline. The SCCAI was 5.8 (2.7) at baseline, 4.9 (4.1) on the 3rd and 3.6 (3.6) on the 4th infusion (p=0.07). 13 (59%) patients had an SCCAI ≤ 4 post induction. Faecal calprotectin was 918 ug/g (690) at baseline and 428 (494) after induction (p<0.01). 8 (53%) patients (n=15) had a calprotectin of <200 after induction and 6 (75%) were CS-free. The length of follow up was 8.2 (3.5) months. The SCCAI on the day of last infusion was 2.3 (2.4) (p<0.01). 12 (55%) patients had an SCCAI of ≤ 2 on their last follow up and 1 had surgery.

In the CD cohort, 4 (27%) were diagnosed at the age ≤ 16 years. The location was ileocolonic in 11 (73%), upper gut in 5 (33%) and perianal disease was present in 7 (47%) patients. Disease behaviour was stricturing in 2 (13%) and penetrating in 6 (40%) patients. Previous or current exposure to TPs was reported in 14/15 (93%). All had been exposed to anti-TNFs. 9 (60%) had undergone intestinal surgery. 5 (33%) were on CS on treatment initiation. HBI at baseline was 8.6 (5.6), 5.5 (4.6) at 3rd infusion (p=0.07) and 5.1 (3.9) at 4th infusion (p=0.24). 6 (40%) patients had HBI of ≤ 4 at the 3rd

Abstract P390 – Table 1. FDX PK parameters

Day	AUC* (ng/h/mL)	C _{max} (ng/mL)	C _{trough} (ng/mL)	T _{max} (h)
1	77.7 (79.8); 22.7, 339; n=14	14.6 (16.1); 2.5, 75.3; n=23	–	2.8 (3.0); 0.5, 11.5**; n=23
5	155.6 (150.9); 38.0, 513; n=11	20.3 (31.8); 1.2, 154; n=23	6.2 (6.5); 0.7, 28.8; n=23	1.3 (0.7); 0.5, 3.0; n=13
10	129.1 (115.0); 19.2, 364; n=11	16.3 (15.1); 4.6, 71.3; n=24	4.4 (3.2); 1.0, 11.6; n=22	2.2 (1.7); 0, 5.4; n=14

Values are mean (SD); min, max. PK parameters were not measured in all patients at each time point; *AUC12 day 1; AUCtau day 5–10; **Outlier (patient had 1.0 h and 1.5 h as Tmax on Day 5 and Day 10, respectively). 8.9 h was second largest Tmax.

infusion. Baseline calprotectin was 1035 (950) and 534 (361) after induction ($p=0.6$). The length of follow up was 4.7 (2.6) months. At last follow up the HBI was 5.2 (5.7) ($p=0.19$).

Conclusions: VDZ demonstrated clinical efficacy in UC. VDZ was more likely to be used after anti-TNF failure in CD than UC. The majority of CD patients had complicated disease. Clinical responses to VDZ were similar to those described in the GEMINI trials and mirrored by reduction in faecal calprotectin. Further real life studies on CD are required to optimize its use through patient selection.

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P392

Comparison of dietary nutrient and food additive intake between patients with moderately active ulcerative colitis, healthy stool donors and the general Australian population

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Background: The increased prevalence of UC has been paralleled by significant changes in diet over recent decades. These changes, coupled with the intimate interaction food has with both the gastrointestinal microbiome and mucosa, has lead to the hypothesis that dietary components play a role in ulcerative colitis (UC) pathogenesis. The aim of this study was to characterise the nutrient and food additive intake of patients with active UC and determine whether these differ between patients and healthy stool donors or the general Australian population.

Methods: Participants with mild to moderately active UC (Mayo score 3–10, endoscopic subscore ≥ 2) were recruited for a randomised control trial of faecal microbiota transplant for active UC. Faecal donors were healthy volunteers with no active medical problems as assessed by medical history, blood and stool screening. Patients with UC and faecal donors each completed a 3-day diet diary, which was analysed using FoodWorks 7 software (Xyris, Australia) to yield macro and micronutrient intake as well as dietary emulsifier and sulphate content for both groups. These were compared to sex-matched Australian population data on nutrient intake sourced from the Australian bureau of statistics (2014).

Results: 82 diet diaries for 65 patients and 17 donors were analysed. Patients were significantly older than donors (mean age 39.8 vs 30.6 years $p=0.01$); however the groups were well matched for gender distribution (UC: 58% male; donor: 47% male, $p=0.42$). The mean daily protein intake was significantly higher in those with UC compared to donors (103.2g, 93–113g vs. 81.0g, 68–93g; $p=0.04$) as was the mean energy intake (8915kj, 8226–9604kj vs. 7453kj, 6377–8529kj; $p=0.04$) and iron intake (UC 10.9g, 9.5–12.2g vs Donors 7.5g, 5.9–9.0g; $p=0.01$). Compared to donors, patients had a numer-

ically higher mean intake of saturated fats (30.5g, 26–34g vs 23.6g, 20–27g, $p=0.09$) sugar (96.3g, 82–110g vs 76.6, 67–88g $p=0.17$) and sulphates (1923g, 1267–2578g vs 825g, 551–1099g, $p=0.10$) however these were not statistically significant. There were no significant differences between the groups for mean intake of: fibre ($p=0.42$), starch ($p=0.39$), total carbohydrate ($p=0.16$) or emulsifier ($p=0.50$). The mean intake of tested macronutrients for the general Australian population fell between the 95% confidence intervals (CI) for both male and female UC patients. The mean intake of sugar for the Australian population was greater than the 95% CI of sugar intake for donors.

Conclusions: Patients with active UC had significantly higher intake of protein and energy intake than healthy faecal donors. However, they had similar intake of these foods to the general Australian population. Donors consumed less sugar than the general Australian population.

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Evaluation of pharmacokinetic profiles of SB2 as a biosimilar of reference infliximab

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Background: Based on the totality of evidence with similar analytical, pharmacokinetic (PK) and clinical results, SB2 was approved by European Medicines Agency as a biosimilar of the reference infliximab (INF) for all indications for which INF has been approved. Here we report the PK profiles of SB2 compared to that of INF in two animal models, healthy subjects and patients with rheumatoid arthritis (RA).

Methods: The pre-clinical PK profiles were evaluated in single and repeated dose studies (1, 3, and 10 mg/kg of SB2, European Union sourced INF [EU-INF] or United States sourced INF [US-INF]) in two animal models (Sprague Dawley [SD] rat and transgenic Tg197 mouse). The clinical Phase I pivotal study for PK was conducted in healthy subjects [1]. The subjects received a single 5 mg/kg intravenous infusion of study drugs (SB2, EU-INF or US-INF) and were observed for 10 weeks. PK equivalence was to be concluded if the 90% confidence interval (CI) for the ratio geometric least squares means (LSMeans) of the primary PK endpoints (area under the concentration-time curve [AUC] from time zero to infinity [AUC_{inf}], AUC from time zero to the last quantifiable concentration [AUC_{last}] and maximum concentration [C_{max}]) were within the standard equivalence margin of 0.8 to 1.25. The steady state PK profile was assessed in a Phase III study in RA patients [2]. In this study, the patients received 3 mg/kg of SB2 or EU-INF at weeks 0, 2, 6 and then every 8 weeks up to 46 weeks. PK analyses were performed up to week 30. Infliximab serum concentration was measured through two different enzyme-linked immunosorbent assays for pre-clinical and clinical studies.

Results: In pre-clinical studies, available PK profiles from animal studies showed no significant differences in C_{max} and AUC_{last} between SB2, EU-INF and US-INF. In healthy subjects, the 90% CIs for the primary PK parameters were within the pre-defined equivalence margin of 0.8 to 1.25 between SB2 and reference products (SB2 vs. EU-INF and SB2 vs. US-INF). In RA patients, the mean trough level was comparable between SB2 (ranging from 1.915 to 17.965 to $\mu\text{g/mL}$) and EU-INF (ranging from 2.224 to 16.954 to $\mu\text{g/mL}$) from week 2 to week 30. The PK profiles were also comparable between SB2 and INF when analysed by the presence of ADA in both Phase I and Phase III clinical studies.

Conclusions: Similar PK profiles of SB2 and reference products were confirmed in pre-clinical and clinical studies. Altogether, the previously demonstrated analytical similarity and the data presented here indicate that similar PK are expected in all indications approved for SB2.

References:

- [1] Shin D et al. (2015), A Randomized, Phase I Pharmacokinetic Study Comparing SB2 and Infliximab Reference Product (Remicade®) in Healthy Subjects.
- [2] Choe J-Y et al. (2015), A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy

P394

Prolonged azathioprine treatment reduces the need for surgery in early Crohn's disease

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Background: Whether an early use of azathioprine (AZA) could alter the natural history of Crohn's disease (CD) remains debated. We aimed to evaluate the impact of AZA on disease progression in a cohort of Chinese patients with early CD.

Methods: This longitudinal cohort study examined patients with early CD defined as disease duration ≤ 18 months and no previous use of disease-modifying agents (immunomodulators/ biologics) according to Paris definition. The primary outcome was the proportion of CD-related intestinal surgery. Cox regression analysis was performed to identify potential predictive factors of CD progression.

Results: One-hundred and ninety patients with early CD were enrolled in the study. After a median follow-up of 57 months (interquartile range, 31.3–76.2), 31 patients underwent abdominal surgeries, 48 patients were hospitalized, and 68 patients experienced clinical flares. The cumulative rate of remaining free of CD-related bowel surgery, hospitalization and flare at 5-year on AZA treatment was 0.65, 0.59 and 0.39, respectively. The median CD-related bowel surgery, hospitalization and flare-free survival were 73.5 months (95% confidence interval (CI), 62.53–84.47), 76.9 months (95% CI 66.59–87.18) and 49.3 months (95% CI 34.9–63.7), respectively. Four independent predictors of CD-related operations were identified: prior bowel resection (hazard ratio (HR), 9.23; 95% CI 3.67–23.23), smoker (HR, 4.00; 95% CI 1.38–11.65), AZA treatment duration < 36 months (HR, 9.62; 95% CI 2.43–38.47) and hemoglobin < 110 g/L at the time of initiation of AZA (HR, 4.36; 95% CI 1.80–10.58).

Conclusions: Prolonged use (≥ 36 months) of AZA was associated with a more favourable disease course of early CD, evident as a lower risk of CD-related surgeries.

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Etrolizumab demonstrated no difference among doses in symptomatic and endoscopic-based evaluation of remission in anti-TNF- α -naïve patients in a post-hoc analysis of the phase 2 ulcerative colitis trial (EUCALYPTUS)

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Background: The use of the Physician Global Assessment (PGA) subscore, a component of the full Mayo Clinic Score (MCS), has been discouraged as a primary endpoint by the US Food and Drug Administration (FDA) and the European Medicines Agency in 2016 draft guidance. Instead, a composite, clinical remission primary endpoint based on stool frequency (SF), rectal bleeding (RB), and endoscopic subscores (ES) (i.e. MCS w/o PGA) is recommended by the FDA. Etrolizumab, a humanized anti- $\beta 7$ mAb, showed greater clinical remission at week (wk) 10 based on the full MCS (w/PGA) compared with placebo (PBO) in the phase 2 EUCALYPTUS trial (Vermeire et al. *Lancet* 2014). The percentage of patients (pts) achieving clinical remission was numerically lower with higher vs lower etrolizumab dose. This treatment effect was more prominent in anti-tumour necrosis factor- α (aTNF)-naïve pts. We evaluated overall symptomatic and endoscopic remission endpoints in aTNF-naïve pts enrolled in EUCALYPTUS.

Methods: EUCALYPTUS was an international, multicentre, double-blind, PBO-controlled, randomised, phase 2 study (NCT01336465) in 124 pts with moderate-to-severe UC who had not responded to conventional therapy. Eligible pts were randomly assigned (1:1:1) to subcutaneous etrolizumab (100 mg at wks 0, 4 and 8, with PBO at wk 2; or 420-mg loading dose at wk 0, followed by 300 mg at wks 2, 4 and 8), or matching PBO. The primary endpoint was clinical remission (full MCS ≤ 2 , with no individual subscore > 1 at wk 10). Post-hoc analyses assessed SF remission (SF ≤ 1 and ≥ 1 -point decrease from baseline), RB remission (RB = 0), symptomatic remission (SF and RB remission — SFRB), endoscopic remission (ES ≤ 1), and a composite of both SFRB and ES remission in aTNF-naïve pts at wk 10.

Results: PBO-adjusted treatment differences observed with symptomatic and endoscopic remission assessments were similar (30–37%) to those of the primary full MCS remission endpoint (36%), except for RB remission, which had the highest PBO rate and the smallest treatment effect size (24%). Remission rates based on symptomatic remission (SF, SFRB), endoscopic remission (ES) or ES + SFRB were similar between the 100 and 300 mg etrolizumab arms.

Conclusions: When PGA is removed from the MCS-defined remission assessment, aTNF-naïve pts experienced similar rates of remission whether treated with low- or high-dose etrolizumab. Treatment effects observed with SFRB remission and ES + SFRB remission were

	Basis for Clinical Remission Definition, n (%)					
	Full MCS	ES + SFRB	ES	SFRB	SF	RB
PBO (n = 15)*	0	1 (7)	2 (13)	3 (20)	3 (20)	5 (33)
100 mg (n = 16)*	7 (44)	7 (44)	7 (44)	8 (50)	9 (56)	8 (50)
300 mg (n = 12)*	3 (25)	5 (42)	6 (50)	6 (50)	7 (58)	8 (67)
Treatment difference, [†] % (95% CI)	36 (13 to 59)	36 (9 to 64)	33 (3 to 63)	30 (-3 to 63)	37 (5 to 70)	24 (-11 to 59)

*Assessments in aTNF-naïve patients. [†]Pooled active doses vs PBO. Abbreviations: ES, endoscopy score; RB, rectal bleeding score; SF, stool frequency score; MCS, Mayo Clinic Score

of similar magnitude to that observed for the primary MCS remission endpoint.

P396 Long-term efficacy of thiopurines as maintenance treatment in 130 patients with ulcerative colitis

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Background: Thiopurines are used as maintenance therapy in ulcerative colitis (UC). However, data about long-term efficacy are limited. The aim of this study was to evaluate their long-term efficacy, and to search for predictive factors of failure.

Methods: In this retrospective monocentric study, we included UC patients responding to treatment by thiopurine alone or associated with 5-aminosalicylates (5ASA) for at least 6 months. Demographic, clinical and biological data were collected at diagnosis, 6 months after thiopurine onset (considered as T0) and at the time of treatment withdrawal, or last follow-up visit.

Clinical status at T0 was classified into two groups: response (clinical improvement but persistence of symptoms or steroids) and remission (no symptoms and no steroids). Therapeutic failure was defined by: need for anti-TNF alpha, surgery, treatment withdrawal due to side effects or flare up at the date of latest news

Results: We included 130 patients (52% males), with a median follow-up of 86 months (IQR 55–130). UC was predominantly left-sided (53%) and pancolic (35%). Major indication for thiopurine was steroid-dependence (45%), and 19 patients (15%) had severe acute colitis prior to thiopurine. Median duration of treatment was 42 months (IQR 23–80), with 119 (92%) patients having azathioprine.

Eighty-seven patients (67%) maintained clinical remission on thiopurine, and 43 (33%) underwent treatment failure. Mean duration of treatment was 25 months in failure group vs 52 months in remission group. Five years after initiation, 36% (n=47) of patients were still on thiopurine. Reasons of treatment withdrawal were: secondary failure (n=31), major side effect (n=9), persistent remission (n=40) and other reason (n=3). In univariate analysis, older age at diagnosis (RR 1.02; CI95% 1.0–1.04; p=0.04) and clinical response at T0 (RR 1.98; CI95% 1.03–3.82; p=0.04) were associated to treatment failure. In multivariate analysis, only clinical response at T0 vs remission was associated with failure (RR 2.07; CI95% 1.07–3.4; p=0.03).

Relapse rate after withdrawal for persistent remission was 43%, with a median time of 29 months.

Forty patients (31%) had a significant side effect, and 9 of them (7%) stopped treatment due to it. Side effects were mainly hematologic and hepatologic. Nine neoplastic and pre-neoplastic lesions were observed

during follow-up: 2 colorectal high risk adenomas, 3 basal cell carcinomas, 1 *in situ* cervix carcinoma and 3 other cancers (prostate, breast, lung).

Conclusions: This study shows a long term efficacy of thiopurine as a maintenance treatment in UC. Risk of relapse after thiopurine withdrawal is significant. Neoplasia rate due to thiopurine seems to be acceptable in this cohort.

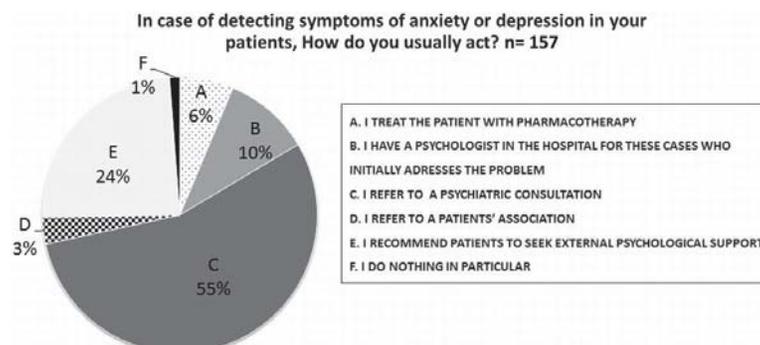
P397 Approach and management of psychological aspects of inflammatory bowel disease described by patients and physicians in Spain. The ENMENTE Project

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Background: ECCO guidelines recommend psychological counseling of IBD patients in clinical practice. The aim of ENMENTE project was to describe patients' and physicians' perceptions on how these aspects are managed in gastroenterology clinics in Spain

Methods: During April 2016 two surveys were made available online, one for IBD patients on the ACCU Spain website (Confederation of IBD Spanish Patients' Associations) and another one for physicians (n=665) members of GETECCU (Spanish Group for IBD treatment). Both invited their members to participate by email and patients' survey was announced in social networks. Patients and physicians responded to closed questions about how they perceive a) the impact of IBD on psychological and social aspects, b) the actual and



Abstract P397 – Figure 1

the ideal care of this impact and c) the management and treatment of psychological morbidities in clinical practice. Quantitative variables are expressed as the mean and standard deviation (SD), qualitative variables are described as percentages

Results: 912 patients (mean age 39 (\pm 10) years, 67% women) and 170 physicians (mean age 44 (\pm 10) years, 58% women) responded to the survey. For 48% of physicians the control of psychological comorbidity is part of the therapeutic objectives. Most physicians reported to have limited (60%) or no experience (33%) in detecting psychological disorders or managing psychotropic drugs. Only 10% have a psychologist as part of the clinical team, and only 6% manage psychotropic drugs in case of anxiety or depression; most of them refer patients to a psychiatrist, psychologist or to patients associations (Figure 1)

Only 15% of physicians reported that patients ask psychological support, although up to 36% of patients declared that they always/mostly spontaneously discuss their emotional status with their doctor. A total of 69% of IBD patients reported that they have never received psychological support to cope with IBD, have never been referred to a psychiatrist (84%), psychologist (77%) nor ever have received a prescription for psychotropic drugs (72%).

Conclusions: Although nearly half of the doctors consider the control of the psychological comorbidity part of the therapeutic objectives, ability or support to manage it is scarce. Only 10% of physicians have a psychologist as part of a multidisciplinary team, and 7 out of 10 patients have never received psychological support to cope with their IBD.

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An objective measure of response to treatment for patients with Crohn's perianal fistulas on anti-TNF treatment

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Background: Magnetic Resonance Imaging (MRI) is the preferred test for assessing fistulising perianal Crohn's disease and its response to anti-TNF therapy. Currently, radiological assessment of perianal fistulas and whether it has responded to treatment is subjective and variable according to radiologist interpretation. This study investigates a complementary objective measurements to reduce inter and intra-observer variability.

Methods: A cohort of patients with perianal Crohn's fistulas treated at a tertiary centre with anti-TNF therapy was identified, and for whom pelvic MRI was available at baseline and follow-up.

Two gastrointestinal radiologists measured fistula volumes, mean signal intensity and time taken to measure fistula volumes on baseline and follow-up MRI scans using a validated open-source segmentation software programme. One gastrointestinal radiologist repeated the measurements after 2 months.

Three different gastrointestinal radiologists also assessed fistula response to treatment (improved/worse/unchanged) by comparing the MRI scans for each patient. Agreement between these radiologists was assessed using the kappa statistic.

Intra-class correlation coefficient (ICC) was used to compare agree-

ment between radiologists and to assess intra-observer variability for one radiologist.

Results: Eighteen patients were recruited of which 6 (33%) were female and median age was 29 years old (range 19–52).

Inter-observer variability was very good for volume and mean signal intensity with ICC of 0.95 (95% CI 0.91–0.98) and 0.95 (95% CI 0.90–0.97) respectively. Intra-observer variability for one radiologist was also very good for volume and mean signal intensity with ICC of 0.99 (95% CI 0.97–0.99) and 0.98 (95% CI 0.95–0.99) respectively. Average time taken to calculate volume measurements was 202 and 250 seconds for readers 1 and 2.

Subjective assessment of response between the 3 radiologists was good; kappa of 0.69 (95% CI, 0.49–0.90). All 3 radiologists agreed in 72% of patients.

A significant association was found between percentage volume change and subjective consensus agreement of response made by the radiologists ($p=0.001$). Median volume change for improved, stable or worsening fistula response was -67% (IQR -78, -47), 0% (IQR -16, +17), and +487% (IQR +217, +559) respectively.

Conclusions: Objective measurements of fistula volume and signal intensity on MRI scans can be made rapidly using segmentation software with good agreement between radiologists. Percentage changes in measured volume are significantly correlated with judgements of response made by radiologists and could potentially be used to decrease variability in fistula assessment. These measurements can potentially be used to track fistula response over time.

P399

Adverse events associated with azathioprine treatment in Korean pediatric inflammatory bowel disease patients

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Background: Azathioprine is proven to be effective for the maintenance of remission in both Crohn's disease and ulcerative colitis, induction of remission in Crohn's disease, and in reducing steroid use in steroid dependent or chronically active inflammatory bowel disease. This study was aimed to evaluate the frequency and course of adverse events associated with azathioprine treatment in Korean pediatric patients with inflammatory bowel disease.

Methods: Total of 174 pediatric patients (age range, 1 to 19 years) with inflammatory bowel disease who received azathioprine in order to maintain remission at Samsung Medical Center (Seoul, Korea) from January 2002 through December 2012 were included in this study. Medical records of these subjects were retrospectively reviewed regarding the development of adverse events associated with azathioprine treatment.

Results: Ninety-eight patients (56.3%) of 174 patients experienced 136 episodes of adverse events, requiring dose reduction in 31 patients (17.8%), and discontinuation in 18 patients (10.3%). The mean dose of azathioprine that had been initially administered was 1.32 ± 0.42 mg/kg/day. Among the adverse reactions, bone marrow suppression developed in 47 patients (27.0%), requiring dose reduction in 22 patients (12.6%) and discontinuation in 8 patients (4.6%). Other adverse events that occurred were gastrointestinal disturbance (15.5%), hair loss (12.1%), pancreatitis (7.5%), arthralgia (6.9%), hepatotoxicity (2.9%), skin rash/allergic reactions (2.9%), headache/dizziness (2.3%), sepsis (0.6%), and oral mucositis (0.6%).

Conclusions: Bone marrow suppression, especially leukopenia was

most commonly associated with azathioprine treatment in Korean pediatric inflammatory bowel disease patients. Close observation for possible adverse events is required in this population with inflammatory bowel diseases who are under treatment with azathioprine.

P400

Risk-adjusted use of thiopurines prevented surgical recurrence in patients with Crohn's disease after intestinal resection

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Background: Thiopurines (TPs) are effective in reducing risk of clinical and endoscopic recurrence in postoperative patients with Crohn's disease (CD). However, whether TPs could prevent surgical recurrence (need for re-resection) remains to be clarified. Our aim was to explore risk factors associated with surgical recurrence (SR) in CD patients after intestinal surgery.

Methods: This was a retrospective cohort study of 246 patients who underwent surgery for CD in a tertiary referral center. Cox proportional hazard model was used to identify independent risk factors associated with SR. Patients were stratified according to the presence of risk factors, and the impact of TPs use on preventing SR in patients with different risk-profile was evaluated.

Results: A total of 50 (20.3%) out of 246 operated patients suffered SR after a median of 54.3±46.4 months. Multivariate analysis showed three risk factors independently associated with SR: penetrating disease behavior (hazard ratio (HR) 8.628; 95% confidence interval (CI) 1.573–47.341; p=0.013), ileocolonic disease location (HR 2.597; 95% CI 1.047–6.445; p=0.040) and isolated upper gastrointestinal (GI) disease location (HR 5.082; 95% CI 1.496–17.267; p=0.009). However, use of TPs after surgery significantly reduced the risk of SR (HR 0.120; 95% CI 0.063–0.231; p=0.000). When stratifying patients into low risk (none of three risk factors) and high risk group (≥one risk factor), there were no statistical difference of SR between patients treated or not by TPs (HR 0.196; 95% CI 0.032–1.190; p=0.077) in low risk group (n=46). However, among patients at high risk (n=200), the patients with TPs use had a lower risk of SR than those without TPs (HR 0.093; 95% CI 0.048–0.178; p=0.000).

Conclusions: Penetrating disease behavior and ileocolonic/isolated upper GI disease are associated with SR in CD patients. TPs use is beneficial in decreasing risk for SR in CD patients at high risk. Large cohorts of low-risk patients are needed to determine the value of TPs in this population.

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Anti-TNF treatments in Crohn's disease and improvement in work productivity and quality of life: an observational study from Turkey

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Background: Patients with Crohn's disease (CD) experience major deterioration in their work productivity and quality of life (QoL). Objectives of this study were to evaluate long-term effects of anti-TNF agents on work productivity and activity impairment (WPAI) in patients with CD and also to evaluate QoL using the Inflammatory Bowel Disease Questionnaire (IBDQ) and the Short Form Health Survey (SF-36).

Methods: Patients with confirmed diagnosis of CD and initiated anti-TNF treatment were included and followed-up for 12 months in this multicenter, prospective observational post marketing study.

Results: A total of 106 patients were included in this study and 64.2% of the patients were male. Mean (±SD) age was 36.9 (±11.1) years. At baseline, fistula information was available for 36 patients and 63.9% of these fistulas were perianal, whereas 36.1% were ileocolic. Intestinal stenosis was detected in 35.6% of the patients (n=38). Most of the stenosis were located in ileum (70.6%) followed by colon (20.6%) and others (8.8%). Extraintestinal symptoms were observed in 25 patients (23.6%). Most frequent extraintestinal symptom was arthritis with 71.4% (n=15). Mean time from first symptom to initiation of anti-TNF treatment was 6.3 (±5.0) years. At 12 months post-start of treatment significant improvements were observed in work productivity comparing to baseline. Improvements in WPAI scores from baseline to the last visit were -24.1% (p=0.003) for work time missed, -18.1% (p=0.006) for activity impairment, -8.5% (p=0.107) for overall work impairment, and -17.0% (p<0.001) for daily activity impairment. Similarly significant improvements (p<0.001) were detected in all components of the IBDQ when compared to baseline. Statistically significant improvements (p<0.05) were detected for all components of SF-36 except for mental health (p=0.109).

Conclusions: Patients with CD experience a significant improvement in their QoL in terms of WPAI, IBDQ and SF-36 during long-term anti-TNF treatment.

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Discontinuation of short-term infliximab maintenance therapy in patients with Crohn's disease: outcomes and risk factors associated with relapse

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Background: According to the current reimbursement policy and need for co-pay in China, most patients diagnosed with Crohn's disease are treated for around six scheduled infusions of infliximab. It is necessary and significant to investigate whether infliximab therapy can be safely discontinued among these patients.

Methods: An observational retrospective study was conducted be-

tween February 2006 and October 2016. We included patients with Crohn's disease who were treated for around six infusions of infliximab with or without an antimetabolite and had been assessed in clinical remission and corticosteroid-free remission at the time of withdrawal. Patients were followed up for at least six months until October 31, 2016. We evaluated the risk of relapse and median time to relapse in patients after withdrawal of infliximab therapy using Kaplan–Meier method. Factors associated with time to relapse was identified using the multiple COX proportional hazards regression analysis. To determine a cutoff value for simplified endoscopic activity score for Crohn's disease (SESCD) score that predicted the relapse with the best sensitivity and specificity, a receiver-operating characteristic (ROC) curve was performed.

Results: A total of 90 eligible patients were included in the study. After a median follow-up time of 15.5 months, 48 patients had a relapse. The median time to relapse was 23.2±2.5 months. The 6-month, 1-year, 2-year, 3-year and 5-year relapse-free survival were 91%, 80%, 49%, 38% and 19% respectively. According to the multivariate analysis, factors associated with time to relapse included age ≤20 years before infliximab initiation (HR=3.56, 95% CI: 1.76–7.18, p<0.001), disease duration ≥2 years before infliximab initiation (HR=1.97, 95% CI: 1.06–3.66, p=0.03), CDAI >220 before infliximab initiation (HR=2.28, 95% CI: 1.20–4.32, p=0.01) and CRP >3 ng/ml (HR=1.92, 95% CI: 1.03–3.55, p=0.01) at infliximab withdrawal. Among patients with six infusions of infliximab, we did not identify mucosal healing or deep remission at the time of drug withdrawal as predictive factors. Through ROC analysis, we found that an SES-CD score of more than 8 at infliximab initiation was the best cutoff for predicting relapse.

Conclusions: Nearly 50% of patients with Crohn's disease who were treated for a short-course infliximab maintenance therapy had a relapse within 2 years after the infliximab cessation. By using combined clinical, biological and endoscopic markers, those with a higher risk of relapse can be identified.

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Golimumab therapy for ulcerative colitis – an Irish multicentre experience

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Background: Golimumab (GLB) is a subcutaneous anti-tumour necrosis factor alpha (anti-TNF) therapy. Randomised controlled trials have demonstrated GLB efficacy in the induction and maintenance of remission in ulcerative colitis (UC). Data are few on the outcome of GLB therapy for UC in routine clinical practice.

Aims: To describe the outcome of GLB therapy for UC in routine clinical practice in Ireland.

Methods: Patients receiving GLB as therapy for UC were identified (n=77) from six Irish Medical centers. Only ambulatory outpatients, with 6 months of follow up post GLB initiation were included (n=69). Baseline clinical, demographic and laboratory data were collected. The primary endpoints were factors associated with durability of GLB response measured by time to drug discontinuation; 3-month clinical response; and 6-month corticosteroid free remission rates. Clinical response was defined as a decrease from baseline in partial Mayo score of at least 3 points and ongoing receipt of GLB. Clinical remission was defined as a partial Mayo score of less than or equal to 2 and continuing receipt of GLB. Secondary endpoints included rates of dose optimisation, dose intervention strategy and adverse events. Raw p values are reported with p values <0.006 (Bonferroni correction) considered significant

Results: The study cohort comprised n=69 UC patients. Baseline characteristics were as follows (continuous variables, median [range]): Age 41.4 years [20.3–76.8]; 55% male; disease duration 6.5 years [0–29.9]; clinical Mayo subscore 6 [0–9]; proctitis, left-sided and extensive colitis in 8%, 54% and 38% respectively; baseline CRP 4.4 mg/L [0.2–134.6]; baseline albumin 42 g/L (16–51). Proportions on concomitant medications at GLB initiation were as follows: 5-aminosalicylate therapy 78%, concomitant immunomodulator 45%, systemic corticosteroids 40% (prednisolone dose, 35mg [5–40]). 36% of subjects were anti-TNF naive. Proportions receiving 50mg and 100mg 4-weekly maintenance regimes were 44% and 56% respectively. 3-month clinical response and 6-month corticosteroid free clinical remission rates were 42% and 42% respectively. 41% of patients required GLB dose optimisation (median [95% CI] time to dose optimisation: 6.5 months [1.4–11.6]); 44% dose increase and 56% interval shortening. Baseline CRP of ≥5mg/L is associated with a shorter time to GLB discontinuation, hazard ratio 3.1 (95% CI 1.4–6.7), p=0.005. Significant adverse events occurred in 3% of patients.

Conclusions: These real world clinical data demonstrate GLB is an effective and safe induction and maintenance agent for UC. GLB dose optimisation is frequently required. A high baseline CRP, likely reflective of increased inflammatory burden, is associated with a less durable GLB response.

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Vaccinations and immunization status in Paediatric inflammatory bowel disease: data from the VIP IBD study

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Background: The prevention of vaccine preventable diseases (VPD) in children with inflammatory bowel disease (IBD) is an increasingly recognised issue. An ESPGHAN commentary providing specific recommendations on VPD was published in June 2012 (1). The aims of this study were to describe the compliance with these recommendations and to evaluate differences among patients diagnosed before and after June 2012.

Methods: This retrospective, multicentre study included 12 pediatric IBD referral centres. The following data were collected from children with a diagnosis of IBD before and after June 2012: demographic details, diagnosis characteristics, therapies, vaccinations and immunization status at diagnosis and at the start of immunosuppressants (IM) and biologics, reasons for incomplete immunization and decision making on IM and biologics.

Results: Between May and November 2016, 394 IBD children [Crohn's Disease (CD): 55.4%; Ulcerative Colitis (UC): 41.6%; Inflammatory Bowel Disease Unclassified (IBD-U): 3%] were enrolled. Among these, 50.2% and 48.8% were respectively diagnosed before and after June 2012. At diagnosis, the percentages of completion for single vaccination were: Diphtheria (99%), Tetanus (99%), Poliomyelitis (99%), Hepatitis B (99%), Pertussis (89%), Haemophilus Influenzae (69.3%), Pneumococcus (17.3%) Meningococcus C (23.9%), Measles (86%), Mumps (79.4%), Rubella (79.4%), Chickenpox (18.4%), HPV (4.1%) and Rotavirus (2%). Complete immunisation, according to the ESPGHAN commentary, was reported in 36% of the children. Among children with incomplete immunisation, specific vaccinations, before starting IM therapy, were recommended in 54.7% patients. In the remaining children, the reasons for not vaccinating were: need for immediate IM therapies (31.3%), parental refuse (8.4%), vaccination costs (3.4%) and other (56.9%). Two-hundred-fifteen (54.4%) out of 394 children started IM [Azathioprine: 204 (94.8%), Methotrexate: 9 (4.1%), other: 0.9%]. Among the children who started AZA, EBV status was only checked in 70 patients (34.3%), with 29 (41.4%) resulting EBV immunised and 41 EBV naive (58.6%). Biologics was started in 154 (39%) children [Infliximab: 79.8%, Adalimumab: 20.1%]. Tuberculosis screening before starting biologics was practised in 94.1% of children with different methods: Tuberculin Skin Test (38.6%), Quantiferon TB Gold (65.5%), T-SPOT TB (0.6%) and chest radiography (71%). Only 29.6% of patients yearly received influenza vaccination. No significant differences were identified between patients diagnosed before and after 2012 in all the analysed variables.

Conclusions: This study suggests a poor compliance with the ESPGHAN recommendations, highlighting the need of new strategies to deal with VPD in IBD children.

References:

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P405

Toxicity of thiopurines in patients with inflammatory bowel disease: inventory and predictive factors

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Background: Thiopurines including azathioprine (AZT) and 6-mercaptoprine (6MP) have proven efficacy in inflammatory bowel disease (IBD). However, thiopurine-related adverse drug reactions are frequent ranging from 5% up to 40%, in both a dose dependent and independent manner. The aim of our study was to assess safety of thiopurine therapy through a retrospective tunisian series.

Methods: We have conducted a retrospective study including patients treated with thiopurines from 2006 and 2012. Epidemiologic, clinical and therapeutic characteristics were abstracted from medical records. Thiopurine-related adverse effects (AE) were sought in each patient so as to determine predictive factors of thiopurine AE. Data entry and analysis were performed by spss version 21.0.

Results: We have colliged 210 patients (98 males and 112 females) of mean age of 29.8 years old. One hundred sixty-nine patients had Crohn's disease (CD), 27 had ulcerative colitis (UC) and 12 had unclassified colitis (UnC). AZT and 6MP were prescribed respectively in 98.1% and 9% of patients. During a mean follow-up period of 28.4 months, digestive intolerance of AZT was noted in 14 patients after 5 months of treatment leading to a switch to 6MP in 10 patients. Immunoallergic reactions occurred in 8 patients (acute pancreatitis (n=5), cutaneous rash (n=3)). Hematologic toxicity was seen in 25 patients after 20 months (2–80) of treatment: lymphopenia (n=19), neutropenia (n=11), anemia (n=15) and thrombopenia (n=11). Treatment withdrawal was decided in 32 patients (15.2%) because of adverse events (n=15) and lack of response (n=17). Six patients had hepatic toxicity: cholestasis at 2 to 3 ULN resulting in a dose reduction in 3 patients. Acute hepatic cytolysis at 3 to 9 ULN occurred in 4 patients after ruling out a viral origin. Regenerative nodular hyperplasia was seen in only 1 patient. There have been one case of acute myeloid leukemia diagnosed 3 months after AZT onset. In univariate analysis, corticosteroid-dependent patients had significantly less AE than other patients (30% vs 70%, p=0.008). Patients with corticosteroid-resistance profile had less AE with trend to marginal significance (6% vs 94%, p=0.08). Patients who had extensive ileal involvement and who were more than 20 years old at disease onset developed digestive intolerance less rapidly (respectively p=0.06 and p=0.04). Immunoallergic reactions seem to occur less commonly among patients who had been previously treated with corticosteroids (p=0.09).

Conclusions: Overall, use of thiopurines in patients with IBD is safe. Hematologic and hepatic toxicities are the most common side effects. Clinicians should consider these side effects so as to optimize thiopurine therapy in IBD patients.

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Clinical correlations of infliximab trough levels and antibodies to infliximab in Korean patients with Crohn's disease

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Background: The clinical implications of infliximab trough levels (IFX-TLs) and antibodies to infliximab (ATI) levels in routine clinical practice are still being debated. Because limited data are available in Asian patients with inflammatory bowel diseases, we analyzed these variables in patients with Crohn's disease (CD) receiving IFX as maintenance therapy.

Methods: IFX-TL and ATI level were measured using prospectively collected samples obtained with informed consent from CD patients being treated at Asan Medical Center, Korea. We analyzed the correlations between IFX-TLs/ATI levels and the clinical activity of CD (quiescent vs active disease) based on the CD activity index (CAI), C-reactive protein level, and physician's judgment of patients' clinical status at enrollment. The impact of concomitant immunomodulators was also investigated.

Results: This study enrolled 138 patients with CD (84 with quiescent and 54 with active disease). In patients with quiescent and active diseases, the median IFX-TLs were 1.423 µg/mL and 0.163 µg/mL, respectively ($p < 0.001$) and the median ATI levels were 8.064 AU/mL and 11.209 AU/mL, respectively ($p < 0.001$). In the ATI-negative and -positive groups, the median IFX-TLs were 1.415 µg/mL and 0.141 µg/mL, respectively ($p < 0.001$). In patients with and without concomitant immunomodulator use, there were no differences in IFX-TLs (0.632 µg/mL and 1.150 µg/mL, respectively; $p = 0.274$) or ATI levels (8.655 AU/mL and 9.017 AU/mL, respectively; $p = 0.083$).

Conclusions: IFX-TL/ATI levels were well correlated with the clinical activity in Korean CD patients. Our findings support the usefulness of IFX-TLs/ATIs in treating CD patients receiving IFX in clinical practice.

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Prospective evaluation of clinical efficacy and safety of golimumab in biologic experienced and naïve patients with moderate to severe ulcerative colitis: experience from a tertiary referral centre

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Background: Golimumab is a fully human monoclonal antibody to TNF α approved for the treatment of patients with moderate to severe ulcerative colitis (UC) with inadequate response or intolerance to corticosteroids or immunosuppressive therapy. The aim of this study is to evaluate the efficacy and tolerability profile of golimumab in both biologic naïve (BN) and biologic experienced (BE) patients.

Methods: Data were prospectively collected from a cohort of UC patients treated with golimumab from March 2015 to November 2016 at our Centre. Descriptive analyses were obtained from two patient cohorts, namely patients who were naïve to anti-TNF α therapies (BN) and patients who have already failed biologic treatment with infliximab or adalimumab (BE) or both. Patients received golimumab 200 mg subcutaneously at week 0, 100 mg sc. at week 2, then 50 mg or 100 mg sc. every 4 weeks depending on body weight. The primary outcomes of interest were clinical response to treatment and rate of adverse events (AE).

Table 1

	Biologic Naïve (BN)	Biologic Experienced (BE)
Patient Characteristics		
Number of patients (n, %)	11 (41)	16 (59)
Sex (n, %)		
Male	7 (64)	6 (38)
Female	4 (36)	10 (62)
Familiarity for IBD (n, %)		
Yes	2 (18)	2 (12)
No	9 (82)	14 (88)
Charlson Comorbidity index (n, %)		
0-1	7 (64)	14 (88)
>2	4 (36)	2 (12)
Extraintestinal manifestation (n, %)		
Yes	2 (18)	5 (31)
No	9 (82)	11 (69)
Age at diagnosis (years) (mean, SD)	43 (15)	32 (11)
Disease duration (years) (mean, SD)	10 (6)	11 (7)
Number of ICS cycles (n, %)		
0-4	1 (9)	3 (19)
>4	10 (91)	13 (81)
Disease extension (Montreal classification) (n, %)		
E1	0 (0)	0 (0)
E2	6 (55)	4 (25)
E3	5 (45)	12 (75)
Endoscopic disease activity (Mayo score) (n, %)		
1	1 (9)	0 (0)
2	1 (9)	3 (19)
3	9 (82)	13 (81)
Study results		
Clinical remission (n, %)		
Yes	5 (45)	4 (25)
No	6 (55)	12 (75)
Adverse events (n, %)		
Yes	3 (27)	4 (25)
No	8 (73)	12 (75)
Surgery required after treatment (n, %)	2 (18)	1 (6)

Results: Overall, 27 patients were enrolled. Of these, 11 (41%) were BN and 16 (59%) BE. Baseline patient characteristics and main results are shown in Table 1. The majority of patients received >5 cycles of systemic steroids before starting golimumab (91% and 82% in the BN and BE groups, respectively). According to the Montreal classification of disease extension, most patients were E2 (55% in BN group, 25% in BE group) or E3 (45% and 75% of the BN and BE groups, respectively). Endoscopic disease activity was scored as Mayo 3 in 82% and 80% for BN and BE patients, respectively. Median (range) duration of golimumab therapy was 3 (1–6) months in the BN group and 3 (1–16) months in the BE group. In 3 (27%) patients in the BN group and 4 (25%) in the BE group AEs were recorded, most of which were skin/genito-urinary infections. Of note, two cases of basal cell carcinoma were registered. The overall remission rate was 45% and 25% in the BN and BE patients, respectively. The main cause of golimumab discontinuation was lack or loss of clinical response (specifically in 71% of BN patients and 92% of BE patients). Among unresponder patients, proctocolectomy was performed in 3 cases.

Conclusions: In our cohort, clinical remission was obtained in almost half of BN patients but only one quarter of BE patients, with a similar rate of AEs. However, treatment duration was highly variable in our series. Although our findings need to be confirmed in larger series, golimumab therapy seems to achieve better disease control in the biologic naïve setting.

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Long-term efficacy of infliximab in patients with ulcerative colitis – an observational study from a single center in Norway

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Background: TNF inhibitor is a well-established treatment in mod-

erate to severe ulcerative colitis (UC). Treatment failure occurs in a large proportion of patients. There are few long-term observational real-life studies and the clinical course in the period following discontinuation of TNF treatment, has been little focused.

Methods: We conducted a systematic review of all patient records for the period of 2001–2014. Demographic, clinical and management data were collected. In addition, disease activity, calprotectin level and ongoing use of TNF inhibitor and/or other anti-inflammatory medication at the last follow-up control was especially emphasized. All data were analysed using PASW version 24.

Results: A total of 87 patients started infliximab treatment until the end of 2011. Of these, 61% were men, mean age 41. Seventy-nine percent had extensive colitis (E3). At start of anti-TNF therapy, 75% used concomitant steroids and 25% used immunomodulators (IMM).

1-year evaluation: Complete remission (CR) (calprotectin <100 mg/kg) was achieved in 45% and partial remission (PR) in 14%. At 1 year, 41% of the patients had discontinued infliximab due to treatment failure or severe adverse events.

The last evaluation (up to 14 years of observation; median 6 years): Eleven patients (13%) were in CR and 3 (3%) in PR, 25 (29%) had undergone colectomy, and 27 (31%) had stopped infliximab due to remission. Of these, 10 patients (37%) restarted anti-TNF (4 years observation), all with complete response.

After discontinuation of TNF inhibitor (up to 13 years of observation; median 4 years): Sixty-five percent of the patients were classified as being in CR and 23% in PR at the last evaluation (excluding all post-colectomy patients). Thirty-seven percent of the patients were using IMM and 19% used oral steroids.

Conclusions: Among patients starting infliximab only 13% were in long-term complete remission. Stopping infliximab due to remission was successful in one third. A high proportion of patients were in steroid free complete remission median 4 years after stopping infliximab. Exit strategies after successful remission-induction anti-TNF treatment in UC patients is highly requested.

P409

Mesalamine enemas for induction of remission in pediatric ulcerative colitis refractory to oral mesalamine: a prospective cohort study

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Background: There are no prospective trials of mesalamine enemas in children with active Ulcerative Colitis (UC). Unlike in adults, most children with UC are not treated with enemas during the first year of disease. The goal of the current study was to prospectively evaluate the ability of mesalamine enemas to induce remission in children with mild to moderate UC failing to achieve remission with high dose oral mesalamine.

Methods: This was a 3-week open label arm of a multicenter, single blinded randomized controlled trial for active UC (i.e. the MUPPIT trial). Children, aged 4–18 years of age, with a PUCAI score between 10–55 were enrolled after failing at least 3 weeks of full dose oral mesalamine. Patients treated with steroids or enemas in the previous month and those with isolated proctitis were excluded. Children received Pentasa enemas 25 mg/kg (max one gram) daily for three weeks in combination with the previous high dose oral mesalamine. The primary endpoint was clinical remission by week 3, defined as PUCAI<10; secondary endpoint was change in PUCAI of 20 points (i.e. response) or remission.

Results: Thirty eight children were enrolled (mean age 14.6±2.3 years; 17/38 (45%) with extensive colitis. Clinical remission was obtained in 42% (n=16) while response rate was 71% (n=27) at week 3. Remission rates were similar between left sided (43%) and extensive (41%) colitis, and did not differ between mild (44%) or moderate (41%) disease (p>0.05 for both). Eight children deteriorated and required steroids. There were no differences in baseline parameters between those who entered or failed to enter remission.

Conclusions: Clinical remission can be markedly increased in children who are refractory to high dose oral mesalamine by adding mesalamine enemas for 3 weeks, prior to commencing steroids.

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Vedolizumab is safe and effective for IBD, but has no effect on liver biochemistry in patients with concurrent PSC

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Background: Blocking of lymphocyte trafficking is a potential mechanism to alter the disease course of primary sclerosing cholangitis (PSC). We studied the effect of the selective $\alpha 4\beta 7$ integrin antibody, vedolizumab, on liver biochemistry and inflammatory bowel disease (IBD) activity in patients with IBD and PSC (IBD-PSC).

Methods: We reviewed electronic medical records of adult patients who had an established diagnosis of IBD-PSC from five tertiary centers. We assessed baseline patient and disease characteristics and treatment exposures. The primary outcome was change in serum alkaline phosphatase at weeks 14 and 30. Secondary outcomes included changes in other liver biochemistries, the Mayo Risk Score for PSC and IBD clinical and endoscopic remission. We also performed a safety analysis for the development of adverse events including liver-related complications.

Results: We identified 34 patients with IBD-PSC. Nine (26%) had a history of orthotopic liver transplant, 7 were on stable doses of ursodeoxycholic acid (UDCA) and 2 patients commenced UDCA

during the study period. Median follow-up was 9 (IQR: 7–16) months; 28 (92%) had at least 6 months of clinical follow-up. Serum alkaline phosphatase activities did not significantly decrease with vedolizumab therapy (median 268 (IQR: 105–551) IU/L at baseline versus 249 (IQR: 183–634) IU/L, $p=0.9899$ at week 30). Of the 18 patients with an abnormal alkaline phosphatase at baseline (>120 IU/L), 11 (61%) had improvement with treatment. In these patients, alkaline phosphatase trended down from 475 IU/L (IQR: 241–757) at baseline to 283 IU/L (IQR: 207–658), $p=0.267$ at week 30 but none of these normalized (Figure 1). Median alkaline phosphatase changes remained similar when patients exposed to UDCA were excluded. Of the 8 patients (31%) with normal alkaline phosphatase at baseline, 4 (50%) had a subsequent increase to abnormal levels by week 30, from a baseline median of 98 IU/L (IQR: 77–102) to 146 IU/L (IQR: 90–203), $p=0.036$ at week 30 (Figure 2). No significant changes in other liver biochemistries or the Mayo PSC Risk Score were demonstrated at week 30. 55% of Crohn's disease and 21% of ulcerative colitis patients achieved clinical remission at week 30. Seven patients (21%) ceased vedolizumab therapy; one for a deterioration in liver biochemistry thought to be a drug reaction and six for IBD primary non-response. Two patients developed ascending cholangitis but continued vedolizumab.

Conclusions: Vedolizumab therapy in patients with IBD-PSC has little overall effect on liver biochemistry, but is safe and does improve IBD clinical activity. Treatment earlier in the disease course of PSC and assessment of longer-term exposure of lymphocyte trafficking blockade in IBD-PSC remains of interest.

P411

Drug persistence and need for dose intensification to adalimumab therapy; the importance of therapeutic drug monitoring in inflammatory bowel diseases

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Background: Therapeutic drug monitoring (TDM) measuring drug trough levels (TL) and antidrug antibodies (ADA) may aid the therapeutic decision in patients with inflammatory bowel disease (IBD) who loose response to anti-TNF therapy. Our aim was to evaluate the frequency and predictive factors of loss of response to adalimumab therapy and the role of the therapeutic drug monitoring to predict the loss of response in adalimumab treated IBD patients.

Methods: 112 IBD patients (with 214 TDM measurements, CD/UC 84/28, male/female 50/62, mean age CD/UC: 36/35 years, mean duration of adalimumab therapy CD/UC: 157.8/70.1 weeks) were enrolled in this consecutive cohort from two referral IBD centres in Hungary. Demographic data were comprehensively collected and a harmonized monitoring strategy was applied. Previous and current therapy, laboratory data and clinical activity at the time of the TL and ADA measurement were recorded. Patients were evaluated either at the time of suspected LOR or during follow-up. TDM measurements were done by commercial ELISA (LISA TRACKER, Theradiag, France).

Results: Among 112 IBD patients, LOR/drug persistence was 25.9%/74.1%. The probability of ADA positivity and low TL (<40

$\mu\text{g/mL}$) was 12.1% and 17.8% in the first year and 17.3% and 29.5% and in the second year after start of adalimumab therapy in Kaplan-Meier analysis. Dose intensification was needed in 29.5% during the study period. There was an association between female gender, ADA positivity and LOR (female gender: $p<0.001$, OR: 7.770 CI95%: 2.483–24.315, ADA positivity: $p=0.007$ OR: 3.616 CI95%: 1.374–9.518)), while no other parameters, including TL was associated with LOR or dose intensification.

Table 1. ADA and TL status in IBD patients treated with adalimumab

	Normal TL	Low TL
ADA negative	58%	21.4%
ADA positive	10.7%	9.8%

Conclusions: Our results suggest that ADA development, low TL and need for dose intensification are frequent during adalimumab therapy and support the use of routine TDM assessment in IBD patients. Female gender, and ADA positivity were predictors of loss of response.

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The Sicilian network of biological therapy in inflammatory bowel disease: preliminary data on efficacy

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Background: The monitoring of appropriateness, costs, and clinical outcomes of biological therapy in inflammatory bowel disease (IBD) is a relevant need. We aimed to evaluate all these issues in Sicily through a web based network of all prescribing centers.

Methods: From January 2013, all IBD patients starting a biological agent (incident cases) or already on treatment (prevalent cases) were entered in a web based software. Herein we report data of incident

cases about the efficacy of biological therapy after twelve weeks and one year of treatment.

Results: From January 2013 to October 2016, 1475 patients were included. Incident cases were 1090. Considering that 16% of patients experienced more than one line of therapy, a total of 1351 treatments were reported. Adalimumab was used in 622 Crohn's disease (CD) patients and in 83 ulcerative colitis (UC)/unclassified colitis patients. Infliximab was prescribed in 275 CD patients (80 biosimilars) and in 279 UC patients (50 biosimilars). Golimumab was used in 32 UC patients, while vedolizumab in 40 CD patients and in 20 UC patients. In patients with CD, after twelve weeks and one year of therapy, the rates of remission with adalimumab were 43.9% and 60.2%, respectively, and the rates of response 40.9% and 25.8%, while the rates of remission with infliximab originator were 46.2% and 50.0%, and the rates of response 40.9% and 32.9% (biosimilars: remission 31.0% and response 51.7% after 12 weeks; remission 45.5% and response 36.4% after one year). In UC, after twelve weeks and one year of therapy, the rates of remission with adalimumab were 43.3% and 57.1%, respectively, and the rates of response 36.7% and 19.0%; the rates of remission with infliximab originator were 41.6% and 48.4%, and the rates of response 35.6% and 32.3% (biosimilars: remission 30.0% and response 63.3% after 12 weeks; remission 20.0% and response 40.0% after one year); the rate of remission after 12 weeks of therapy with Golimumab was 22.2%, and the rate of response was 33.3%. After twelve weeks of therapy with Vedolizumab, 28.6% of CD patients were in remission and 32.0% had a response, while the rates of remission and response in UC patients were 33.3% and 22.0%, respectively. Multivariable logistic regression analysis showed that age >50 years was independently linked to lower rates of remission/response at 12 weeks in CD patients (OR 0.613, p=0.046).

Conclusions: In one of the largest series of IBD patients on biological therapy reported to date, CD patients older than 50 years showed a higher rate of non response at 12 weeks of treatment. Efficacy of biosimilars was overall comparable to that reported for infliximab originator.

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Exclusive enteral nutrition provides an effective bridge to safer interval elective surgery for Crohn's disease

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Background: Despite data reporting that exclusive enteral nutrition (EEN) improves nutritional status and inflammation in patients with Crohn's disease, few studies have reported its systematic use in the perioperative setting. EEN involves the use of a liquid nutrition formula to meet all of an individual's dietary requirements. We sought to test the hypothesis that EEN provides a safe and effective bridge to surgery and reduces post-operative complications in adult patients with Crohn's disease requiring urgent surgery for stricturing or penetrating complications.

Methods: Fifty-one patients who were treated with EEN prior to planned surgery for stricturing or penetrating complications of Crohn's disease were identified from our specialist dietician's database. Thirty eight out of these fifty-one patients had surgery and

they were each matched with two control patients for disease behaviour, type of surgery, age at diagnosis and disease duration. Data on disease phenotype, nutritional status, operative course, and post-operative complications were obtained.

Results: Clinical status improved in 25% [13/51] of the EEN patients such that they no longer required surgery. EEN had no effect on pre-operative weight, but it significantly reduced median [interquartile range (IQR)] serum CRP levels (baseline 36 [13–91] vs. pre-operation 8 [4–31] mg/L, p=0.02). The median [IQR] length of surgery was shorter in patients pre-optimised with EEN than controls (3.0 [2.5–3.5] vs. 3.5 [3.0–4.0] hours respectively, p<0.001). Multivariable logistic regression analysis confirmed that going straight-to-surgery compared with EEN pre-optimisation was associated with a nine-fold increase in the incidence of post-operative abscess and/or anastomotic leak (OR 9.1 95% CI [1.2–71.2], p=0.04).

Conclusions: EEN in adult patients presenting with stricturing or penetrating complications of Crohn's disease is associated with a reduction in systemic inflammation, operative times and the incidence of post-operative abscess or anastomotic leak. Further controlled trials are needed to elucidate how EEN may improve operative outcomes and to confirm that EEN provides a safe and effective bridge to surgery.

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Vedolizumab in Pediatric inflammatory bowel diseases: a retrospective multi-center experience from the paediatric IBD Porto group of ESPGHAN

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Background: Vedolizumab (VDZ) has proven as an effective medication in adult Inflammatory Bowel Disease (IBD). There has been increased off-label use of VDZ also in children but with very limited published experience. Therefore we aimed to describe the short-term effectiveness and safety of VDZ in children with IBD in the largest pediatric cohort to date.

Methods: Retrospective review of children (2–18 years) treated with VDZ from 17 centers affiliated with the Paediatric IBD Porto group of ESPGHAN. Baseline characteristics and explicit prior and current clinical data were recorded on a standardized REDcap case-report forms. Primary outcome was treatment success at week 14 and last follow-up, defined as steroid-free remission (i.e. wPCDAI<12.5 or PUCAI<10) without the need for new medications or surgical intervention. Safety data were also explicitly recorded.

Results: Of the 55 included children, 33 (60%) had UC/IBDU, and 22 (40%) had Crohn's Disease (CD); [28 (51%) male, mean age at first VDZ dose 14.5±2.8 years, and median disease duration 3.5 years (IQR 1.8–5.1)]. All were previously treated with anti-TNF (27% primary failure, 49% secondary failure, 15% adverse reaction and 9% for other reasons) and 8 (15%) had prior surgical intervention.

Success rates at week 14 were 21% in UC, and only 9% in CD ($p=0.24$). Median follow-up period was 22 weeks (IQR 14–22) from VDZ initiation (range 6–76). Success rates by last follow-up were 39% in UC and 27% in CD ($p=0.36$). By the last follow-up 8 (15%) new children required surgery, of whom 6 had colectomy for UC (18% of the entire UC cohort). There were three mild adverse events to VDZ, including pruritis, transient dyspnea and mild periorbital oedema; there were no serious drug-related adverse events. Median fecal calprotectin decreased from 1168mcg/gm (IQR 609–1409) prior to treatment to 412mcg/gm (IQR 54–745) following treatment when available ($p=0.013$).

Conclusions: In this largest real-life cohort of VDZ use in pediatric refractory IBD to date, VDZ was safe and effective in 21% and 39% of UC at 14 weeks and last follow-up whereas in CD the rates were 9% and 27%. These data thus support previous findings of slow induction rate of VDZ, particularly in CD.

P415 Trends in narcotic and corticosteroid prescriptions in patients with inflammatory bowel disease in the United States ambulatory care setting from 2003 to 2011

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Background: Prior to the availability of biologic therapies, corticosteroids and narcotics were frequently used in inflammatory bowel disease (IBD) patients due to a paucity of disease modifying therapies. The increased accessibility to effective biologics for IBD over the last decade should be leading to less use of corticosteroids and narcotic medications.

Methods: Data from the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) were used to examine visits of patients with IBD. Trends in corticosteroid and narcotic prescriptions were explored, and predictors of use were assessed using survey-weighted chi-square tests.

Results: From 2003 to 2011, a total of 1119 patients with IBD had visits recorded in the NAMCS and NHAMCS databases. Although

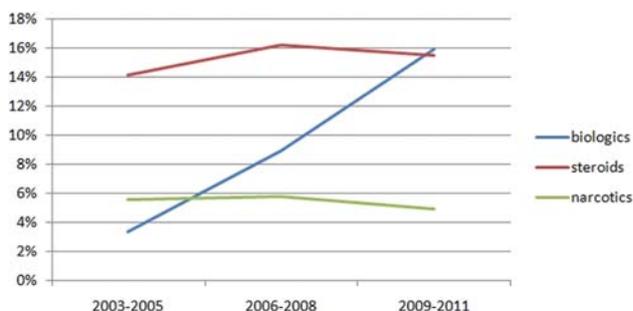


Figure 1. Frequency of medication prescriptions during ambulatory visits for IBD patients.

biologic prescriptions significantly increased from 3.3% in 2003–05 to 15.9% in 2009–11 ($p=0.004$), there was no significant decrease in corticosteroid or narcotic prescriptions during this same time frame (Figure 1).

Patients with IBD were less likely to receive narcotics (odds ratio (OR) = 0.38) when seeing a medical specialist compared to primary care physicians or surgeons.

Conclusions: Despite the availability of more effective biologic therapies, prescriptions for corticosteroids and narcotics did not decline in IBD patients visiting U.S. ambulatory clinics and emergency departments from 2003 to 2011.

P416 Real world data on the effectiveness and safety of vedolizumab in the treatment of Crohn's disease and ulcerative colitis: the Edinburgh experience

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Background: The GEMINI clinical trials programme has demonstrated the efficacy and safety of vedolizumab in the induction and maintenance of Crohn's disease and ulcerative colitis. 2 years after licensing and subsequent approvals (eg. NICE/SMC), there is great interest in real world effectiveness and safety data from early adopters. Here, we present the short and medium term outcomes from a single centre cohort of IBD patients treated with vedolizumab.

Methods: A vedolizumab treatment pathway was agreed. The following were prospectively collected for all patients at each infusion: observations, routine haematology, biochemistry and inflammatory markers, clinical disease activity score, faecal calprotectin (FC) and adverse events. Clinical effectiveness was evaluated by assessing changes in HBI and SCCAI at 12–14 weeks and 26 weeks. Clinical remission was defined as a HBI <5 and SCCAI <3. Response was defined as a change in disease activity ≥ 3 . Changes in CRP/FC were also analysed.

Results: By the end of November 2016, 94 patients had received vedolizumab treatment. 63/94 (27 CD, 33 UC, 3 IBDU) had completed 12–14 week follow-up and are included in the primary analysis of clinical efficacy. Median disease duration was 7.9 years (IQR 4–15) with 36/63 (57%) patients previously exposed to anti-TNF therapy. Median HBI and SCCAI at baseline were 4 (IQR 2–7) and 5 (IQR 2–6) respectively. At 12–14 weeks median HBI was 3 (IQR 1–7) ($p=0.37$) with SCCAI dropping to 1 (IQR 1–3) ($p=0.004$). At 26 weeks median HBI fell to 2 (IQR 0.5–3, $n=15$) ($p=0.02$) and SCCAI remained at 1 (IQR 0–1, $n=26$) ($p=0.0001$). 23/63 (37%) patients were in clinical remission at baseline (59% on steroids) with 42/63 (67%) at 12–14 weeks (24% on steroids) and 35/41 (85%) at 26 weeks (12% on steroids). Clinical response and remission rates of those patients with clinically active disease at baseline were 61% and 53% at week 12–14 ($n=36$), and 78% for both at week 26 ($n=24$). Median FC was 730 μ g/g (IQR 215–858, $n=50$) at baseline, 170 μ g/g (IQR 60–465, $n=36$) at week 12–14 ($p=0.00018$) and 70 μ g/g (IQR 30–180, $n=29$) at week 26 ($p=0.00001$). No significant drug related complications were observed. Arthralgia was the most commonly reported side effect (12/94). 7/94 (7%) patients underwent surgery within 30 weeks of starting vedolizumab. 2 pregnancies and 1 colorectal cancer were reported in our cohort.

Conclusions: Our experience further supports the clinical effectiveness and safety data for the use of vedolizumab. We demonstrate

a clear benefit in clinical/biochemical disease activity in a cohort of IBD patients many of which had complex and previously refractory disease.

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Non-invasive assessment of liver fibrosis by transient elastography and AST to ALT ratio in patients with Crohn's disease treated with methotrexate

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Background: One of the most feared concerns about the use of methotrexate (MTX) is the risk of developing chronic liver injury. Transient elastography is a simple, non-invasive method for estimating liver fibrosis. AST to ALT ratio (AST/ALT ratio) is also a good easy-to-use indicator of the risk of fibrosis in chronic liver diseases. The aim was to assess the risk of chronic liver injury induced by MTX in a cohort of patients with Crohn's disease (CD) at a high-volume tertiary center.

Methods: Cross-sectional study including CD patients treated with methotrexate. Clinical and laboratorial data, duration of treatment, and cumulative dose of methotrexate were obtained. Liver stiffness was assessed by FibroScan®, and the cutoff values for significant liver fibrosis (according to METAVIR) was $F \geq 2$: 7.1 kPa. AST/ALT ratio was considered significant for risk of fibrosis if > 1 . Patients with chronic hepatitis B or C, excessive daily consumption of alcoholic, non-alcoholic steatohepatitis, or other known causes of chronic liver disease were excluded. Estimates of the presence and severity of steatosis according to the parameter of controlled attenuation (CAP) were also evaluated, considering the absence of significant steatosis (S0) if less than 200 dB/m, mild (S1) if 200–249 dB/m, moderate (S2) if 250–299 dB/m, and severe (S3) if 300 dB/m or greater.

Results: 62 patients were included, 35 female (56.5%), with a mean age of 37.5 ± 11.3 years. MTX was the first-line immunosuppressant in 9 patients (14.5%). Indications for initiating MTX included: adjuvant to anti-TNF agent (43.5%), intolerance to azathioprine (27.4%), corticoid dependence (19.4%) and corticoid resistance (9.7%). Mean treatment duration was 88 ± 86 weeks. Mean cumulative MTX dose was 998 ± 871 mg. All patients received MTX subcutaneously. In sixteen patients MTX was discontinued due to changes in liver function tests. The mean value of Fibroscan was 5.3 ± 1.5 kPa, and in 11.1% of cases the value was considered significant for fibrosis (≥ 7.1 kPa). In none of the cases was a value compatible with METAVIR F4 (> 11 kPa). The mean CAP value was 198 ± 58 dB/m, distributed as follows: S0 63.3%, S1 16.7%, S2 13.3% and S3 6.7%. The mean AST/ALT ratio was 1.12 ± 0.43 and was considered significant (> 1) in 58.7% of the cases. Fibroscan values correlated directly with ALT (0.44, $p=0.026$) and bilirubin (0.426, $p=0.038$), but not with duration of treatment or cumulative dose. Likewise, these variables did not correlate with the AST/ALT ratio.

Conclusions: Excluding patients with other risk factors for chronic liver disease, the use of methotrexate regardless of the cumulative dose appears to be safe in the medium to long term in CD patients according to non-invasive methods.

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Pharmacodynamic biomarkers demonstrate dose-dependent pharmacological activity of the IL-22Fc fusion protein UTTR1147A in healthy volunteers in a phase 1a clinical trial

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Background: Interleukin-22 (IL-22) belongs to the IL 10 cytokine family [1] and binds specifically to the IL-22 receptor (IL-22R) heterodimer, expressed on a variety of epithelial cells [2]. IL-22 modulates innate immunity via activation of STAT3 and induces subsequent regenerative and protective properties [3]. UTTR1147A, IL-22Fc, is a recombinant fusion protein in development for IBD.

In cynomolgus monkeys, UTTR1147A demonstrated dose-dependent increases in serum levels of regenerating islet-derived protein 3A (REG3A), an antimicrobial C-type lectin as well as serum amyloid protein A (SAA), a STAT3-dependent anti-microbial protein and acute phase protein C-reactive protein (CRP). This observation was corroborated in mice where murine IL-22Fc induced dose-dependent increases in serum REG3 β , the murine homologue of Reg3A, and SAA. Therefore, REG3A, SAA, and CRP are attractive pharmacodynamic (PD) biomarkers that are supportive of IL 22R target engagement.

Methods: The safety and tolerability of UTTR1147A was assessed in a first-in-human observer-blinded, placebo-controlled single ascending dose Phase 1a study in healthy volunteers at a single center. Subjects were given either intravenously (IV) placebo or subcutaneous (SC) UTTR1147A at doses ranging from 1 to 120 $\mu\text{g}/\text{kg}$. To assess pharmacological activity of UTTR1147A, exploratory PD biomarker levels of REG3A, SAA and CRP were measured in serum samples obtained predose and at defined postdose time points.

Results: UTTR1147A induced dose-dependent increases in serum SAA, REG3A and CRP levels compared to placebo. Levels of all three biomarkers peaked at higher concentrations and at earlier time points following IV compared to SC administration. Increases of REG3A were sustained longer compared to increases seen with SAA and CRP. Normalized Reg3A levels remained slightly above baseline at end of study following 90 and 120 $\mu\text{g}/\text{kg}$ IV and 120 $\mu\text{g}/\text{kg}$ SC dose levels, whereas lower dose groups were near baseline by day 43. The observed increases in CRP were a direct pharmacologic effect of exposure to UTTR1147A. Consistent with nonclinical studies, no signs or symptoms of systemic inflammation accompanied these increases in CRP.

Conclusions: In conclusion, dose-dependent increases in serum levels of PD biomarkers REG3A, SAA, and CRP were observed following treatment with UTTR1147A compared to placebo. These PD biomarker data provide evidence that UTTR1147A effectively engaged its target receptor IL-22R and demonstrate dose-dependent pharmacological activity of UTTR1147A in healthy volunteers.

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Concentrations of anti-TNF agents in non-inflamed intestinal tissue are associated with the long-term outcome of patients with Crohn's disease

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Background: Many reports show that high serum trough levels of anti-tumor necrosis factor (TNF) agents are required for the sustained remission in patients with Crohn's disease (CD). However, the pharmacokinetics of anti-TNF agents in intestinal mucosa was poorly investigated. The aim of our study was to investigate the correlation between the tissue concentration of anti-TNF agents and long-term disease outcome.

Methods: This was a prospective single center study and 25 patients with CD administered infliximab or adalimumab as a maintenance therapy were enrolled. All participants received colonoscopy or balloon-assisted small bowel endoscopy two weeks after the administration of anti-TNF agents. Biopsy samples obtained from the inflamed and non-inflamed intestinal tissue were immersed in distilled water in the concentration of 0.1 mg/ μ l. Tissue concentrations of anti-TNF agents were evaluated by enzyme-linked immunosorbent assay and the correlation with serum trough levels was compared. Moreover, we investigated the association between tissue concentrations of anti-TNF agents and the time to therapeutic interventions defined as no additional medical, endoscopic, and surgical treatment for 24 months.

Results: Concentrations of anti-TNF agents in the inflamed tissue were significantly higher than that in the non-inflamed tissue (1.7 versus 1.0 μ g/g, median, $p=0.0011$). Crohn's Disease Activity Index score and modified Rutgeerts score were not associated with the levels of anti-TNF agents in either inflamed or non-inflamed tissue. Serum trough concentrations of infliximab and adalimumab were 2.3 μ g/ml (median, range [0.2–7.0]) and 10.4 μ g/ml (0.8–22.8), respectively. When the patients were divided by median serum trough levels of each anti-TNF agent, patients with high serum trough concentrations of anti-TNF agents had significantly higher anti-TNF agents levels in the non-inflamed tissue than those with low serum trough concentrations (1.2 versus 0.0 μ g/g, median, $p=0.0346$), but the difference was not observed in the inflamed tissue. Patients with high concentrations of anti-TNF agents in the non-inflamed tissue (>1.3 μ g/g) had significantly longer time to therapeutic interventions than those with low concentrations of anti-TNF agents (15.5 versus 3.0 months, HR 0.33; 95% CI: 0.09–0.93).

Conclusions: The concentrations of anti-TNF agents in the non-inflamed mucosa can reflect sustained remission and be a biomarker for monitoring therapeutic intensity in CD patients receiving anti-TNF agents.

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Anti-TNF for post-operative prevention in Crohn's disease: the detection of anti-drug antibodies at time of surgery is associated with an increased risk of endoscopic recurrence

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Background: Anti-TNF monoclonal antibodies (mAb) are efficient for the prevention of postoperative recurrence in Crohn's disease (CD). Measurement of trough serum levels and anti-drug antibodies may help to determine the mechanisms of anti-TNF failure. We previously identified two risk factors associated with endoscopic recurrence in the REMIND cohort: tobacco (OR =2.3) and anti-TNF (OR =0.35). The aim of our study was to correlate efficacy of anti-TNF mAb with their pharmacokinetics within the same cohort.

Methods: The REMIND group conducts a prospective nationwide study in nine French academic centers of ileal and/or ileocolic CD patients. Samples are taken from the surgical specimen at the time of surgery (M0) and at the time of endoscopy (M6), stored centrally in a bio-bank, and analyzed to identify factors associated with recurrence. This study was performed in the 60 patients treated post-operatively with anti-TNF in the REMIND cohort (198 patients included on the date of the analysis).

The trough levels of infliximab (IFX) and adalimumab (ADA) and anti-drug antibodies (ATI and ATA) were analyzed by ELISA method. Limits of detection were 10 ng/ml for both ATI and ATA. Trough levels of detection of anti-TNF drugs was 0.3 μ g/ml. Therapeutic thresholds levels were 3 μ g/ml for IFX and 4,9 μ g/ml for ADA. Endoscopic recurrence was defined by a Rutgeerts \geq i2 score. The fisher test was used for the bivariate analysis.

Results: Sixty subjects received an anti-TNF agent (ADA n=47, IFX n=8) after surgery. Only 14 patients (23%) were naive of anti-TNF. Twenty-six patients (43%) had an endoscopic recurrence and 34 (57%) had a normal colonoscopy. ATA or ATI were detected in 8 patients at M0; 6 of them (75%) had an endoscopic recurrence. In contrast, of the 41 patients who did not have anti-drug antibodies at the time of surgery, 13 (32%) had endoscopic recurrence ($p=0.04$). At M6, the trough drug levels were analyzed in 32 patients. In the group of patients with endoscopic recurrence, trough drug levels were below therapeutic threshold in 10 of 15 patients (67%) compared to the 3/17 patients (18%) in the group of patients with endoscopic remission ($p=0.01$).

Conclusions: The presence of anti-drug antibodies at the time of surgery is associated with a higher risk of endoscopic recurrence. Infra-therapeutic trough levels at M6 were associated with a higher risk of endoscopic recurrence. In clinical practice, these results demonstrate that detection of anti-drug antibodies may influence the choice of postoperative therapy.

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Comparative efficacy and impact on patient-reported outcomes of pharmacological therapies for moderate to severe ulcerative colitis: a systematic review and network meta-analysis

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Background: We performed a systematic review and network meta-analysis to assess efficacy and impact on patient-reported outcomes (PRO) of pharmacological therapies for moderate to severe ulcerative colitis (UC).

Methods: Medline, Embase, CENTRAL, and grey literature sources were systematically searched up to October 2016. We included randomized controlled trials in adults with moderate to severe UC that compared infliximab, adalimumab, golimumab, vedolizumab and tofacitinib to each other or placebo. Efficacy outcomes were induction and maintenance of remission, response and mucosal healing. PRO endpoints included change in IBDQ score and IBDQ response (a ≥ 16 -point increase from baseline). We combined direct and indirect evidence through multivariate random-effects network meta-analyses and relative ranking of treatments was assessed using surface under the cumulative ranking (SUCRA) probabilities. We conducted subgroup analyses based on prior anti-TNF therapy.

Results: We included thirteen randomized, double-blind, placebo-controlled trials (4 with infliximab, 3 with adalimumab, 2 with golimumab, 1 with vedolizumab and 3 with tofacitinib). All interventions were effective against placebo. When used for induction, infliximab had higher rates of clinical response and mucosal healing compared to adalimumab (OR 2.27; 95% CI 1.47 to 3.50 and OR 2.03; 95% CI 1.32 to 3.12 respectively) and golimumab (OR 1.88; 95% CI 1.18 to 3.02 and 1.68; 95% CI 1.05 to 2.69 respectively), and was ranked first (SUCRA 97.5 and 89.7, respectively). However, it was comparable (SUCRA 75.1) with vedolizumab (SUCRA 72.6) and tofacitinib (SUCRA 72.4) in achievement of clinical remission.

In patients who prior anti-TNF exposure, tofacitinib was ranked as the most effective agent and it was superior to adalimumab for all efficacy outcomes. Infliximab (OR 2.35; 95% CI 1.62 to 3.41), adalimumab (OR 1.38; 95% CI 1.07 to 1.79) and tofacitinib (OR 2.07; 95% CI 1.59 to 2.70) resulted in higher IBDQ response rates compared to placebo. Greater improvement in IBDQ score was observed following treatment with vedolizumab (OR 18.00; 95% CI 11.08 to 24.92) and infliximab (OR 18.58; 95% CI 13.19 to 23.97).

Finally, we could not synthesize indirect effect estimates for maintenance of remission for all agents due to differences in study designs. Remission (OR 0.95; 95% CI 0.49 to 1.83) and response (OR 0.79; 95% CI 0.45 to 1.39) rates were comparable between infliximab and adalimumab at the end of maintenance phase.

Conclusions: All pharmacological therapies equally improved quality of life. Infliximab was ranked first across efficacy outcomes. Short-term treatment with tofacitinib seems effective with high ranking, especially in patients with previous anti-TNF exposure.

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Patient-near Infliximab trough-level testing by a novel quantitative rapid test; the Quantum Blue Infliximab assay

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Background: Therapeutic drug monitoring (TDM) has become standard clinical practice and overwhelming clinical evidence indicates that dose-optimization improve clinical outcome by decreasing the risk for anti-drug-antibodies (ADA) and improves the efficacy of the

drug itself. There is also another aspect for advocating TDM, that is improving the health economic aspect of these very expensive drugs. However, this has been hampered by the high cost of and the absence of a near patient testing.

Aims of the study: The study had two aspects; first is to correlate a CE -marked rapid test for IFX trough level, the Quantum Blue Infliximab test (QB-IFX) (BÜHLMANN Laboratories, AG, Basel, Switzerland) to an assay very similar to the Loeven assay. Secondly, to correlate the performance of such a test done by; A) a nurse and B) a trained laboratory person

Methods: The study comprised 64 pts with IBD receiving IFX treatment; 14 Remicade and 50 Remsina. At the day of infusion, blood for IFX-trough level was collected in addition to 3 ml serum for QB-IFX rapid test.

Part A: A nurse (IL) received one hour of "laboratory" training before running the QB-IFX under supervision of AR. The serum was diluted 10uL in 190 uL assay buffer and vortexed for 5 sec. 70uL was applied to the rapid test cassette and read after 15 min using the Q B reader.

Part B: The same procedure was followed by an experienced lab technician (GHM). In addition, 5 aliquots from three sera-levels was collected (3, 7 and 10ug/ml) and tested to establish CV for the upper and lower trough level values as well as for one high level value.

Results: There was a very good correlation between the QB-IFX rapid test and the laboratory ELISA test, $r=0.90$, $p<0.001$, the slope was 1.1. Furthermore, the correlation between the results obtained by the nurse and a skilled lab person was acceptable with $r=0.92$, $p<0.001$. The CV for the upper and lower trough level was 4.7 and 7.8% respectively. CV for the high level was 14.7%

Conclusions: This is the first study that documents a close correlation between a 15 min. rapid test for IFX trough level with that of a standard lab-test. We have shown that such a test can accurately be performed by a nurse. The CV for the three different serumlevels was way lower than expected for a lateral flow rapid test. This means that TDM now can be moved from a distant laboratory to the near patient facility like the infusion centre to ensure correct dosing in IBD and other patients on IFX treatment.

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Early improvement in quality of life in patients with luminal Crohn's disease treated with adalimumab. Data from RAPIDA trial

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Background: Clinical response and patient's quality of life improve as a result of the direct benefit of Crohn's disease (CD) effective treatment. Rapidity of response to treatment in CD is a field of major interest, due to the importance of achieving the highest benefit in the shortest possible time. There are no studies specifically designed for early evaluation of the quality of life in patients with active CD receiving adalimumab therapy.

The aim of this study was to evaluate the rapidity of improvement of quality of life in response to adalimumab therapy in adult anti-TNF naïve patients with active luminal (Harvey-Bradshaw Index ≥ 8) moderate-to-severe CD, and with no response to a full and adequate course of therapy with corticosteroids and/or immunosuppressants.

Methods: To this purpose we designed an interventional, prospective, open label, single arm and multicenter clinical trial. Quality of life was evaluated by using the validated questionnaires EuroQol-5D (EQ-5D) and the 36 items version of the Inflammatory Bowel Disease Questionnaire (IBDQ-36). Questionnaires were administered at baseline, day 4 and weeks 1, 2, 4 and 12 with standardized adalimumab treatment (160 mg – 80 mg – 40 mg eow).

The modified intention to treat (mITT) population was the primary population for analysis and consisted of those patients enrolled in the study who had received at least one dose of adalimumab.

Statistical analyses were performed by the t-test or the Wilcoxon signed rank test, as applicable.

Results: Eighty patients were included. At baseline, the median EQ-5D index score was 0.68. EQ-5D scores improved significantly versus baseline, at day 4 and weeks 1, 2, 4 and 12, with median changes of 0.05 ($p < 0.01$), 0.05 ($p < 0.001$), 0.11 ($p < 0.001$), 0.10 ($p < 0.001$) and 0.12 ($p < 0.001$), respectively. Similarly, EQ-5D VAS median scores also improved significantly, compared to baseline (median score at baseline: 55.00), at day 4 and thereafter, with median changes of 6.00, 5.00, 10.00, 10.00 and 13.00, respectively ($p < 0.001$ at all time-points).

The comparison, versus baseline, of the IBDQ-36 overall score (median score at baseline: 143.50) at day 4 and weeks 1, 2, 4 and 12, also yielded statistically significant differences, with median improvements of 14.0, 18.0, 30.0, 42.0 and 32.0 respectively ($p < 0.001$ at all time-points). Restoration of normal health (IBDQ-36 score > 209) was obtained in 11% of patients at day 4 and increased to 31% at week 12.

Conclusions: Adalimumab produces rapid improvement of quality of life since day 4 in patients with moderate-to-severe Crohn's disease.

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Association between infliximab trough levels, clinical remission, mucosal healing and quality of life in patients with inflammatory bowel disease on maintenance therapy

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Background: Adequate infliximab (IFX) trough levels (TL) are associated with clinical remission (CR) and mucosal healing (MH). We

aimed to investigate the association between ITX TL and quality of life (QoL) in inflammatory bowel disease (IBD) patients.

Methods: We carried out a prospective cohort study in IBD patients in IFX maintenance therapy. IFX levels were determined using a quantitative rapid test immediately before drug infusion. Disease activity indices (MAYO/HBI), endoscopic scores (MAYO/SES-CD) were obtained. QoL was assessed using the Inflammatory Bowel Disease Questionnaire (IBDq). The study was approved by the Institutional Review Board and informed consent was obtained from all patients.

Results: Seventy-one consecutive subjects were included in the study (59 with Crohn's disease and 17 with ulcerative colitis). Drug levels were considered satisfactory ($TL \geq 3 \mu\text{g/mL}$) in 29 patients (39.4%) and unsatisfactory ($TL < 3 \mu\text{g/mL}$) in 43 (60.6%). Satisfactory TL were associated with higher rates of clinical remission (85.7% x 27.9%, $p < 0.001$) and mucosal healing (85.7% x 18.6%, $p < 0.001$). Higher TL were also associated with improved IBDQ scores (183 ± 32 x 161 ± 28 , $p = 0.006$), particularly regarding bowel symptoms (59.6 ± 9.3 x 52.3 ± 8.5 , $p = 0.001$), systemic function (27.3 ± 5.6 x 22.7 ± 5.2 , $p = 0.001$) and social function (30.8 ± 5.7 x 26.7 ± 7.4 , $p = 0.015$).

Conclusions: Satisfactory IFX levels were associated with higher rates of CR, MH and improved QoL in IBD patients on maintenance therapy.

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Biosimilar infliximab in real-life Crohn's disease treatment in anti-TNF-alpha naïve and non-naïve patients in comparison to biologic originator: a comparative observational cohort study

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Background: Recently we have shown, that biosimilar infliximab (I) in the treatment of Crohn's disease (CD) patients, is equivalent to biologic originator (R) in terms of efficacy and safety. However data comparing response in anti-TNF naïve and non-naïve patients with CD are still limited and controversial.

The aim of the study was to assess the efficacy, tolerability, and safety of biosimilar infliximab in comparison to biologics originator in anti-TNF-alpha naïve and switch CD patients.

Methods: This was a retrospective, one center study enrolled a cohort of 168 consecutive adult CD patients. The patients received either R (73) or I (95) on the basis of the same inclusion criteria (CDAI > 300 or active perianal fistula). According to local national regulations, treatment was stopped after one year. Assessments included treatment-emergent adverse events (TEAEs) and disease-specific clinical response and remission after induction therapy, one year of treatment and during 12 months of follow-up.

Results: Both group were comparable according to age, sex, duration and type of disease, concomitant medications and smoking. 47 patients from R group and 68 from I were anti-TNF-alpha naïve. We did not observe differences between anti-TNF-alpha naïve and non-naïve patients in respect to clinical response and remission rate after induction and 1 year of treatment (R – 80.9% vs. 73.1% respectively; I – 79.4% vs. 74.1%). The relapse rate during 1 year follow-up was significantly higher in anti-TNF non-naïve patients

($p < 0.001$) in comparison to naïve, however with no significant differences between R and I groups. TEAEs were mostly mild-moderate in severity and occurred more often in anti-TNF non-naïve patients, with no difference between R and I group (13.33% vs 17.65%). Surprisingly in anti-TNF naïve patients we observed higher rate of TEAEs in I group in comparison to R (8.11% vs 1.92%), however this difference did not reached statistical significance.

Conclusions: Positive outcomes for response/remission in both groups were reported regardless of whether patients had received prior infliximab or not. Biosimilar infliximab was well tolerated and efficacious in both groups. Further study for immunogenicity and interchangeability with long-term follow-up periods are needed to confidently integrate biosimilars into IBD treatment.

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Supra-therapeutic infliximab levels are not associated with a higher risk of infection in IBD patients

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Background: Anti-TNF agents are associated with an increased risk

of infection. Data evaluating the relationship between infliximab (IFX) concentration and toxicity are limited. The aim of this study was to evaluate the frequency of adverse events (AEs) in IBD patients with supra-therapeutic (ST) IFX levels compared to those with “normal” range (NR) levels.

Methods: We performed a retrospective analysis of 180 patients with at least one measurement of serum IFX using a homogenous mobility shift assay (HMSA) assay (Prometheus Laboratories) from November 2012 through June 2016. The cohort was divided according to an IFX level cut-off of 15 µg/ml (ST and NR levels). Frequencies of AEs including infections, skin manifestations and infusion reactions were compared between the 2 groups. A similar analysis was performed after dividing the patient cohort into 3 subgroups according to levels ($< 8/8-20/ > 20$). An “intra-individual” case series analysis was also performed comparing infection rates in patients with 2 reported levels, one in each range (NR and ST). Multivariate logistic regression was applied to assess factors associated with an increased risk for infection

Results: Patients with ST levels did not have an increased rate of infections in comparison to patients with NR levels (12% vs 19%; $p=0.3$). Serious infections, opportunistic infections and skin manifestations were also similar between the 2 groups. Using the 3 subgroups determined by levels, infection rates were still comparable. Total AEs and infusion reactions were found to be significantly more common in the NR cohort (42% vs 21%; $p < 0.01$ and 10% vs 1%; $p < 0.01$, respectively). For the “intra-individual” analysis with

Abstract P426 – Table 1. Demographic and clinical characteristics of patients with IFX levels lesser or greater than 15 µg/ml

	IFX <15 (n=90)	IFX >15 (n=90)	P value
Female, n (%)	44(49)	42(51)	0.88
Age at measure of level (y), Median(IQR)	31.5 (40-22.25)	26 (30.75-21)	$p < 0.01$
Age at diagnosis(y), Median(IQR)	21 (29-15)	17(23-13)	$p=0.01$
Disease duration (y), Median(IQR)	9.5 (13-5)	7 (11-4)	$p=0.01$
IBD subgroups			
CD	53 (59)	49(54)	0.65
UC	30(33)	33(37)	0.75
IBDU	7(8)	8(9)	1
CD location (Montreal classification, n (%))			
ileal (L1)	15(28)	12(24.5)	0.65
colonic (L2)	11(21)	12(24.5)	0.99
ileo-colonic (L3)	27(51)	25(51)	0.84
Perianal (p)	20(38)	25(51)	0.43
CD phenotype (Montreal classification), n (%)			
Inflammatory B1	20(38)	20(41)	1
Stricturing B2	21(40)	18(37)	0.68
Penetrating B3	12(22)	11(22)	0.99
Prior surgery for CD, n (%)	21(40)	14(29)	0.21
UC extent, n (%)			
Distal colitis (E1)	2(7)	2(6)	1
Left-sided colitis (E2)	6(20)	6(18)	0.76
Pancolitis (E3)	22(73)	25(76)	0.53
Prior colectomy, n (%)	1(3)	1(3)	1
Smoker status, n (%)			
Non smoker	81(90)	83(92)	0.8
Current Smoker	9(10)	7(8)	0.79
Extra-intestinal manifestation	45(50)	32(36)	0.21
Family history of IBD	24(27)	27(30)	0.74
Previous immunosuppressant, n (%)	79(88)	74(82)	0.4
Previous Anti-TNF's	6(7)	10(11)	0.43
Concomitant immunosuppressant, n (%)	21(23)	32(36)	0.1
Concomitant steroids	10(11)	15(17)	0.38
Disease status, n (%)			
Clinical remission	29(38.6)	60(75)	< 0.01
Endoscopic remission	20(36)	26(52)	0.11
Elevated CRP (>5 mg/L)	21(26)	22 (29)	0.72
CRP (mg/ml), Median(IQR)	1.9(5.17-0.8)	2(6.1-0.8)	0.7
IFX concentrations (µg \ml), Median(IQR)	4.4(7.9-0)	34(34-22.4)	< 0.01
Anti-drug antibodies, n(%)	21(23.3)	1(1)	< 0.01

2 measured levels in the same subject, higher levels were not associated with an increased risk of infection. Disease activity, concomitant immunosuppression and steroids were not significantly associated with rates of infection.

Table 2. Adverse effects in patient with lesser and greater levels than 15 µg/ml

n=47, %	IFX < 15	IFX > 15	P value
Adverse effects, n(%)	38(42)	19(21)	p<0.01
Serious adverse effects, n(%)	3(8)	3(8)	p=1.0
Infections, n(%)	17(19)	11(12)	p=0.3
Skin manifestations, n(%)	2(2)	3(3)	p=1.0
Infusion reactions, n(%)	10(11)	1(1)	p<0.01
Other, n(%)	5(17)	2(12)	p=0.44

Conclusions: This is the first study to directly compare rates of infection in IBD patients exposed to high and NR levels of IFX. Higher IFX serum concentrations were not associated with higher rates of infections, even in patients exposed to very high levels. Clinicians and patients should be aware of the risks of AEs with IFX therapy but higher levels do not appear to be associated with a higher than expected rate of adverse events.

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Neutrophil-to-lymphocyte ration in ulcerative colitis predicts sustained response to infliximab

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Background: Neutrophil-to-lymphocyte ratio (NLR) has been used to determine the outcome in malignancies and coronary heart disease. However, the predictive value of the NLR as a prognostic marker in patients with ulcerative colitis (UC) has not been reported. This study aimed to evaluate the clinical significance of the baseline NLR in patients with UC treated by infliximab.

Methods: Patients with moderate-to-severe active UC who received the first infliximab infusion in our hospital between 2010 and 2015, who showed clinical response during the induction period, were retrospectively evaluated for long-term outcomes and risk factors for loss of response (LOR) during infliximab maintenance therapy. LOR was defined by recurrence of the patients' symptoms during follow-up. Baseline inflammatory markers including NLR were measured within one week before the initiation of infliximab. LOR-free survival was analyzed using the Kaplan-Meier method and Cox regression model.

Results: Fifty-nine patients with moderate-to-severe active UC started treatment with infliximab and 37 patients (62.7%) experienced clinical response after induction therapy. Fourteen of 37 patients on maintenance therapy lost the response during follow-up. Baseline NLR of patients with LOR was significantly higher than in patients with sustained response. The NLR cut-off value of 4.488 was predictive of LOR, using receiver operating characteristic analysis (sensitivity: 78.6%, specificity: 78.3%). A univariate analysis revealed a significant relationship between relapse-free survival and the NLR (p=0.018). Multivariate analysis indicated the NLR as an independent prognostic factor for LOR (hazard ratio =3.86, 95% confidence interval: 1.20–12.4, p=0.023).

Conclusions: Baseline NLR in moderate to severe active UC predicts

sustained response to infliximab, and may contribute to appropriate clinical management.

P428

Optimizing thiopurines in Crohn's disease: low dose and low 6-TGN level are effective for maintenance of remission in Asian population

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Background: Lower dose of azathioprine (AZA) was suggested in Asian patients with Crohn's disease (CD). However, there was still no recommended dose and 6-TGN level for this population. Our aim was to identify AZA dose and 6-TGN level associated with maintenance of remission in Chinese patients with CD, and to evaluate the putative gain in remission rate by incremental increases in AZA dose and 6-TGN level.

Methods: This was a retrospective cohort study of 349 events with CD who used AZA for maintenance of remission CD in a tertiary referral center. The primary endpoint was disease relapse. AZA dose and 6-TGN level were compared in remission group and relapse group. Remission rate was compared across the increased dose range and 6-TGN level.

Results: 124 (35.5%) out of 349 events underwent relapse at a median follow-up of 14.2±13.7 months. The AZA dose was higher in remission group compared with that in relapse group (1.63±0.48 mg/kg vs. 1.40±0.53; p=0.000). The association between dose of AZA and rate of remission reached a plateau at 1.5 mg/kg/d, whereas increasing dose of AZA beyond 180 pmol/8×10⁸ RBC produced negligible gain in rate of remission. Frequency of adverse events significantly increased in patients with 6-TGN level >355 pmol/8×10⁸ RBC (8.0% with 6-TGN>355 pmol/8×10⁸ RBC vs. 2.7% with 6-TGN<355 pmol/8×10⁸ RBC, p=0.035).

Conclusions: Lower dose of AZA and lower level of 6-TGN were required for maintenance of remission for Chinese CD patients. We proposed that 6-TGN level of 180–355 pmol/8×10⁸ RBC is adequate for maintenance of remission in 75.3% of Chinese patients with CD, and this could be considered as a "therapeutic window". Exceeding this level could not produce gain in remission rate but adverse events rate.

P429

Mucosal healing after 3 months of conventional IBD treatment: real life data

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Background: Mucosal healing has become a primary target in the treatment of inflammatory bowel disease (IBD), as it is associated with an improved disease course. However, real life data concerning mucosal healing after conventional treatment are scarce.

Methods: Our aim was to assess the rate of mucosal healing and clin-

ical remission after 3 months of conventional treatment in a cohort of newly diagnosed IBD patients.

171 patients with ulcerative colitis [UC; N=123 (72%)] or Crohn's disease [CD; N=48 (28%)] aged 16 years and above, were consecutively included in a prospective study.

Demographic data, medication, Partial Mayo Score (PMS) for UC or Harvey Bradshaw Index (HBI) for CD, fecal calprotectin and CRP were obtained, and colonoscopy performed at baseline and after 3 months of conventional treatment. Inflammatory activity was assessed according to the Mayo Endoscopic Score (MES-UC) for UC and the Simple Endoscopic Score (SES-CD) for CD. Baseline data are given in Table 1.

Table 1 Baseline characteristics		
Variable	UC	CD
Patients, No.	123	48
Male gender, No.	71	23
Age (years)	37 (16–73)	34 (16–78)
CRP (mg/L)	6.4 (1.0–117.0)	7.9 (1.0–139.0)
Fecal calprotectin (mg/kg)	620 (21–5466)	160 (15–4432)
PMS / HBI	5 (0–9)	5 (0–16)
MES-UC / SES-CD	2 (1–9)	7 (1–37)
Disease distribution, No.		
Rectum	29	
Left sided colon	36	
Extensive / Total colon	57	
Ileum		22
Colon		8
Ileocolon		18
Medication, No.		
5-ASA		
oral only	49 (39.8 %)	
topical only	13 (10.6 %)	
oral and topical	61 (49.6 %)	
Corticosteroids	50 (40.7)	32 (66.7 %)
Antibiotics	17 (7.6 %)	10 (20.8 %)
Immunomodulators	2 (1.6 %)	12 (25 %)
Abbreviations: PMS, Partial Mayo Score; HBI, Harvey Bradshaw Index; MES-UC, Mayo Endoscopic Score; SES-CD, Simple Endoscopic Score for Crohn's Disease; 5-ASA, 5-aminosalicylic acid. Values are absolute numbers or medians (ranges).		

Mucosal healing was defined as MES-UC \leq 1 or SES-CD \leq 2, clinical remission as PMS \leq 2 or HBI $<$ 5.

Results: Mucosal healing was achieved by 101 (59%) and clinical remission by 100 (58%) of all patients, whereas 74 (43%) reached a combined endpoint of mucosal healing and clinical remission (Figure 1A).

Eighty-six (70%) UC patients achieved mucosal healing, 68 (55%) clinical remission and 60 (49%) combined mucosal healing and clinical remission (Figure 1B). Median PMS was reduced from 5 to 1 ($p < 0.001$), CRP from 6.4 to 1.9 mg/L ($p < 0.001$) and f-calprotectin from 620 to 67 mg/kg ($p < 0.001$).

Fifteen CD patients (31%) achieved mucosal healing, 32 (67%) clinical remission and 14 (29%) combined mucosal healing and clinical remission (Figure 1C).

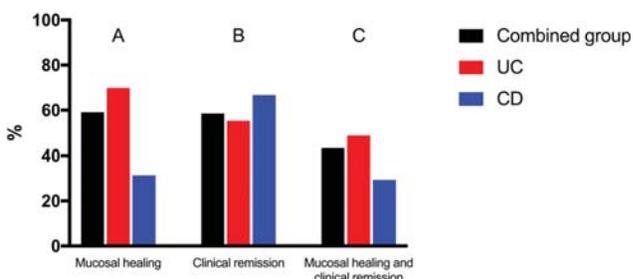


Figure 1. Outcomes.

Median HBI was reduced from 5 to 3 ($p = 0.01$), CRP from 7.9 to 4.1 mg/L ($p = 0.002$) and f-calprotectin from 160 to 38 mg/kg ($p < 0.001$).

The mucosal healing rate was higher in UC than in CD patients ($p < 0.001$); no difference in clinical remission was observed ($p = 0.18$). **Conclusions:** Nearly 60% of newly diagnosed IBD patients achieved mucosal healing as well as clinical remission following three months of conventional treatment in a real life setting. Mucosal healing rate was significantly higher in UC than in CD patients. Conventional treatment appears effective for mucosal healing in UC patients.

P430

EirSwitch echoes of NorSwitch: switching biosimilar therapy in an IBD cohort an Irish experience

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Background: A Biosimilar therapy CT-P13 (Celltrion, Korea; Pinewood Healthcare Ireland) was licenced in Ireland in 2013 for treatment of IBD patients. A Physician-led protocol was adopted in our Institution to switch all IBD patients receiving Infliximab (Remicade) Starting Jan 2015. The Nor-Switch study (UEG 2016) data has confirmed the safety profile and clinical effectiveness of biosimilar infliximab (Remsima). We present our 12-month Outcome Data, the first from Ireland, from a single Institution in a Private Practice Insurance reimbursed setting

Methods: All IBD patients attending our Infusion centre for Remicade were approached over a two-month period for approval to switch to the biosimilar infliximab (Remsima). All patients were subsequently switched to biosimilar infliximab (Remsima) at their next clinic visit. Data was collected over the next 12 months for the primary end-point loss of response to therapy. Data was also collected on development of antibodies and adverse reactions and surgical events.

Results: Prior to switch date 52 IBD patients received Infliximab (median duration of therapy 23 months, range (2–76 months). 74% patients maintained a long-term response to Infliximab.

33 IBD patients were therefore switched to biosimilar infliximab (Remsima) (15 CDS) - 85% remain on Biosimilar at 1 yr. 2 patients were switched during induction phase (both UC); 1 remains on biosimilar infliximab (Remsima) and 1 switched to Humira due to Antibody development. 11 patients were switched within 12 months of commencement of Infliximab therapy (10 UC); 73% (8 patients) remain on biosimilar infliximab (Remsima) at 1 year; 3 stopped due to development of antibodies (switched therapy – 1 Humira; 1 Entyvio; 1 discontinued therapy). 22 Patients were switched following more than 12 months of therapy with Remicade; 91% (20 patients) remain on therapy at 12 months; 2 stopped and subsequently switched to Humira (1 adverse side effect, 1 Antibody positive).

Conclusions: We have confirmed the recently published Nor-switch study outcomes in our small cohort of patients. Our Data confirms the safety and clinical effectiveness of the Biosimilar Remsima in an Irish setting compared to Remicade. In addition, we have confirmed the effectiveness of the Biosimilar Remsima in maintaining remission in a cohort patients previously treated with Remicade.

References:

[1] Jørgensen K et al. (2016), LB15 – Biosimilar infliximab (CT-P13) is not inferior to originator infliximab: results from the 52-week randomized NOR-SWITCH trial. Abstract presented at the United European Gastroenterology (UEG) Week meeting 2016, 15–19 October, Vienna, Austria.

P431 Colonic Treg levels are reduced in patients with ulcerative colitis achieving clinical remission, but are not differentially affected by etrolizumab dose

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Background: Etrolizumab, an anti- $\beta 7$ mAb targeting integrins $\alpha 4\beta 7$ and $\alpha E\beta 7$, showed efficacy and safety compared with placebo (PBO) at induction in patients (pts) with moderate-to-severe ulcerative colitis (UC) in the phase 2 EUCALYPTUS trial. The percentage of pts achieving clinical remission was numerically lower with the higher dose of etrolizumab compared with the lower dose, which has been hypothesized to be due to dose-related inhibition of regulatory T-cell (Treg) migration to the colon. Using an epigenetic approach, we showed that etrolizumab treatment increased blood levels of CD3⁺ T cells and Tregs, compared with PBO (Fuh F et al. UEGW 2015). Here, we use the same approach to evaluate changes in cellular composition in colonic biopsies to explore the effect of etrolizumab dose on leukocyte infiltrate in the gut.

Methods: Epigenetic analyses were conducted in colonic biopsies taken from 60 EUCALYPTUS (Vermeire et al. *Lancet* 2015) pts treated with etrolizumab 100 mg (n=23), 300 mg + loading dose (n=18) or PBO (n=19). Samples were collected at screening, wk 6 and wk 10 post-dose. Relative percentages of T cells, B cells, neutrophils/granulocytes, and those committed to Treg or Th17 lineages were assessed by measuring epigenetic activation (demethylation) of respective gene loci. Epigenetic modification of a cell-lineage specific DNA CpG motif was detected using a demethylation-specific qPCR analysis that quantifies active loci. Data are expressed as percentages of total GAPDH positive cells. Results were cross-validated with matched immunohistochemical and qPCR data.

Results: There were no significant changes from baseline in colonic Tregs, CD3⁺ T cells, Th17 cells, neutrophils/granulocytes, or B cells at wk 6 or wk 10 following treatment with etrolizumab or PBO. No significant differences were observed between pts treated with the low and high doses of etrolizumab. However, there was a significant reduction from baseline in colonic Tregs ($p=0.028$) and B cells ($p=0.050$) in etrolizumab-treated remitters at wk 10 (n=6). These reductions were not observed in responders–non-remitters or non-responders regardless of treatment, except for a trending decrease in colonic Tregs in PBO clinical responders at wk 10 (n=7).

Conclusions: Pts treated with etrolizumab 100 mg had similar levels of colonic Tregs at wk 6 and wk 10 compared to pts treated with etrolizumab 300 mg. However, etrolizumab-treated remitters at wk 10 showed a significant reduction in Treg levels, suggesting that

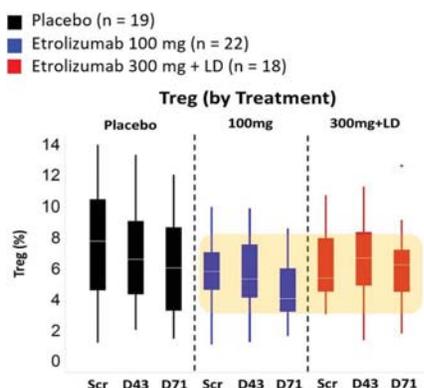


Figure 1

decreases in colonic Tregs may be associated with improvements in disease activity.

P432 Therapeutic approaches for perianal fistula in paediatric and adolescent onset Crohn's disease – a multicentre cohort study

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Background: There is no clear consensus on the management of Crohn's disease related perianal fistulae (CD-PAF) in paediatric and adolescent onset CD due to paucity of data on management approaches. We aimed to evaluate therapeutic interventions and their efficacy in a multicentre cohort with paediatric and adolescent onset CD-PAF.

Methods: 7 centres in Europe participated in the study. Patients with paediatric and adolescent onset CD-PAF diagnosed since 2010 with followup of at least 6 months since onset of CD-PAF were included. Patients with non-fistulising perianal CD and those with rectovaginal or recto-vesical fistulas were excluded. Data were collected on demographics, clinical variables, pelvic MRI and surgical interventions. Complete clinical fistula healing was defined as the absence of any draining fistulas on clinical examination. Reinterventions were defined as the need for repeat abscess drainage, seton reinsertion, diverting stoma or proctectomy. Univariate and multivariate analysis was done for predictors of fistula healing and reintervention.

Results: 116 patients were included (74 boys and 42 girls). The mean age at diagnosis of fistula was 12.9 years. MRI was done in 85 of the patients with complex fistula in 57 (67%). Proctitis was evident at presentation in 33%. 55% had an abscess drainage but only 17 having a seton inserted. After onset of CD-PAF there was significant increase in the use of biologics (13.7% before and 83% after) and immunosuppressant (29% before and 80% after). Antibiotics were used 67% of the patients with median number of courses being 4 (range 1–8). Clinical fistula healing data was available in 78 patients of which 55 had complete and 18 had partial healing. There was significant difference in healing based on type of fistula (simple fistula 78%, complex fistula 26%, $p=0.001$). Follow up MRI scan (n=40) demonstrated partial healing in 29 and but complete healing in only 6 patients. Anti TNFs were continued in majority (86) of the patients. In the 10 patients stopping anti TNFs (6 – planned withdrawal, 4 – patient preference), 7 had recurrence of perianal fistula. Repeat surgical intervention was required only in 16% of the patients (repeat EUA and abscess drainage – 9, diverting stoma = 3 and reinsertion of seton = 2). Complex fistula type ($p=0.015$), those with proctitis ($p=0.04$) and those needing abscess drainage ($p=0.02$) were more likely to need reintervention and patients with anti TNF therapy (0.01) less likely to need repeat surgery.

Conclusions: Perianal fistula in paediatric onset CD is managed with combined medical and surgical management in majority of patients. Significant proportion of patients had complete or partial clinical

healing. Repeat surgical intervention in CD-PAF is only required in 16% of the patients.

P433

Postsurgical recurrence in Crohn's disease. Multicenter study in the region of Murcia, Spain of GEMELL group

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Background: Postsurgical recurrence in Crohn's disease is a frequent problem. Severity of endoscopic recurrence, correlates with the later development of clinical recurrence, its severity and also with complications and requirement of new surgery. The objective of the present study is to describe the characteristics of Crohn's disease patients included, determining associated presurgical parameters with the intervention, and characteristics associated with the postsurgical recurrence of the disease, evaluating the endoscopic recurrence through the Rutgeerts Index in the 12 months after the surgery.

Methods: Multicenter retrospective longitudinal study in the Region of Murcia in Spain. 6 hospitals participated. Includes patients of Ileocecal Crohn's disease during 5 years, from January of 2008 to January of 2013. Variables: sociodemographics, tobacco, Montreal classification, disease severity, treatment prior to intervention and after surgery, cause of intervention, endoscopic control during the year of the intervention and need of therapeutic intensification based on the endoscopic activity after surgery. Statistical analysis by means of Epiinfo program: bivariate analysis of association between the different variables gathered and variable results defined by the necessity of surgery, the postsurgical recurrence and the response to the medical treatment after the surgery.

Results: 71 patients: (49 men and 22 women) with average age of 35.8 years (DS: 13.2). Inflammatory phenotype 27%, fibro-estenotic 24% and fistulizing 49%. Smokers to diagnosis 49%. Rutgeerts endoscopic index at the year of surgery: 75% i0-i1; 25% superior to i1. In the bivariate analysis the positive findings for association were: presurgical corticoid dependence and presence of endoscopic activity at the year of the surgery (Rutgeerts >i0) with OR=3.24 (CI 1.04-10.07); previous biological treatment to Surgery: with Infliximab and Rutgeerts recurrence >i0 with OR=5.9583 (CI 1.5707-22.6018). With Adalimumab OR=3.8462 (CI 1.0849-13.6350). Association between sex, age, phenotypic pattern (Montreal), tobacco or cause of surgery with endoscopic recurrence to the year of surgery has not been obtained.

Table 1. Bivariate analysis

Bivariate analysis: positive association findings	OR (95% CI)
Infliximab treatment prior surgery + postsurgical endoscopic recurrence Rutgeerts index >i0	5.9583 (1.5707-22.6018)
Adalimumab treatment prior surgery + postsurgical endoscopic recurrence Rutgeerts index >i0	3.8462 (1.0849-13.6350)
Corticoid dependence prior surgery + postsurgical endoscopic recurrence Rutgeerts index >i0	3.24 (1.04-10.07)

Conclusions: Only 25% of our patients presented index of endoscopic recurrence to the year of the surgery of high risk of progression (i2-i4 of Rutgeerts). In our environment, the biological treatment and corticoid dependence previous to the surgery are associated with endoscopic activity in the year of the surgical intervention.

P434

Joint Inflammatory Bowel Disease-Obstetric clinics: outcomes in 95 pregnancies at a tertiary centre over a 3-year period

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Background: Management of pregnant patients with inflammatory bowel disease (IBD) can be complex, requiring joint specialist multidisciplinary clinical knowledge and skills. To this end, a joint IBD-Obstetric clinic was started in May 2013. The aim of this study was to identify the benefits of a joint service in improving adherence to ECCO guidelines and pregnancy outcomes.

Methods: Retrospective review of records to obtain: patient demographics, clinic attendance, disease parameters, drug, surgical and obstetric history, investigations, treatment changes, mode of delivery and birth weight over a period of 3 years from May 2013 till May 2016.

Results: A total of 95 pregnancies in 89 women (mean age 31, age range 19-43) were identified. 39 women had Crohn's disease, 49 ulcerative colitis and 1 IBD-unclassified. 37 women were on 5ASA, 20 Azathioprine, 5 Infliximab, 4 Adalimumab and 2 on combination Azathioprine-Anti-TNF-Ab. Treatments started or reinstated during pregnancy: 25 prednisolone, 16 5ASA and 30 topical therapy in keeping with ECCO Statement 5C. No women were started on anti-TNF Ab but two women had an increase in Adalimumab dose. 5/6 women had infliximab till week 25 in accordance with ECCO Statement 5D. 93% women were well pre-conception and 49% had no flare during the pregnancy. Delivery: 31 women had an elective section, 17 an emergency section and 7 instrumental deliveries. The commonest indication for elective and emergency sections were maternal choice and pathological CTGs. 8 deliveries were preterm (32-36 weeks), 2 spontaneous, 6 planned. There were 5 births that were small for gestational age, 1 stillbirth and 2 cardiac congenital anomalies in this cohort, which is not statistically different from a recent large Australian population study by Shand et al. Haemoglobin, platelets, albumin and C-reactive protein were not predictive of preterm delivery or stillbirth. Most women were seen at least three times during the pregnancy, co-ordinating clinic appointments with scans at 20, 28 and 32 weeks, with an average of 100 appointments per year and a rising trend with time. Investigations: 9 women had small bowel ultrasound performed by a single experienced Radiologist, 4 non-gadolinium pelvic/small bowel MRIs and 2 sigmoidoscopies. All 15 investigations aided management decisions.

Conclusions: This study shows that an experienced joint IBD-Obstetric service improves adherence to ECCO guidelines with outcomes that compare favourably to existing published data of IBD care in pregnant patients.

P435 The mean corpuscular volume flow – prognostic value for inflammatory bowel disease under thiopurine treatment

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Background: The difficult access to thiopurine metabolites therapeutic drug monitoring led to the search for accessible markers to estimate thiopurine's efficacy. The difference in mean corpuscular volume (Δ MCV) ≥ 7 fL at week 26 of azathioprine monotherapy (Aza) or combined with infliximab (AzaI) was shown to be associated with favourable outcomes in Inflammatory Bowel Disease (IBD). Objective: To confirm the association of Δ MCV ≥ 7 at week 26–28 with favourable outcomes in IBD in a Portuguese population.

Methods: Retrospective assessment of patients with IBD under Aza or AzaI at time-point: Week 26–28 of treatment. Demographic characterization and severity of pre-treatment disease was evaluated (location, previous surgery status, Mayo score and Crohn's disease activity index [CDAI]). Quantification of Δ MCV and association with time-point outcomes: Steroid-free clinical remission (Rem-sf, CDAI < 150 , Mayo < 2); mucosal healing (MH); C-reactive protein (CRP) normalization < 5 . Patients with vitamin B12 deficiency were not included. Statistic: Chi-square test or Fisher exact test.

Results: A total of 122 patients with IBD were evaluated [(71 Crohn's disease, 28% operated); 57.4% women; mean age 40 ± 15.6 years] at week 26–28 of treatment with Aza (86.9%) or AzaI (13.1%).

In both treatment groups the mean Δ MCV was ≥ 7 (Aza 7.9 vs. AzaI 8.1) and this was achieved in the same proportion of patients (66 vs. 62.5%). There was a strong association between Δ MCV ≥ 7 and remission outcomes (Rem-sf: $p < 0.05$; CDAI < 150 /Mayo < 2 : $p < 0.001$) and MH ($p < 0.05$), but not with CRP normalization. However, CRP ≤ 10 was related to remission outcomes (Rem-sf: $p < 0.05$; CDAI < 150 /Mayo < 2 : $p < 0.001$) and MH ($p = 0.004$).

Conclusions: This work confirmed the prognostic importance of Δ MCV ≥ 7 in our population. The correlation of Δ MCV ≥ 7 with clinical remission and mucosal healing outcomes occurred in Crohn's disease and Ulcerative Colitis and was independent of the anti-TNF association.

P436 Secondary loss of response to anti-TNF in inflammatory bowel diseases. Therapeutic drug monitoring. Utility in clinical practice

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Background: Secondary loss of response (LOR) occurs in 23–46% when determined according to dose intensification. Intensification of treatment is effective in about 60–90% of the cases and switching to non anti-TNF drugs in 19–68%. Immunogenicity is not the only factor affecting anti-TNF drug clearance and efficacy. The assessment of disease activity by measuring the seric levels of anti-TNF drug levels facilitates rational decisions on management of LOR.

Methods: Restrospective study in our institution in patients with ulcerative colitis (UC) or Crohn's disease (CD) with LOR and thera-

peutic drug monitoring from february 2015 to september 2016. The measurement of anti-TNF drug levels and anti-drugs antibodies (ADAS) levels was performed with ELISA assays drug concentration. The cut-off for drug levels in therapeutic range was 3–5 ug/mL for infliximab and 5–8 ug/mL for adalimumab.

Results: A total of 42 patients were included, 32 with CD (76%) with Harvey-Bradshaw Index (HBI) > 4 points and 10 patients with UC with Partial Mayo Score (PMS) > 2 points with increase in C-reactive protein (PCR) or fecal calprotectin. 18 patients underwent in treatment with infliximab and 24 with adalimumab. The average time of evolution of disease was 12.6 ± 8.77 years. The average time under biological treatment was 55.92 ± 30.6 months. 38% had previously received another biological drug, 52% had previous intensifications and 58% received concomitant immunomodulators. 24% of patients presented levels in therapeutic range, 40% had low drug levels and absence of anti drugs antibodies (ADAS-), 10% had undetectable drug levels and positive anti drug antibodies (ADAS+), 26% of patients had high drugs level. The therapeutic strategy chosen for each group was: 15% of patients no change in treatment, 44% increase anti-TNF dose or decrease infusion interval (intensification), 10% switch to another anti-TNF drug, 24% switch to non anti-TNF. The clinical response (decrease of the PMS for UC ≥ 3 points and decrease of HBI ≥ 3 points for CD) was reached in 42.8% of patients and remission (PMS ≤ 2 for CU and HBI ≤ 4 for CD) in 57% at the end of follow-up. The baseline CRP was associated with a baseline mean CRP of 4.12 ± 4.98 mg/L ($p = 0.018$). A HBI > 8 and a PMS > 8 allowed to identify low drug levels with accuracy AUC = 0.689 and 0.88 ($p < 0.0001$) respectively.

Conclusions: Patients with LOR frequently had low drug levels and negative anti-drug antibodies. Intensification treatment sought to be effective despite the high number of patients who previously needed an increase in the dose of their anti-TNF treatment. 26% of patients needed to switch to non anti-TNF and, in these patients, monitoring anti-TNF, drug levels might allow to change the drug prescribed in order to avoid non-effective treatments.

P437 Autologous hematopoietic stem cell transplantation for refractory Crohn's disease: predictive factors of relapse

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Background: Autologous hematopoietic stem cell transplantation (HSCT) is considered as an option for patients with severe refractory Crohn's disease (CD). Although $> 80\%$ of patients achieve remission early after HSCT, a proportion of relapses occur over time. The aim of the study was to establish predictive factors of relapse after HSCT. **Methods:** Patients with refractory CD were prospectively enrolled between 2007–2016. Patients underwent monthly evaluations of clinical status and biomarkers. Endoscopic and/or magnetic resonance (MR) were performed at years 0.5, 1, 2 and 4, or when relapse was clinically suspected. Relapse was defined by presence of ulcers

at endoscopy and/or MR. Variables analyzed included demographic factors, disease characteristics, and transplant related events. Univariate analysis was used to explore statistically relevant variables. The best predictive models were obtained by using a model for all possible equations.

Results: Thirty patients were included (70% F, mean age 28.6) with a median follow up (FU) of 80 weeks (27/30 patients with at least one year of FU). Relapse occurred in 19/30 patients (63%), 12 of them during the first year after HSCT. Variables with statistical significance at univariate analysis for relapse during the first year were: perianal disease ($p=0.01$), Erythrocyte Sedimentation Rate (ESR) ($p=0.04$) and C-Reactive Protein ($p=0.05$). The univariate analysis considering 5 years of FU included: albumin ($p=0.01$), ESR ($p=0.01$), number of days of neutropenia after conditioning ($p=0.01$) and perianal disease ($p=0.05$). The table shows the best predictive models for relapse

Table 1. Best predictive models for relapse.

One year after HSCT	Perianal disease	OR 18.30, SE 28.9
	Days neutropenia after conditioning	OR 0.50, SE 0.2
	SES-CD	OR 1.15, SE 0.1
	Disease location	
	Ileal ± upper (reference category)	
	Ileocolonic	OR 0.01, SE 0.02
	Colonic	OR 0.01, SE 0.02
5 years FU	Perianal disease	HR 10.98, SE 8.29
	Days neutropenia after conditioning	HR 0.67, SE 0.10
	Albumin	HR 0.88, SE 0.06
	Prior surgery	HR 0.17, SE 0.16
	Disease location	
	Ileal ± upper (reference category)	
	Ileocolonic	HR 0.05, SE 0.05
Colonic	HR 0.08, SE 0.09	

Conclusions: Patients with perianal disease, ileal and/or upper disease, and short time of neutropenia after conditioning are at higher risk of relapse after HSCT. Early reintroduction of conventional therapy after HSCT should be considered in this subset of patients and explored in future trials.

P438 Adalimumab dose escalation and de-escalation in ulcerative colitis: incidence and predictors of success. A real life Belgian cohort study

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Background: Adalimumab (ADM) is efficacious in inducing and maintaining remission in ulcerative colitis (UC). Randomized trials show dose escalation from 40 mg every other week (EOW) to 40 mg every week (EW) in up to 20–25% within 1 year. Real life data show higher escalation rates and attempts for dose de-escalation in UC have not been described. This study aimed to assess the need for,

the outcome of, and predictors of dose escalation and de-escalation in a large cohort of UC patients (pts) treated with ADM.

Methods: A detailed retrospective chart review was performed on consecutive pts from 10 Belgian centres that initiated ADM treatment for active UC, including pts demographics, disease characteristics, previous and concomitant medication including prior infliximab (IFX) use and the reason for discontinuation. Primary clinical benefit was based on physician global assessment (PGA) and no rectal bleeding at week 10. Success of dose-escalation was defined based on a positive PGA and absence of rectal bleeding on two consecutive visits at least 3 months apart. Persistent use of ADM 40mg EOW for ≥ 6 months after dose de-escalation, defined success of dose de-escalation. Variables associated with a primary clinical benefit of ADM, success of dose escalation and success of dose de-escalation were identified using Cox regression and backward Wald multivariate analysis.

Results: We included 231 pts [67% male, median (IQR) age at diagnosis 30.6 (22.9–44.8) years, median disease duration at start of ADM 5.5 (2.6–11.8) years, 63% previously exposed to infliximab (IFX)]. A primary clinical benefit was achieved in 101 pts (44%) and was less frequent in pts previously failing IFX [37% vs. 50%, OR 0.51 (95% CI 0.28–0.95), $p=0.035$]. 164 pts (71%) needed ADM discontinuation (N=56) or dose escalation (N=129) after a median of 2.8 (1.7–5.1) months (Fig 1). Disease duration < 5 years [1.72 (1.25–2.33), $p=0.001$]; IFX discontinuation for primary non-response or loss of response [1.41 (1.03–1.93), $p=0.032$] and absence of primary clinical benefit [3.33 (2.38–4.76), $p<0.001$] were independently associated with ADM discontinuation or dose escalation. Dose escalation was successful in 77/129 (60%). Only primary response independently predicted successful dose escalation [3.08 (1.46–6.49), $p=0.003$]. Dose de-escalation was attempted in 71% (55/77) and was successful in 80%, but no predictive markers could be identified.

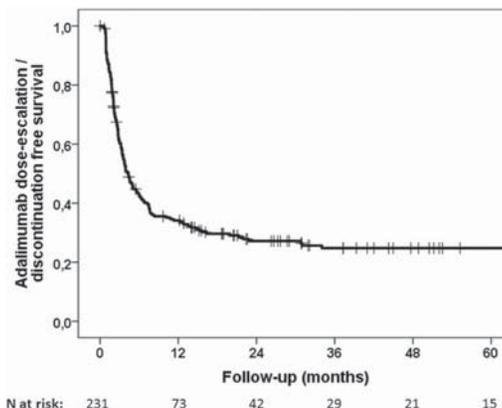


Figure 1. Adalimumab dose-escalation or discontinuation free survival.

Conclusions: ADM is efficacious in UC, but an individualized therapy including dose escalation is often mandatory, being successful in the majority of patients

P439 Diagnosis and management of latent and active tuberculosis in the context of biologic therapy in inflammatory bowel disease

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Background: Anti-TNF treatments have improved the outcomes for

patients with inflammatory bowel disease (IBD). However, they are associated with an increase in risk of Tuberculosis (TB). The aim of this study is to determine the proportion of latent TB infections (LTBI) in our IBD cohort treated with anti-TNFs and the management of these patients. We also examined the effect of different immunosuppressive drugs on the indeterminate rate of the interferon-gamma release assays (IGRA) in LTBI screening

Methods: We conducted a retrospective review of all patients treated with biologics between March 2007 and November 2015. Patient notes and electronic records were reviewed. LTBI screening was assessed using a risk assessment form, chest x-ray, and tuberculin skin test (TST) or IGRA for the screening for LTBI and the nature of the immunosuppressive treatment was documented.

Results: 732 patients with IBD were screened for LTBI before starting a biological treatment during the study period. 31 of 732 (4%) IBD patients were diagnosed and treated for LTBI with no significant side effects. 596 of 732 received their biologic treatment with a median delay of 86 days in initiating biologics. 6 of 596 patients who received biologic treatment developed active TB; 5 of whom were Caucasian.

247 patients were screened with an IGRA test. 6 were positive, 162 were negative and 79 patients were indeterminate. 45% with indeterminate IGRA had a repeat; half were negative and half remained indeterminate.

73% of the patients were receiving immunosuppressive (IMM) medication(s). There was a higher indeterminate rate of the IGRA in the IMM group compared to the no-IMM group (32% compared to 9%). The combination of steroids and thiopurines gave the highest rate of an indeterminate IGRA. High and low doses of steroids were equally likely to result in an indeterminate IGRA result.

Conclusions: 4% of patients screened had LTBI and 1% of patients treated with biologics developed active TB. Delays in initiating biologics due to LTBI screening may have detrimental effects on the IBD management. Almost one third of patients on immunosuppressants had an indeterminate IGRA, which supports the need for a guideline incorporating a risk stratification strategy based on factors such as country of birth and local TB prevalence. There is a need to remain vigilant for TB regardless of baseline LTBI results or epidemiological factors.

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Therapeutic drug monitoring of infliximab for the management of loss of response in inflammatory bowel disease: an observational multicenter study

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Background: Therapeutic drug monitoring (TDM) of infliximab for inflammatory bowel disease (IBD) is being increasingly proposed, particularly for managing the loss of response (LOR), as an alter-

native to empirical dose adjustment. Our aim was to verify in a prospective multicenter cohort the usefulness and cost-effectiveness of applying an algorithm based on TDM, modified from Steenholdt C. et al. 2014.

Methods: We recruited consecutive IBD patients, experiencing a LOR to infliximab while on maintenance therapy from at least 4 months, for which the assay of infliximab trough levels (ITL) and of antibodies to infliximab (ATI) was available for subsequent therapeutic decisions. We compared this cohort with a retrospective one composed of patients for which a serum sample was collected at the time of LOR diagnosis although the clinical decisions were made blinded to ITL and ATI results. We evaluated the clinical outcome after 12 weeks, also in term of direct costs for anti-TNF therapy, verifying the agreement with an algorithm considering a therapeutic ITL cut-off of 3 ug/ml. ITL and ATI were assayed by ELISA technique (Lisa Tracker-Duo[®] Infliximab, Theradiag, Marne-la-Vallée, France).

Results: Ninety-six patients were evaluable in the prospective cohort, and they were compared with 52 retrospectively studied. The two cohorts were similar in characteristics and distribution of TDM results. In the prospective cohort, however, we observed that less optimizations (infliximab dose increase and/or interval decrease) were performed compared to the retrospective one (45% versus 71%, p=0.003). In parallel, more patients were shifted to adalimumab in the prospective cohort than in the retrospective one (25% versus 4%, p=0.001). No difference was detected among the two cohorts in terms of clinical efficacy of the therapeutic modifications: the percentage of patients achieving a clinical response at 12 weeks were 52% and 54%, respectively. However, we estimated a cost saving of up to 98.872 Euros if the algorithm was correctly applied to the retrospective cohort, avoiding unjustified dose optimizations in 28 cases, with a global cost for TDM of 4.160 Euros for the whole retrospective cohort.

Conclusions: In our IBD population, applying TDM for infliximab LOR management resulted in 26% less drug dose optimizations, without loss of efficacy as compared to empirical treatment adjustment. TDM use in LOR management appears to be cost-effective, allowing a more rational use of infliximab without unjustified dose intensification.

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Thalidomide induces clinical remission and mucosal healing in adults with active Crohn's disease: a prospective open-label study

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Background: Thalidomide is effective in inducing clinical remission and longer-term maintenance of remission in children and adolescents with refractory Crohn's disease (CD). However, little is known about efficacy and safety of thalidomide therapy for adult CD patients—particularly with respect to mucosal healing.

Methods: We conducted a prospective observational open-label study (ClinicalTrials.gov, NCT02501291) between January 2013 and April 2015. Forty-seven adult patients with active CD who were resistant or intolerant to corticosteroids and/or immunomodulators or biologics received 50–100mg of thalidomide daily. Primary outcome was clinical remission evaluated at week 8. Endoscopic assessment was performed at week 24 and defined as endoscopic response (decrease in CDEIS score >5 points from baseline CDEIS of 6 or

more), endoscopic remission (CDEIS score <3) and mucosal healing (no ulceration).

Results: The clinical remission rate was 14.9% and 23.4% at week 4 and 8, but increased to 46.8% at week 12 and 53.2% at week 24 out of all 47 included patients (intention-to-treat analysis). Out of the 47 patients, 32 consented and underwent ileocolonoscopy at week 24. The rate of endoscopic response and endoscopic remission were 68.4% and 43.8%. Mucosal healing (no ulceration) was achieved in 28.1% of patients. Adverse events occurred in 27 (57.4%, 27/47) patients but necessitated therapy discontinuation in only 5/47 (10.7%) of patients.

Conclusions: Low-dose thalidomide was effective and tolerated for inducing and maintaining clinical remission in adult patients with active CD, but the optimal time frame for thalidomide to induce clinical remission may be longer than previously appreciated and is probably optimal at 12 weeks. Mucosal healing could be reasonably achievable with thalidomide.

P442
Incidence of pneumonia and other respiratory tract infections with vedolizumab treatment for inflammatory bowel disease: clinical trial experience

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Background: Vedolizumab (VDZ) is a humanised monoclonal antibody that binds to $\alpha_4\beta_7$ integrin and selectively blocks gut-specific lymphocyte trafficking. Although upper respiratory tract infections (URTIs) have been reported with VDZ [1] its gut selectivity may reduce the risk of respiratory tract infections (RTIs), including pneumonia, compared with therapies producing systemic immunosuppression (e.g. anti-tumour necrosis factor-alpha [TNF α] agents). We aimed to determine the incidence of RTIs associated with VDZ treatment in the clinical trial setting.

Methods: Safety data from VDZ phase 3 randomised controlled trials (RCTs) in ulcerative colitis (UC; GEMINI 1) and Crohn’s disease (CD; GEMINI 2) and a phase 3 open-label extension (OLE);

Abstract P442 – Table 1. Incidence of LRTIs and URTIs – number of patients with AEs in the maintenance phase (time-adjusted incidence rate per 100 patient-years)

	GEMINI 1 and GEMINI 2 pooled				Open-label extension	
	VDZ (n=1434)		Placebo (n=297)		VDZ (n=2243)	
	Total patient-years=1058		Total patient-years=171		Total patient-years=5430	
	All*	Serious	All*	Serious	All*	Serious
Any LRTI	79 (7.7)	5 (0.5)	14 (8.5)	1 (0.6)	248 (5.0)	20 (0.4)
Any URTI	339 (38.7)	2 (0.2)	50 (33.0)	0	857 (23.5)	6 (0.1)
AE leading to discontinuation						
LRTI	2 (0.2)	1 (0.1)	0	0	0	0
URTI	1 (0.1)	0	0	0	1 (<0.1)	0
Deaths						
LRTI	0	0	1 (0.6)	1 (0.6) [†]	0	0
URTI	0	0	0	0	0	0
LRTIs						
Bronchitis	57 (5.5)	1 (<0.1)	10 (6.0)	0	170 (3.3)	0
Pneumonia	11 (1.0)	2 (0.2)	2 (1.2)	0	49 (0.9)	18 (0.3)
LRTI	10 (1.0)	1 (<0.1)	1 (0.6)	0	45 (0.8)	0
Lobar pneumonia	0	0	0	0	5 (<0.1)	2 (<0.1)
Bronchopneumonia	1 (<0.1)	0	1 (0.6)	1 (0.6)	1 (<0.1)	0
Lung infection	1 (<0.1)	1 (<0.1)	0	0	1 (<0.1)	0
Pneumonia primary atypical	1 (<0.1)	0	0	0	1 (<0.1)	0
URTIs						
Nasopharyngitis	180 (18.6)	0	21 (12.8)	0	485 (10.9)	1 (<0.1)
URTI	106 (10.5)	0	19 (11.6)	0	298 (6.1)	1 (<0.1)
Sinusitis	44 (4.3)	1 (<0.1)	3 (1.8)	0	194 (3.8)	2 (<0.1)
Pharyngitis	24 (2.3)	0	1 (0.6)	0	65 (1.2)	0
Rhinitis	13 (1.2)	0	4 (2.4)	0	34 (0.6)	0
Tonsillitis	5 (0.5)	1 (<0.1)	0	0	25 (0.5)	0
Laryngitis	3 (0.3)	0	2 (1.2)	0	19 (0.4)	1 (<0.1)
Tracheitis	3 (0.3)	0	1 (0.6)	0	2 (<0.1)	0
Acute sinusitis	2 (0.2)	1 (<0.1)	1 (0.6)	0	8 (0.2)	0
Acute tonsillitis	2 (0.2)	0	1 (0.6)	0	16 (0.3)	0
Chronic sinusitis	2 (0.2)	0	0	0	7 (0.1)	0
Tracheobronchitis	1 (<0.1)	0	0	0	1 (<0.1)	0
Rhinolaryngitis	0	0	1 (0.6)	0	0	0
Sinobronchitis	0	0	0	0	2 (<0.1)	0
Peritonsillar abscess	0	0	0	0	1 (<0.1)	1 (<0.1)
Pharyngotonsillitis	0	0	0	0	1 (<0.1)	0

*Includes serious and non-serious AEs

[†]Patient on placebo died due to bronchopneumonia, which was a serious AE

LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; VDZ, vedolizumab

Abstract P442 – Table 2. Predictors of LRTI AEs in GEMINI 1 and GEMINI 2

Variable	All patients (n=1731)	Patients with LRTI AEs (n=93)	HR (95% CI)	p-value
Female sex, n (%)	827 (48)	59 (63)	1.84 (1.19–2.83)	0.006
Current smoker, n (%) [*]	297 (17)	25 (27)	1.97 (1.17–3.31)	0.011
Prior use of anti-TNF α therapy, n (%)	991 (57)	65 (70)	1.70 (1.06–2.73)	0.028
Former smoker, n (%) [*]	473 (27)	31 (33)	1.74 (1.06–2.87)	0.029
Disease duration ≥ 7 years, n (%)	750 (43)	52 (56)	1.35 (0.88–2.09)	0.173
On-study surgery, n (%)	203 (12)	14 (15.1)	1.65 (0.78–3.49)	0.195
Baseline disease activity, mean score (SD)	5.8 (1.7)	5.9 (1.7)	1.07 (0.95–1.22)	0.278
Concomitant corticosteroid use, n (%) [†]	897 (52)	43 (46)	0.83 (0.55–1.25)	0.382
Concomitant narcotic use, n (%)	463 (27)	28 (30)	0.87 (0.55–1.39)	0.565
VDZ treatment, n (%)	1434 (83)	79 (85)	0.85 (0.48–1.52)	0.585
Concomitant immunomodulator use, n (%) [†]	578 (33)	29 (31)	0.96 (0.62–1.50)	0.862
Age, mean (SD)	37.9 (13)	39.3 (13)	1.00 (0.98–1.02)	0.994

*HR estimates relative to non-smokers

[†]Assessed at baseline

LRTI, lower respiratory tract infection; TNF α , tumour necrosis factor-alpha; VDZ, vedolizumab

C13008 ongoing study in both UC and CD) were used to calculate the incidence of lower RTIs (LRTIs), including pneumonia, and UR-TIs using the MedDRA High Level Terms “lower respiratory tract and lung infections” and “upper respiratory tract infections”. A Cox proportional hazards model was used to identify potential predictors of these AEs for the pooled GEMINI 1 and 2 results.

Results: Of 1731 patients in the pooled RCT population and 2243 patients in the OLE, mean (SD) ages were 37.9 (12.7) years and 39.1 (13.2) years, respectively; 43% and 50%, respectively, had disease duration ≥ 7 years; and 57% and 59%, respectively, had prior anti-TNF α therapy. In the RCTs, the rate of LRTIs, including pneumonia, was similar in the VDZ and placebo groups (Table 1). Rates of LRTIs were higher for VDZ-treated patients with CD than with UC. Most LRTI and URTI AEs were not serious and did not result in treatment discontinuation. Predictors of increased incidence of LRTIs were identified as being a current or former smoker, female sex and prior anti-TNF α therapy (Table 2). Predictors of URTIs were: being a current smoker, concomitant narcotic use and prior anti-TNF α therapy.

Conclusions: In this post hoc analysis, VDZ treatment of IBD was not associated with an increased incidence of LRTIs, including pneumonia, compared with placebo. Continuing pharmacovigilance will supplement these data and ongoing observational studies will further characterise these findings.

References:

- [1] Takeda Pharmaceuticals America, Inc. (2014), ENTYVIO[®] (vedolizumab) Prescribing Information

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Systematic review of internet decision making resources for patients considering surgery for ulcerative colitis

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Background: Accessing health information online is an inevitable consequence of the ever-increasing use of the internet. New guidelines for surgeons in the UK advocate patient use of online resources to assist in decision making [1]. Our aim was to assess the quality of online health resources to facilitate decision making for patients considering surgery or ongoing medical management for ulcerative colitis (UC).

Methods: We undertook a systematic review based on PRISMA guidelines. This was registered on the PROSPERO database. We searched Google and the Decisions Aids Library Inventory using several lay search terms for information about UC and surgery. Exclusion criteria included material not discussing UC or not aimed at patients, online fora and YouTube videos. Quality of content on websites was assessed using the validated DISCERN instrument and a modified International Patient Decision Aid Standards (IPDAS) checklist. Decision aids were assessed by the modified IPDAS checklist. Readability of written content was assessed using the Flesch-Kincaid score.

Results: Our search strategy identified 175 websites and one decision aid for assessment – 119 results were excluded at initial screen and 32 were excluded at full text assessment, leaving 24 websites for re-

DISCERN ratings by website	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1. Are the aims clear?	3	1	1	1	1	1	1	4	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1
2. Does it achieve its aims?	5	1	1	1	1	1	1	4	1	1	1	1	1	5	1	1	1	1	1	1	1	1	1	1
3. Is it relevant?	5	2	2	2	3	3	3	4	3	3	3	3	3	5	2	4	3	2	4	2	4	3	4	2
4. Is it clear what sources of information were used?	1	3	3	2	1	4	4	2	2	1	1	1	3	1	3	1	4	1	1	3	1	3	3	1
5. Is it clear when the information reported was produced?	2	4	4	3	2	4	5	4	3	1	1	1	4	1	2	2	5	1	1	5	1	2	1	1
6. Is it unbiased?	5	5	5	4	4	5	5	5	4	4	3	5	5	5	5	4	4	1	5	4	5	5	4	1
7. Does it provide details of additional support?	5	1	1	3	3	2	1	4	2	1	1	1	1	5	1	1	3	1	2	1	5	4	1	1
8. Does it refer to areas of uncertainty?	2	2	1	2	4	3	3	2	3	2	2	2	1	2	1	3	1	1	2	2	2	3	2	1
9. Does it describe how each treatment works?	5	3	3	3	5	5	5	5	5	3	3	4	4	5	4	3	2	2	4	2	5	4	3	3
10. Does it describe the benefits of each treatment?	2	2	2	2	4	5	3	4	4	2	3	2	2	3	5	3	1	2	3	1	4	3	3	3
11. Does it describe the risk of each treatment?	3	3	3	3	5	5	2	3	3	2	2	2	2	3	3	4	1	1	2	4	4	4	1	1
12. Does it describe happens if no treatment is used?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
13. Does it describe how treatment affects QoL?	5	1	2	3	4	4	2	4	3	2	2	2	2	5	2	4	1	2	2	2	3	4	2	3
14. Is it clear that there may be more than one possible treatment choice?	3	3	3	3	5	4	5	5	4	2	3	4	3	3	5	5	5	2	5	3	5	5	4	1
15. Does it support shared decision making?	3	1	5	1	1	5	2	5	3	2	1	5	1	2	1	1	2	1	3	1	3	3	2	1
16. Overall quality (out of 5)	3	1	1	1	3	5	3	5	3	1	1	1	1	3	1	3	1	1	1	1	3	3	1	1

Abstract P443 – Figure 1. DISCERN domains (scored out of 5) by website analysed at full text.

view. The decision aid scored 9/12 on the IPDAS checklist. This was created by a private company with guidance from a gastroenterologist and GP, but without a surgeons input. Most websites originated from the US (n=17) with the remainder from the UK (n=7). The mean Flesch-Kincaid score was 44.9 (±9.73, range 28.1–61.4), suggesting material was difficult to read. Nine websites (37.5%) discussed both surgical and medical options. No websites compared surgery vs medical management or traded off patient preferences. The mean IPDAS score was 4.63/12 (±1.61, range 1–7). The mean global score based on the DISCERN rating was 2/5 (±1.32, range 1–5), identifying most websites as poor quality. A summary of DISCERN domains by website can be seen in Figure 1.

Conclusions: Only a small number of websites discuss both surgical and medical therapies – with none of these websites trading off patient preferences. Health care professionals should be aware at the lack of online support resources available for those with UC considering surgery. Professional organisations should engage in the production of decision support websites. The development of a new decision aid to support patients considering surgery for UC is recommended.

References:

- [1] Royal College of Surgeons England, (2016), Consent: Supported Decision-Making, <https://www.rcseng.ac.uk/library-and-publications/college-publications/docs/consent-good-practice-guide/>, 2016–11–03

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Does one size truly fit all? Co-prescription of allopurinol and thiopurine therapy results in variation of TGNs outside the therapeutic range in more than half of patients

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Background: Co-prescription of low dose thiopurine with allopurinol is an increasingly used treatment strategy in IBD for patients who experience adverse effects or who have hypermethylation with thiopurine monotherapy. However, there remains debate as to whether monitoring of thioguanine nucleotide levels (TGNs) is necessary in this group of patients.

Methods: All patients switched from thiopurine monotherapy to combination therapy with allopurinol were identified from pharmacy electronic records. Clinical records of these patients were retrospectively reviewed. The first TGN value taken after the change in treatment was noted along with 3 consecutive values if available. Patients full blood count results were reviewed to identify cases of leucopenia.

Results: 202 patients started on or switched to thiopurine-allopurinol combination therapy were identified. 51 patients were excluded due to monotherapy not being prescribed at our centre or lack of follow up data.

Of the remaining 151 patients, 112 (74%) were prescribed azathioprine and 39 (26%) mercaptopurine. 80 patients (53%) were switched due to hypermethylation, 41 (27%) due to intolerance and 25 (17%) as a result of hepatotoxicity. The thiopurine dose was reduced to a mean of 28% of the original weight-based dose. 148 (98%) patients were prescribed 100mg allopurinol daily with the remaining 3 taking either 200mg or 300mg daily to treat gout.

The median thioguanine nucleotide (TGN) and methylated mercaptopurine (MeMP) levels on monotherapy were 202 (normal range 235–450 pmol/8×10⁸ RBC) and 4215 (normal range <5700 pmol/8×10⁸ RBC) respectively, and the first values on combination therapy were 301 and 147 respectively.

Only 71 (47%) TGNs were within therapeutic range after switching to combination therapy with 41 (27%) being subtherapeutic (median

TGN 188 (IQR 153–212)) and 39 (26%) being suprathreshold (median TGN 580 (IQR 494–711)). Of these patients, 56 (70%) remained outside of therapeutic range when the TGNs were rechecked resulting in 33 (41%) having a change to their thiopurine dose.

During the 1 year follow up, 3 patients with suprathreshold TGNs developed leucopenia (defined as WCC $<2.5 \times 10^9/L$ or lymphocytes $<0.5 \times 10^9/L$ or neutrophils $<1 \times 10^9/L$). During this time period, there were no other clear signals of toxicity related to combination therapy.

Conclusions: Over half of the patients in this cohort did not have therapeutic TGNs after switching to combination therapy. While allopurinol-thiopurine co-prescription remains a useful therapeutic strategy, there are potential hazards and drug monitoring post switch should be considered. This approach could identify inadequate drug doses and the potentially increased risk of long term adverse effects. Further studies are required to confirm these findings.

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Perioperative use of vedolizumab seems not associated with short-term postoperative infectious complications in patients with Crohn's disease undergoing right hemicolectomy with ileocolonic anastomosis

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Background: Vedolizumab (VDZ), a bowel focused anti-adhesion molecule, is effectively used in patients with Crohn's disease (CD). Since preoperative use of VDZ was recently associated with increased risk of short-term postoperative infectious complications, we assessed this risk in a cohort of patients with CD undergoing right hemicolectomy with ileocolonic anastomosis (RHC)

Methods: Chart review was performed in all patients referred for RHC between 2006 and September 2016 to identify those receiving VDZ within 14 weeks of RHC. Age- and sex-matched control patients were identified who received anti-TNF within 8 weeks of RHC, a moderate-to-high dose of steroids, or no therapy at RHC. Short-term postoperative infectious complications were evaluated within 30 days and included anastomotic leakage, surgical site and other infections. Comprehensive complication index (CCI) was calculated based on all events reported within 30 days of RHC

Results: We identified 12 patients receiving VDZ within 14 weeks of RHC (75% female, age 31 years, disease duration 12 years, previous

RHC 33%). Surgery was laparoscopy-assisted in 9 patients (75%). Compared to the VDZ group, control groups did not differ significantly, except for patients in the moderate-to-high steroid dose group who had a shorter disease duration and more often used concomitant immunosuppressive therapy at RHC. No significant difference could be observed between the VDZ, steroids and no therapy group regarding postoperative complications. Although patients in the selected anti-TNF group more often experienced non-infectious complications including prolonged ileus, venous thrombosis and urinary retention [67% vs. 8%, Odds ratio 22.22 (95% CI 2.05–250.00), $p=0.009$], a similar infectious complication rate [58% vs. 50%, 1.40 (0.28–6.99), $p=0.682$] and a similar CCI [10.5 (8.7–28.8) vs. 4.4 (0.0–22.2), $p=0.128$] was observed. The postoperative hospitalization stay tended to be higher in this anti-TNF group [9 (6–10) vs. 6 (4–10) days in the VDZ group, $p=0.078$]. CCI and postoperative hospitalization stay were not significantly different between the other treatment categories

Conclusions: In this small matched case-control study with CD patients undergoing RHC, we could not observe an increased risk of postoperative (infectious) complications in patients receiving VDZ. On the contrary, compared to anti-TNF therapy a decreased risk of postoperative non-infectious complications could be observed. Larger multi-center data sets are required to provide more evidence of a safe use of VDZ in the preoperative setting

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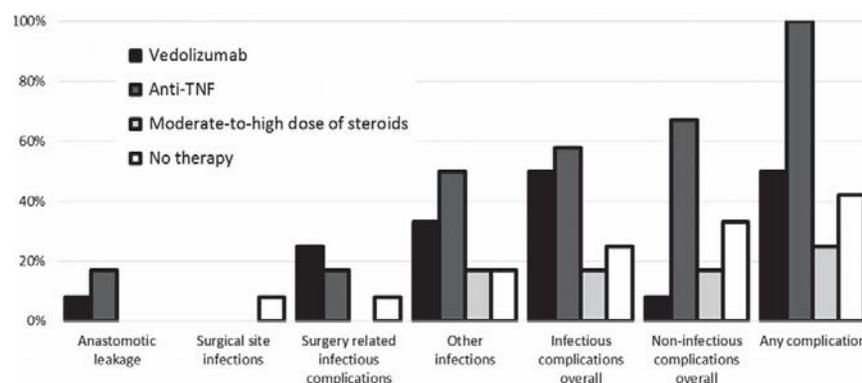
Characterization of ulcerative colitis patients in the Golimumab PURSUIT-Maintenance study: post-hoc analyses of patients who maintained and did not maintain clinical response through week 54

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Background: Assess clinical characteristics, serum GLM concentrations (conc), & immunogenicity to GLM of moderate-severe UC pts who maintained clinical response (MCR) & did not maintain clinical response (nMCR) to GLM through wk54 of PURSUIT.

Methods: In the PURSUIT program, 456 GLM induction responders were randomized at wk0 of maintenance (maint) to PBO (n=154), GLM 50mg (n=151), & GLM 100mg (n=151) q4wks maint treatment through wk52. Partial Mayo scores (pMS) were assessed q4wks; pts with an increase from baseline (BL) (Wk0 of maint) in pMS ≥ 2 with an absolute pMS ≥ 4 or an absolute pMS ≥ 7 were



Abstract P445 – Figure 1. Short-term postoperative complications.

considered in clinical flare & required to undergo endoscopy to confirm if pt lost response (i.e. no longer demonstrated a decrease from wk0 of induction of $\geq 30\%$ & ≥ 3 points in the Mayo score with a decrease in the rectal bleeding score ≥ 1 or a rectal bleeding score of 0 or 1). In this post-hoc analysis, the clinical characteristics (at BL & wk6 of induction), serum GLM conc, & anti-GLM antibody status (during maint) of nMCR & MCR pts were compared.

Results: There were no significant differences in pt demographics or the majority of UC disease characteristics (e.g. Mayo score or extent of disease) between nMCR & MCR pts. However, among nMCR pts, median conc of fecal inflammatory markers fCal & fLac were significantly higher at induction BL & wk6 following induction GLM therapy (Table 1). No significant difference was seen for median conc of CRP. At induction BL, the proportion of pts with elevated fCal (≥ 250 mg/kg) & CRP (≥ 8 mg/L) was significantly higher for nMCR pts vs MCR pts, 82.4% vs 71.4% ($p=0.03$) & 36.7% vs 24.8% ($p=0.029$), respectively. Among pts with elevated fCal & CRP at BL, the proportion of pts who normalized at wk6 of induction was not significantly different between nMCR & MCR pts. Median serum GLM levels during maint were significantly lower for nMCR pts vs MCR pts ($p<0.05$); no significant differences were observed during induction. The incidence of pts positive for anti-GLM antibodies was low overall; among nMCR pts, 7 (4.7%) were positive for anti-GLM antibodies vs 2 (1.4%) of MCR pts.

Table 1

		Maintained Clinical Response Through Week 54	
		No	Yes
Fecal Inflammatory Marker Concentrations at Week 0 of Induction			
Patients with fCal samples (N)		142	133
fCal (mg/kg)	Mean±SD	1973 ± 3041	1553.43 ± 2704
	Median	834	595
	P-value		0.031
Patients with fLac samples (N)		143	131
fLac (µg/mL)	Mean±SD	363.5 ± 598.25	270.02 ± 345.15
	Median	175.2	123.28
	P-value		0.0445
Fecal Inflammatory Marker Concentrations at Week 6 of Induction			
Patients with fCal samples (N)		145	142
fCal (mg/kg)	Mean±SD	779.03 ± 1824.5	320.26 ± 402.19
	Median	241	168.5
	P-value		0.0042
Patients with fLac samples (N)		144	139
fLac (µg/mL)	Mean±SD	292.29 ± 1077.3	131.29 ± 556.76
	Median	50.79	14.38
	P-value		0.0088

Conclusions: Pts who did not maintain clinical response to GLM therapy had higher median fCal & fLac levels prior to & following GLM induction treatment. Median CRP conc did not distinguish these pts; however, there was a higher proportion of pts with elevated CRP conc at BL. Other UC disease characteristics did not distinguish between nMCR & MCR pts. During maint treatment, serum GLM conc were lower among pts who did not maintain clinical response compared to those who did.

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Vedolizumab induces significantly higher endoscopic remission rates at week 16 in ulcerative colitis as compared to Crohn's disease

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Background: Vedolizumab (VDZ) is approved for treatment of moderately-severely Crohn's disease (CD) and ulcerative colitis (UC). Reports on clinical response and remission in registration trials and real world cohorts have shown efficacy, however data on endoscopic response are limited. In this study, we assessed endoscopic response and remission at week 16 and 52.

Methods: Adult patients with CD, UC and IBD unclassified (IBDU) that started VDZ between October '14 and July '16 were prospectively included. Scopic disease activity was assessed at baseline, week 16 and week 52 using the simple endoscopic score (SES) in CD, Rutgeerts score for postoperative CD and MAYO score in UC and IBDU. Endoscopy scoring was randomly performed and blinded for patient characteristics and time points. Endoscopic response was defined as SES-CD reduction $\geq 50\%$, Rutgeerts reduction of ≥ 1 and MAYO score reduction of ≥ 1 . Endoscopic remission was defined as SES-CD < 4 or Rutgeerts score ≤ 1 for CD patients and endoscopic MAYO score ≤ 1 for IBDU and UC patients. Generalized multivariate analysis were performed to identify predictors of endoscopic response and remission at week 16.

Results: In total, 58 (M24/F34) patients with median age of 39 years (IQR29–47) were started on VDZ after a median disease duration of 11 years (IQR6–16). The study population included 39 CD, 15 UC and 4 IBDU patients. IBDU patients were included in the UC group for analysis. In total 57/58 (98%) patients received previous anti TNF therapy. The start of VDZ was combined with corticosteroid induction therapy in 44/58 (79%) patients. Endoscopic response was achieved in 15/39 (40%) of CD and 10/19 (53%) of UC patients at week 16 ($p=0.34$). Endoscopic remission at week 16 was achieved in respectively 7/38 (18%) and 8/19 (42%) ($p=0.05$). At week 16, a significant decrease in mean SES-CD of 5 points was observed ($p=0.01$), 1 point decrease in Rutgeerts score ($p=0.02$) and similarly a mean MAYO score decrease of 1 point was observed ($p=0.01$). After clinical and endoscopic evaluation at 16 weeks, 32/58 (55%) patients continued VDZ. Endoscopic response at week 52 was achieved in 6/16 (38%) CD and 3/6 (50%) UC patients ($p=0.59$). Endoscopic remission at week 52 was achieved in resp. 1/17 (6%) and 3/6 (50%) ($p=0.01$). In multivariate analysis, IBD phenotype of CD patients with perianal disease was associated with a decreased likelihood of endoscopic response at week 16 ($p=0.03$), whereas demographics, disease duration, smoking status, previous surgery and previous medication use did not.

Conclusions: VDZ treatment induces endoscopic response at week 16 in 40% and endoscopic remission in 26% of IBD patients with anti-TNF refractory disease. In UC, endoscopic remission at week 16 is significantly higher as compared to CD.

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Biologic therapy and immunomodulators are associated with decreased risk of cardiovascular events in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis

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Background: Immune-mediated inflammatory diseases (IMIDs) are associated with an increased risk of cardiovascular events. Studies, particularly in patients with inflammatory bowel diseases (IBD), have shown variable impact of disease-modifying therapy on cardiovascular risk, in part due to confounding by disease severity. Additionally, comparative cardiovascular risk modification by biologics and immunomodulators is unclear. We conducted a systematic review with meta-analysis, to evaluate the impact of exposure to biologics and immunomodulators on cardiovascular risk in patients with IMIDs.

Methods: Through a systematic literature review through March 2016, we identified cohort studies in adults with IMIDs (IBD, rheumatoid arthritis, psoriasis and psoriatic arthritis and spondyloarthropathies) reporting the association between biologics and immunomodulators and risk of cardiovascular events (myocardial infarction, stroke, cardiovascular mortality). Random-effects meta-analysis, including a priori subgroup analyses based on adjustment for disease severity, was performed.

Results: On meta-analysis of 24 studies, exposure to biologics was associated with a 30% lower risk of cardiovascular events (OR, 0.70; 95% CI, 0.59–0.82), with substantial heterogeneity (I²=66%). Overall magnitude of decline in cardiovascular risk was comparable across IMIDs, cardiovascular event type and location (Table 1). Magnitude of protective association was comparable in studies that adjusted for baseline disease severity (8 studies; OR, 0.68; 95% CI, 0.52–0.88) and those which did not (16 studies; OR, 0.70; 95% CI, 0.56–0.88) (p=0.87).

Similarly, on meta-analysis of 12 studies, exposure to immunomodulators was associated with a 32% lower risk of cardiovascular events (OR, 0.68; 95% CI, 0.57–0.81), with considerable heterogeneity (I²=82%). Overall magnitude of decline in cardiovascular risk with immunomodulators was higher in patients with IBD, and higher for cardiovascular mortality (Table 1). Magnitude of protective association was comparable in studies that adjusted for baseline disease severity (4 studies; OR, 0.73; 95% CI, 0.50–1.06) and those which did not (8 studies; OR, 0.65; 95% CI, 0.53–0.79) (p=0.59). Overall magnitude of decline in cardiovascular risk was comparable with biologic exposure and immunomodulator exposure.

Conclusions: Exposure to biologics and immunomodulators is associated with a lower risk of cardiovascular events in patients with IMIDs. Future studies evaluating the impact of response, rather than just exposure, to therapy, are warranted to determine the effect of

Table 1

Subgroups	Categories	No. of studies	OR (95% CI)	P _{interaction}
Biologics (vs. no biologics)				
Disease type	IBD	3	0.39 (0.05-2.86)	0.66
	Rheumatoid arthritis	12	0.73 (0.62-0.86)	
	Psoriasis-Psoriatic arthritis	8	0.71 (0.52-0.98)	
	Spondyloarthropathy	1	0.48 (0.23-0.99)	
Cardiovascular event	Myocardial infarction	14	0.56 (0.43-0.75)	0.39
	Stroke	6	0.76 (0.55-1.05)	
	Cardiovascular death	2	0.69 (0.44-1.07)	
Location	Europe	11	0.75 (0.61-0.93)	0.38
	North America	12	0.85 (0.51-0.83)	
Immunomodulators (vs. no immunomodulators)				
Disease type	IBD	2	0.49 (0.40-0.61)	0.03
	Rheumatoid arthritis	5	0.71 (0.52-0.95)	
	Psoriasis-Psoriatic arthritis	5	0.72 (0.57-0.91)	
Cardiovascular event	Myocardial infarction	6	0.68 (0.51-0.91)	0.04
	Stroke	1	0.89 (0.81-0.98)	
	Cardiovascular death	1	0.30 (0.15-0.62)	
Location	Europe	3	0.75 (0.52-1.09)	0.37
	North America	8	0.66 (0.57-0.76)	
	Asia	1	0.48 (0.29-0.80)	

modification of specific inflammatory pathways and overall reduction in inflammation, on cardiovascular risk in patients with IMIDs.

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Patient support program for adalimumab-treated patients with Crohn’s disease in Brazil: impact on patients’ adherence and persistence

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Background: The Brazilian public healthcare system covers treatment with adalimumab (ADA) for multiple indications, including Crohn’s disease, in line with local guidelines. Patients treated with ADA in Brazil can opt-in to a patient support program (PSP) called Humanizar offered by AbbVie. The impact of this program on patient outcomes in the Brazilian setting has not been studied previously in patients with Crohn’s disease. Here, we evaluate the relationship of PSP enrollment and treatment utilization outcomes (adherence and persistence) among patients with Crohn’s disease who initiate ADA. **Methods:** Longitudinal data on the utilization of AbbVie’s PSP were linked with the Brazilian Health System claims database called DATASUS, which includes all inpatient and outpatient procedures on patients with Crohn’s disease who initiated treatment with ADA between 2013 and 2015. Patients using ADA in DATASUS not matched with the AbbVie PSP database were categorized as non-users (non-PSP). Adherence was calculated using proportion of days covered (PDC), defined as the number of months of treatment with ADA divided by the number of months of patient follow-up. Patients were considered adherent if they had a PDC ≥80% [1]. Persistence

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Table: Differences in percentage of patients with PDC ≥80% between PSP users and non-PSP users, according to the ICD-10 codes K50.0, K50.1, and K50.8.

Follow-up	N		% PDC ≥80%			P-value
	PSP User	Non-PSP User	PSP User	Non-PSP User	Difference	
6 months	626	3,212	89.6%	82.6%	7.0%	<0.05
12 months	434	2,374	86.2%	71.9%	14.3%	<0.05
24 months	180	1,020	72.2%	60.6%	11.6%	<0.05

ICD-10, 10th revision of the International Statistical Classification of Diseases and Related Health Problems; K50.0, Crohn’s disease of the small intestine; K50.1, Crohn’s disease of the large intestine; K50.8, Other Crohn’s disease; PDC, proportion of days covered; PSP, patient support program.

was calculated as the interval between treatment initiation and treatment discontinuation (defined as a gap of 90 days since the last obtainment of ADA). Adherence and persistence were compared between the PSP and non-PSP cohorts using *t* tests. Results were segmented for patients with at least 6, 12, and 24 months follow-up.

Results: 3,838 patients were included in the analysis: 626 in the PSP cohort and 3,212 in the non-PSP cohort. Patient characteristics were similar between groups: 54% were female, with an average age of 40 years. The percentage of patients with a PDC \geq 80% was significantly higher in PSP users compared with non-PSP users at 6, 12, and 24 months follow-up (Table). The average treatment persistence was consistently significantly longer in PSP users compared with the non-PSP cohort at all follow-up time points (PSP vs non-PSP: at 6 months, 5.85 vs 5.73 months; at 12 months, 11.64 vs 11.01 months; at 24 months, 21.89 vs 20.04 months; all $p < 0.05$).

Conclusions: For patients with Crohn's disease, ADA users participating in AbbVie's free-to-patient PSP demonstrated improved adherence and persistence to treatment compared with patients not participating in the PSP.

References:

[1] Brown MT et al, (2011), *Mayo Clin Proc*, 86:304–14

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Reliability assessment of endoscopic scoring tools using central video review of colonoscopies in paediatric patients with ulcerative colitis: data from the Canadian Children IBD Network

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Background: Reliable and consistent endoscopic assessment of mucosal disease severity is important in the evaluation of patients with Ulcerative Colitis (UC). Of the commonly used assessment tools, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) is likely more responsive to change than the Mayo Endoscopic Score (Mayo-ES). Neither have been formally evaluated in paediatric patients. Using videos of colonoscopies performed in patients from the Canadian Children IBD Network, we undertook to assess inter-rater reliability (IRR) for the UCEIS and Mayo-ES amongst Pediatric IBD physicians familiar with the tools, as well as non-IBD pediatric gastroenterologists.

Methods: Video recordings of ileo-colonoscopies of paediatric patients with UC undergoing endoscopic assessment at Network sites were utilised for the analysis. 8 physicians (4 IBD experts) reviewed the videos, blinded to clinical information, collecting data encompassing the UCEIS and Mayo-ES. A global assessment of endoscopic lesion severity (GELS) was also recorded using a visual analogue scale. IRR was measured using Intraclass correlation coefficients (ICCs). Correlation between scoring tools was measured using Spearman's test of correlation (*r*).

Results: There was a broad range of endoscopic severity within the endoscopic assessments (median UCEIS 6 (range: 3 to 8)). The IRR for both Mayo-ES and UCEIS was excellent amongst IBD physicians. However, whilst the IRR for Mayo-ES was very good amongst non-IBD gastroenterologists, for UCEIS it was only moderate (see table). Amongst IBD physicians, there was good correlation between the UCEIS score and Mayo-ES ($r=0.75$, $p < 0.001$), as well as between each score and the GELS (Mayo ES: $r=0.78$, $p < 0.001$; UCEIS:

$r=0.72$, $p < 0.001$). Within the 3 items of the UCEIS, the most common sources of disagreement between readers were estimation of the degree of bleeding by all physicians, and evaluation of erosions/ulcers by non-IBD gastroenterologists (see table).

Table 1. Inter-rater reliability using ICC of UCEIS and Mayo Endoscopic Score for IBD physicians and non-IBD gastroenterologists

	IBD gastroenterologists	Non-IBD gastroenterologists
Median UCEIS score (min-max)	6 (3–8)	7 (3–8)
ICC – Total UCEIS score (95% CI)	0.87 (0.74–0.94) $p < 0.001$	0.55 (–0.25–0.84) $p = 0.01$
ICC – Vascular pattern (95% CI)	0.80 (0.60–0.91) $p < 0.001$	0.81 (0.52–0.93) $p < 0.001$
ICC – Bleeding (95% CI)	0.50 (0.11–0.77) $p = 0.01$	0.51 (–0.89–0.83) $p = 0.03$
ICC – Erosions and ulcers (95% CI)	0.88 (0.76–0.95) $p < 0.001$	0.15 (–0.35–0.55) $p = 0.20$
ICC – Mayo endoscopic score (95% CI)	0.88 (0.77–0.94) $p < 0.001$	0.72 (0.27–0.89) $p = 0.01$

Conclusions: Centralised video review of colonoscopy is feasible for assessing endoscopic severity in paediatric UC. Assessment of the scoring tools (UCEIS and Mayo-ES) using video recordings showed excellent IRR in the hands of IBD physicians familiar with the tools. For non-IBD gastroenterologists, IRR of the Mayo-ES was good, however reliability with the UCEIS score was poorer, perhaps reflective of unfamiliarity with the tool. Repeat assessments following training in the application of the tool are planned.

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Compound IBD patient profiles are related to specific information needs – an Israeli national survey

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Background: Recent studies show that a majority of IBD patients receive insufficient information regarding their disease. The wide range of knowledge needs necessitates resources that may improve patient adherence and outcomes. The aims of this nationwide survey of IBD patients were to relate specific patient profiles to unique information needs, with the intent of constructing an interactive, patient tailored, knowledge resource.

Methods: Patients from the Israeli Crohn's & Colitis Foundation were asked to complete a questionnaire aimed at rating the amount of information received at time of diagnosis, the importance of information to be delivered for newly diagnosed patients, and the current importance of information topics for patients with longstanding disease. We performed an exploratory factor analysis of the baseline questionnaire responses, and analyzed the responses of a predetermined set of 20 patient profiles generated by the study team

Results: A total of 571 patients (52% males) completed the questionnaire, 382 with Crohn's disease, 179 with ulcerative colitis and 10 with IBD-Undefined. Little information was received at disease

onset, with a low rating spanning the whole questionnaire (average rating of 0.9 out of 5). The rating of importance of information topics averaged 4.2/5, thus reflecting unmet needs. Average rating of current information needs was also rated high (average 3.5/5), implying continued relevance to the experienced patient. Factor analysis for current needs grouped the responses into six knowledge domains (factors), namely: therapy & complications; nutrition; stress & coping; social & religion; work & disability; and long term complications, all rated as highly important (6/8), except for social & religion (3.2/8). Analysis of the data by single questions or by knowledge domains did not yield specific associations to demographic and clinical characteristics. Analysis by patient profiles found significant, clinically relevant associations to specific knowledge domains. For instance, patients newly diagnosed at an age > 50 and patients diagnosed more than 10 years ago showed less interest in information regarding work & disability, while patients with active disease showed more interest in information regarding work & disability, stress & coping and therapy & complications. Patients in remission but on mesalamine or no therapy showed less interest in all factors except for nutrition and long term complications

Conclusions: Our study clearly demonstrates unmet patient information needs, spanning all knowledge domains. Analysis per compound patient profiles revealed unique associations to information topics, and paves the way to building a patient tailored information resource

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Silent anaemia predicts treatment change in patients with Crohn's disease in clinical remission

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Background: Some patients with Crohn's disease (CD) in clinical remission experience disease progression despite feeling well. We need simple ways to recognize those patients and treat them accordingly and in a timely manner. Anaemia is believed to have prognostic significance as highlighted by previous research.

Methods: We observed changes in treatment upto 12 months after the initial evaluation in a cohort of patients with CD in clinical remission with Harvey Bradshaw Index (HBI) <4. Baseline measurements of C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and hemoglobin were available for all patients. Treatment change was defined as surgery, new therapy added, switch or escalation of existent biologic therapy. World Health Organization criteria were used for the definition of anaemia.

Results: A total of 90 CD patients (median age 39 years; 50% female) were included with a mean HBI of 2.33; 95% confidence interval (CI) 1.76–2.9. Anaemia was observed in 25% of patients. During the one year follow up 36% required a change in management (surgery or different medical treatment). In multivariate logistic regression analysis anaemia was the only factor significantly associated with a treatment change: Odds Ratio (OR)=4; 95% CI 1.3–12; p=0.015. Age, gender, disease duration, treatment with immunomodulators, treatment with biologics, ESR and surprisingly CRP (OR=1.4; 95% CI 0.46–4.42; p=0.537) were not associated with treatment change. Nevertheless CRP showed statistically significant linear correlation with anemia in CD (r=-0.035). When the same analysis was conducted in a cohort of 42 ulcerative colitis patients in clinical remission (mean partial Mayo Score 1.56;

95% CI 0.83–2.29) only ESR (OR=2.5; 95% CI 1.15–5.45; p=0.21) was significantly associated with treatment change. Anaemia in CD has probably stronger prognostic value than inflammatory markers, because it reflects not only inflammation but actual bowel damage.

Conclusions: Anemia was a stronger predictor of treatment change compared to CRP in this cohort of Crohn's disease patients in clinical remission followed up for one year. Silent Crohn's disease with anemia is associated with disease complications or subclinical inflammation and should be therefore investigated and managed appropriately. Further studies of the true significance of anaemia in quiescent Inflammatory Bowel Disease are needed.

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Efficacy of therapeutic drug monitoring of anti-TNF therapy in the control of patients with inflammatory bowel disease

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Background: Infliximab (IFX) and Adalimumab (ADA) are effective drugs in the treatment of inflammatory bowel disease (IBD). Studies suggest that therapeutic drug monitoring (TDM) may allow optimization of drug treatment, but it remains unclear if this strategy is associated with greater therapeutic efficacy and better outcomes.

Methods: We compared clinical-based adjustment (CB) with drug-monitoring adjustment (DM) in patients with IBD under IFX and ADA on several outcomes including hospitalization, surgery, clinical remission and therapeutic failure at 48 weeks of treatment. We also determined the number of therapeutic adjustments, C-reactive protein (CRP) and faecal calprotectin (FC) values (negative <0.5 mg/dl and <50 ug/ml) at 48 weeks of treatment. Clinical remission was defined as absence of hospitalization, surgery and failure or switch of anti-TNF at 48 weeks of treatment.

Results: 117 patients were included: 98 with Crohn's disease (CD) and 19 with Ulcerative Colitis (UC). 54.7% were male with a mean age of 29.1 years (range 7–65). 117 were allocated to the DM group and 101 to the CB group.

Therapeutic escalation was more frequent in the DM group (47.0% vs 10.9%, p<0.001). DM was associated with longer time to relapse (8.74±42 vs 6.00±3.1 months, p=0.045) and, in patients with positive baseline CRP, with higher probability of clinical remission (p=0.05). The number of patients with negative FC was higher in DM group (77.3% vs 54.2%, p=0.029).

There was a trend for higher therapeutic failure in the CB group (5.9% vs 1.7%, p=0.097). There were no differences in the rates of surgery (5.0% vs 6.8%, p=0.385), Hospitalization (6.9% vs 6.8%, p=0.593) or clinical remission (73.5% vs 78.2%, p=0.258).

The prevalence of infratherapeutic IFX serum levels (IFX <3.5) and positive antibodies (>10) was 33.6% and 17.7%. In the DM group, escalation occurred mainly due to Infratherapeutic serum levels and not due to positive antibodies (p<0.001 and p=0.175). Clinical remission (78.7% vs 60.5%, p=0.036) was more common in patients with higher drug serum levels (7.12±7.34 vs 4.56±3.81, p=0.018).

Conclusions: Our results suggest some benefit from DM-based management. The high rates of clinical remission found in both cohorts (73.5% vs 78.2%) may have partly been responsible for the absence of a significant difference between both cohorts. However, the rates of escalation were 4 times higher in the DM group. We hypothesize

that longer follow-ups would allow us to reach a difference between both cohorts.

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Can calcineurin inhibitors induce a durable remission that is maintained with vedolizumab in IBD?

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Background: Vedolizumab (Vedo) is an anti-integrin antibody approved for use in IBD. Sick patients often need a bridging therapy to induce an initial clinical response or remission. We describe our success using tacrolimus (TAC) or cyclosporin (CSA) to induce a clinical response or remission to be maintained with VEDO.

Methods: All IBD patients treated with an induction course of oral TAC or IV/oral CSA with a subsequent maintenance regimen of VEDO at the University of Chicago were identified. Demographics, duration of therapy, drug levels, serious adverse events (deaths, hospitalizations, operations) and drug related adverse effects (AEs) were recorded. The Harvey Bradshaw Index (HBI) or Simple Clinical Colitis Activity Index (SCCAI) were prospectively assessed at each patient encounter. Remission was defined as an HB \leq 4, or SCCAI \leq 2, with response as a decrease in either score by \geq 3 from baseline. Clinical activity was assessed at baseline, 14 weeks, 6 months and 1 year after induction with Vedo. Patients with at least 6 months of follow-up were included in the analysis

Results: 22 patients (11 UC, 11 CD) were identified; 16 were induced with TAC, and 6 with CSA. Mean age 35.6 (20–64); 13 were female. Patients excluded: liver transplant (2, TAC); <6 month follow-up (2 TAC, 1 CSA); initiation of TAC after VEDO (2). 10 TAC and 5 CSA patients were included in the final analysis.

Median duration of TAC induction was 5 months (1–12); median trough level was 8.95 (1.5–18.4). Median duration of CSA was 3 months (1–8); median trough level was 336.5 (92–415) for IV CSA and 293 (37–758) for oral CSA.

3/15 patients were in clinical remission at initiation of VEDO; 2 on TAC, 1 on steroids. At week 14, 9/15 (6 TAC, 3 CSA) were in clinical remission. 6 and 12 month clinical remissions were seen in 4/14 (28.5%) and 5/9 pts, respectively. Of patients who achieved clinical remission at 14 weeks, 2 remained in remission at 6 months; 1 at 12 months (the other lost to follow-up).

Table 1. Clinical results

Parameter	Number of patients
Active disease at baseline	12/15
14 week: Clinical remission	9/15
14 week: Clinical response	9 /15
6 month: Clinical remission	4/14
6 month: Clinical response	8/14
1 year: Clinical remission	5/9
1 year: Clinical response	5/9

11 patients were steroid dependent at baseline; 6 successfully weaned off steroids (2 at 6 months and 4 at a year).

4 patients underwent colectomy. AEs attributed to TAC included tremor, malaise, gum sensitivity, headache, leg cramps, herpes outbreak and marrow suppression. CSA was associated with acute kidney injury and a possible allergic reaction. There were no deaths.

Conclusions: Calcineurin inhibitors successfully induced remission in over 1/2 of patients; vedolizumab maintained remission in 28.5% at 6 months and 55.6% at 1 year. Steroids were weaned in over half of patients.

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Clinical features of tuberculosis infection in inflammatory bowel disease patients on anti-TNF therapy

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Background: According to the WHO the incidence of active tuberculosis (TB) in Spain is high 13 cases per 100.000 inhabitants, reaching in Galicia (a region located in the North-west of Spain 20 cases per 100.000 inhabitants. Otherwise patients on anti-TNF treatment have an increased risk of active TB too. We aimed to analyze the clinical features of active tuberculosis infection in inflammatory bowel diseases (IBD) patients on anti-TNF drugs.

Methods: We perform a case-control study. Our database was searched for IBD patients on anti-TNF who developed active TB from 2000 to 2014. Controls were selected among patients with active TB infection matched for sex, age and year of diagnosis of tuberculosis. All their clinical features were analyzed and in the statistical analysis p values below 0.05 were considered significant.

Results: The incidence of active TB in IBD patients on anti-TNF drugs was 3.4% (10/290). The median time to the development of active TB after initiation of anti-TNF therapy was 6 months range (2–60). TB skin test (TST) was performed in 90% cases, but only 50% had two-step TST. Three patients had a positive TST and received anti-TB prophylaxis. Prior anti-TNF chest radiographies do not suspected TB. Previous TB exposition, time from symptoms to TB diagnosis and hospital stay were similar to controls. IBD patients had a higher laboratory identification of mycobacterium TB prior anti-TB treatment (p=0.03) and had previous 3 months exposition to steroids or immunodepressant (p=0.01) than controls. They suffered from more extrapulmonary TB (p=0.01) with primary resistances to anti-TB drugs (p=0.03), had to receive TB treatment for a longer time (p=0.04) and had more complications related to TB p=0.008) than controls.

Conclusions: IBD patients on anti-TNF drugs suffer from more complicated extrapulmonary and drug-resistant TB infections, needing longer course of TB treatment.

In these patients two-step TST must be performed and positive findings must be treated.

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Comparative analysis of oral versus intravenous iron in patients with inflammatory bowel disease and iron deficiency/anaemia – impact on hospitalisation in Germany

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Background: Anaemia is the most common complication of inflammatory bowel disease (IBD). While 36–90% of IBD patients have iron deficiency (ID), about one-third have manifest anaemia. In IBD, ID results from chronic blood loss and poor iron intake and/or absorption, with symptoms of anaemia including fatigue, headache and shortness of breath or tachycardia, affecting patients' quality of life and use of healthcare resources. While oral iron is often still used as first-line therapy for ID or IDA (ID/A) in patients with IBD, IV iron is known to be safe and effective, providing rapid replenishment of iron stores. This study aimed to compare hospitalisation rates of IBD patients with ID/A in Germany when newly treated with IV or oral iron.

Methods: Pooled anonymised individual claims data of ca. 75 German health insurances were searched to identify patients with Crohn's disease or ulcerative colitis and ID/A who first received oral or IV iron in 2013, with pre- and post-index periods of 4 and 3 quarters, respectively. Oral and IV iron groups were matched for age, gender and comorbidities. Outcome measures were the number and duration of hospitalisations, and ID/A-related inpatient stays were defined by ICD-10-GM codes as primary or secondary diagnosis.

Results: In total, 2,379 IBD patients were diagnosed with ID/A in 2013. Of these, 589 received oral iron and 442 patients IV iron, while 1,348 received no iron replacement. Most IV-treated patients (62.9%) received iron(III)-hydroxide-polymaltose complex, while 24.9% received iron(III)-sodium-gluconate complex. After matching, 380 patients remained in each treatment cohort. All-cause hospitalisation rates between matching and initiation of iron treatment were 38% (oral group) and 42% (IV group). ID/A-related hospitalisation was 4% in both cohorts. In the post-index period, significant differences between the cohorts were identified, with 48% vs. 37% all-cause ($p=0.001$), and 14% vs. 5% ID/A-related ($p<0.001$) hospitalisations in the oral and IV groups, respectively (Fig. 1). Mean duration of ID/A-related hospitalisation was significantly shorter after IV therapy (9.6 vs. 7.0 days; $p<0.001$), whereas the difference before treatment initiation was insignificant (1.9 vs. 2.4 days, $p=0.67$).

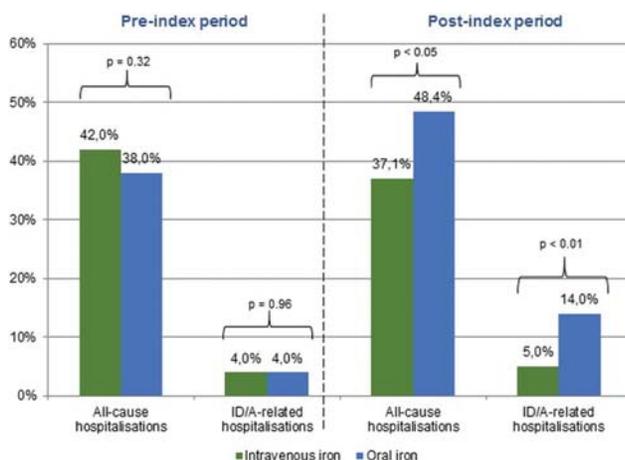


Figure 1. Comparative analysis of hospitalisations before and after/during iron treatment (percent of patients).

Conclusions: IV iron treatment was associated with fewer all-cause and ID/A-related hospitalisations after treatment. Moreover, duration of ID/A-related hospitalisations was reduced compared to patients treated with oral iron. Further research is warranted to assess long-term effects of iron treatment.

P457 Rapid faecal calprotectin test and symptom index for monitoring the disease activity in colonic IBD

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Background: Faecal calprotectin (FC) is a reliable surrogate marker for inflammatory activity in IBD. Providing a patient with an option for self-monitoring of the disease has been proven to empower patients, increase adherence and help cut the costs of health care with increasing amount of IBD patients.

In this study, we validated a symptom index suitable for ulcerative colitis and colonic Crohn's disease. By combining the symptom index with a rapid semi-quantitative FC test, we constructed a new activity index based on the highest AUC:s, using histological remission as a reference. We also evaluated the correlation of the patient-reported influence of the IBD in the daily life, measured with a VAS scale, with the inflammation activity.

Methods: The disease activity of 72 patients with ulcerative colitis or colonic Crohn's disease was determined by endoscopic activity scores (SES-CD/UCEIS). The patients provided stool samples for determination of FC with an ELISA test and a rapid FC test (Prevent ID CalDetect, Preventis, Immunodiagnosics AG, Bensheim, Germany), and filled in a questionnaire about their symptoms during the last week.

Results: The results of the symptom index demonstrated a statistically significant correlation with the FC tests, histological inflammation activity and the VAS scale. The sensitivity and specificity of the new index in distinguishing inactive from active disease were comparable to those of FC. The specificity of the VAS scale in detecting histologically inactive disease was low, and no correlations were found between the VAS scale and FC or the histological inflammation activity.

For the combination index, the highest AUC for the histologically inactive disease was achieved using the following formula:

1.6 (if pIBD-SI is ≥ 2) + 1 (if CalDetect is 50–200) + 2.4 (if Caldetect is >200)

The sensitivity of the combination index to detect active inflammation was slightly superior to FC test alone.

Table 1. Comparison of different indices and FC in detecting histologically inactive disease

Variable	Cut-off	Sensitivity	Specificity
Symptom score	2 points	73%	72%
FC (measured with ELISA)	100 $\mu\text{g/g}$	81%	68%
FC (measured with ELISA)	200 $\mu\text{g/g}$	69%	75%
Rapid semi-quantitative FC test	200 $\mu\text{g/g}$	67%	79%
Combination index	2 points	87%	69%
VAS scale	2 points	87%	39%

Conclusions: The new symptom score and the combination index are simple non-invasive means for distinguishing remission or mild inflammation from active inflammation in colonic IBD. With the VAS scale we can pick up patients who need psychosocial support because of the disease burden, even if their IBD is in remission. With these new indices patients are able to monitor their disease activity at home, and contact the outpatient clinic only when needed.

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Sleep problems in inflammatory bowel disease: When bed becomes a battleground

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Background: Sleep disturbance in patients with Inflammatory Bowel Disease is prevalent (49%), increasing during relapse (70–80%) (1). Sleep problems contribute to reduced quality of life and may increase risk of flare (2). Cognitive behavioural therapy for insomnia can improve sleep problems in other chronic conditions (3) A qualitative study was undertaken to explore the sleep disturbances of patients with IBD and assess the acceptability of psychological input to address this

Methods: Using convenience sampling, 15 adult patients with sleep disturbance were recruited from IBD clinics and interviewed by a single experienced sleep researcher. A semi structured interview technique was used, followed by three questionnaires: the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale and the Hospital Anxiety and Depression (HAD) Scales.

The 7 male and 8 female participants had a mean age of 48 years (range 24–71). Eight had ulcerative colitis and seven Crohns disease, 3 had a stoma. The mean time since diagnosis was 12 years (range 4 month to 30 years). 10 were employed, 1 participant was not working and 4 had retired.

Results: All patients reported that their sleep had deteriorated since their diagnosis.

Table 1

	Anxiety and Depression Score (HADS)	Sleepiness score (Epworth)	Sleep Quality Index (Pittsburgh)
Score range (normal)	0–21 (<10)	0–24 (<10)	0–21 (<6)
Study subjects score (mean)	15	14	13

Seven participants described problems in falling asleep, 12 experienced problems waking during the night. The mean amount of sleep each night was 4.5 hours. Sleep questionnaires indicated highly disturbed sleep. Patients tended to normalise their difficulties as part of their IBD.

Three distinct themes emerged: factors related to physical symptoms and treatments for IBD, psychological factors, such as stress and hypervigilance, and also poor sleep “hygiene” such as watching TV in bed.

Of the 7 who had sought help each had been prescribed night sedation, but only one had found this useful. None had heard of psychological intervention for sleep, 11 were keen to try it. A CBT like intervention was perceived as useful, especially for adults of working age. The mechanism by which such intervention could be delivered was discussed with no single preferred option

Conclusions: For these IBD patients bed is a battleground, not a place of rest. This study highlights the complexity of the problem, its im-

port and the limited understanding of it. An IBD specific CBT-like intervention could empower patients to manage their own sleep in the longterm and improve quality of life

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Obesity in patients with an ileoanal pouch due to ulcerative colitis is not associated with an increased risk for pouchitis

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Background: Obesity is characterized by low grade inflammation in the visceral fat tissue (VFT) which may be a major causative factor in the development of insulin resistance (IR). A surrogate marker for IR is the ratio between triglycerides (TG) and high density lipoprotein (HDL). VFT wrapping the small bowel characterizes Crohn's disease (CD) and has been shown to produce proinflammatory cytokines. Patients with ulcerative colitis (UC) undergoing proctocolectomy with ileal pouch-anal anastomosis (IPAA) commonly develop pouchitis-*de novo* inflammation in a previously normal small bowel. We hypothesize that pouchitis may represent the small intestinal inflammation characterizing CD. We aimed to assess whether obesity affected intestinal inflammation in obese UC-pouch patients.

Methods: Retrospective case control series in UC pouch patients recruited at a tertiary referral center. Clinical and biochemical indices were compared between obese (BMI ≥ 30 kg/m²) and normal BMI (nBMI, 18.5–24.9 kg/m²) pouch patients, matched for age and gender. Nutritional trends were obtained from food frequency questionnaires (FFQs).

Results: Thirty one patients (8.6% of pouch patients in our cohort, 20 females) were obese with a mean BMI of 33.9 ± 4.5 kg/m², pouch patients with nBMI - 22.9 ± 2.6 kg/m². Groups were comparable for smoking, disease duration, indication for surgery and pouch age. However, significantly lower rates of pouchitis were detected in the obese compared to nBMI group, 41% vs 79% (p=0.028) respectively. Obese patients had significant metabolic abnormalities: Glucose 103.5 ± 39.9 vs. 83.8 ± 10.7 mg/dl (p=0.028); HDL 47.9 ± 14.2 vs 63.9 ± 17.08 mg/dl (p=0.003); TG 190.33 ± 124.8 vs 118.7 ± 58.76 mg/dl (p=0.015), respectively. TG/HDL ratio was higher in the obese group 4.4 ± 3.4 vs 2.1 ± 1.4 (p=0.006 vs. nBMI). Sugared beverages consumption was significantly higher in the obese group (p < 0.01 vs. nBMI).

Conclusions: Pouchitis rates were surprisingly lower in obese UC-pouch compared to nBMI UC pouch patients. This may be due to

dietary intake restriction in patients with pouchitis, potentially contributing to lower weight so obesity may prevail mainly in patients with a normal pouch, eating freely. An alternative explanation may be that in pouchitis metabolic expenditure is increased contributing to lower BMI. Obese UC-pouch patients are prone to metabolic abnormalities and IR. A high consumption of simple carbohydrates may impact TG levels and weight gain in these patients. Dietary treatment for IBD patients should target all nutritional aspects including metabolic abnormalities to improve health status and quality of life.

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Early use of therapeutic drug monitoring to individualize infliximab therapy in paediatric IBD: a multicentre prospective COHORT study

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Background: Therapeutic drug monitoring (TDM) during infliximab (ifx) maintenance therapy is regularly used in Canada to assess loss of response and to aid in dose optimization, with pre-infusion trough levels in the range of 5–10ug/ml recommended as targets. Levels achieved early following standard induction dosing among pediatric patients are highly variable, and often inadequate even at week 12. Limited data exist in adults or children concerning the role of TDM and target levels during induction. Within the Canadian children IBD Network, we proposed to measure ifx levels during induction, aiming to determine the optimal levels required to achieve target 5–10 ug/ml at the start of maintenance.

Methods: Beginning in May 2016, children initiating ifx at SickKids

Hospital and at other centres within the CIDsCANN inception cohort study had trough levels measured by ELISA at the time of the final induction and first maintenance infusions (doses 3 and 4). Induction regimens were at the discretion of the treating physician, but often intensified among patients with severe UC. Influence of patient demographics and baseline disease activity (PGA, wPCDAI/PUCAI) on early trough levels were assessed.

Results: From May to December 2016 at 9 participating sites, 66 children (median age 11.8 years, 53% male, 52% CD, 48% UC/IBD-U; IBD duration at start of biologic 4.3mos (IQR 14.02–13.02 mos). Induction regimen was “standard” (0, 2, 6 weeks) in 77% and intensified in 23% (0, 1, 4 weeks; all steroid refractory colitis). Table 1 gives characteristics of those receiving standard vs intensified regimens As shown in Table 1, IFX levels were highly variable prior to 3rd induction dose. Within the standard induction dosing cohort, the interval between dose 3 and 4 was shortened to 6 weeks in 50%. 41% attained targeted 5–10 dose 4 levels. Despite higher dosing per kg during induction and shorter interval prior to dose 4 in the intensified regimen, IFX levels at start of maintenance were comparable to patients receiving standard induction.

Conclusions: Variability in infliximab exposure is evident during induction. Adjusting dose intervals based on pre 3rd dose induction levels, increases the likelihood of entering maintenance dosing on target. An intensified regimen is necessary for patients with active colitis to achieve comparable post induction levels. The results suggest that the use of TDM during induction to individualize dosing more consistently ensures adequate drug exposure at start of maintenance.

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Comparison of efficacy of different oral 5-aminosalicylic acid doses for maintenance of remission in ulcerative colitis: a systematic review and meta-analysis

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Abstract P460 – Table 1. Basic demographic data Induction Infliximab TDM Study

	Standard induction	Intensified induction
Population (n)	51	15
Gender (% male)	53%	23%
Age in yrs (median, IQR)	12.0 (7.9–14.3)	9.4 (6.5–13.8)
Type of IBD	60% CD; 40% UC/IBD-U	86% UC/IBD-U; 14% CD
PGA at first infusion	30% severe; 16% moderate; 38% mild; 16% none	60% severe; 20% moderate; 20% mild
Mean dose (mg/kg)	6.04 mg/kg	7.95 mg/kg
Induction duration (weeks)	6	4
Pre-dose 3 level (median, IQR)	16.4 µg/ml (10.1–26.7)	16.2 µg/mL (IQR 11.9–28.8)

Background: The efficacy of 5-aminosalicylic acids (5-ASAs) for maintenance of remission in quiescent ulcerative colitis (UC) has been studied previously in meta-analyses. However, there was no previous meta-analysis evaluated the effect of absolute dosage of active 5-ASA component used. We performed a systematic review and meta-analysis of all relevant randomized controlled trials (RCTs) comparing efficacy of the different dosages of 5-ASAs for maintenance of remission in patients with quiescent UC.

Methods: We searched for all relevant studies published through March 2016 using MEDLINE, EMBASE and the Cochrane Library. Review articles and conference proceedings were also searched to identify additional studies. Eligible trials recruited adults with quiescent UC, comparing different doses of 5-ASAs. Drug doses were classified according to the absolute dose of active 5-ASA component. Comparison was performed using three different dosing points of reference including 1.5 g, 2.0 g and 3.0 g: (1) <1.5 g vs. 1.5 g to 2.5 g, (2) <2.0 g vs. 2.0 g to 3.0 g, and (3) 1.5 g to 2.5 g vs. 3.0 g to 4.8 g per day. Dichotomous data were pooled to obtain relative risk (RR) of persistent remission of disease activity in quiescent UC, with a 95% confidence interval (CI) using RevMAN 5.3. Data were analyzed on an intention-to-treat basis.

Results: Ten RCTs (1865 patients) were included in the meta-analysis. Of these, 6 RCTs compared 5-ASA doses of <1.5 g with 1.5 g to 2.5 g per day, with the RR of persistent remission with dose of 1.5 g to 2.5 g of 1.16 (95% CI 1.06–1.27). There were 5 RCTs comparing 5-ASA doses of <2.0 g with 2.0 g to 3.0 g per day. Doses of 2.0 g to 3.0 g were more effective than <2.0 g for maintenance of remission (RR of persistent remission =1.74; 95% CI 1.3–2.26). There were 3 RCTs comparing 5-ASA doses of 1.5 g to 2.5 g with 3.0 g to 4.8 g per day. Doses of 3.0 g to 4.8 g appeared more effective than <2.0 g for persistent remission (RR =1.68; 95% CI 1.23–2.31). In one study that evaluated the effect of high dose 5-ASA (4.8 g/day) in UC patients with history of frequent relapses (mean of at least 3/year during the 3-year period preceding enrollment), the high dose proved to be significantly more effective than standard dose (2.4 g/day) for maintaining remission in patients with extensive disease (90.9% vs. 46.7%, $p=0.0064$).

Conclusions: 5-ASA doses of 2.0 g to 3.0 g per day are more effective than dose of <2.0 g for preventing relapse in quiescent UC. High doses of 5-ASAs (3.0 g to 4.8 g) may be more effective than standard doses (2.0 g to 2.5 g) for maintenance of remission in UC, especially for patients with extensive colitis or with frequent relapses.

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Long-term outcomes of anti-TNF therapy discontinuation in patients with penetrating Crohn's disease

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Background: Discontinuation of anti-TNF maintenance therapy in patients with Crohn's disease (CD) in remission should be considered in order to reduce the potential long term side effects and costs. Several studies have evaluated relapse rate after discontinuation treatment, but data in penetrating CD are scarce.

Methods: Retrospective observational study including patients with penetrating CD in clinical and endoscopic remission who underwent discontinuation of anti-TNF therapy. Clinical, biological and therapeutic variables were analyzed. Clinical relapse was defined as the

presence of symptoms and/or fistule activity with the need of retreatment with anti-TNF.

Results: Twenty-six patients were included: 54% men; median age 39 years (IQR 15–71); 18/26 (69.2%) had perianal disease, 4/26 (15.4%) internal penetrating and 4/26 (15.4%) internal penetrating and perianal disease; 54% treated with Adalimumab, 46% Infliximab. Median time with anti-TNF treatment before discontinuation was 61 months (IQR 6–146). All patients were in clinical remission at the time of anti-TNF discontinuation: in 62% of cases treatment was stopped because of sustained remission, in 16% due to adverse effects and in 12% by patient request.

Median time of follow-up was 38 months (IQR 4–95). During follow-up 7/26 patients (27%) had a clinical relapse, with a median time until relapse of 14 months (IQR 3–29); all these patients regained clinical response after reintroducing anti-TNF treatment. Patients who continued maintenance immunosuppressive therapy after stopping anti-TNF treatment had numerically lower relapse rate [2/15 (13%) vs 5/11 (46%), $p=0.081$]. Time to relapse was significantly prolonged in patients under immunosuppressive therapy (40.9 ± 12.3 vs. 82.2 ± 8.4 months, $p=0.04$).

Conclusions: A high proportion of patients with penetrating CD in clinical and endoscopic remission, have prolonged remission after discontinuation of anti-TNF therapy. Treatment with immunosuppressant prolongs the duration of remission after anti-TNF discontinuation.

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Recurrence of Crohn's disease after the first surgical intervention

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Background: The Crohn Disease (CD) is characterized by a segmental and transmural inflammation that can affect the whole digestive tract. The 80% of the patients will require surgery and between 20–80% of them will suffer postoperative recurrence, which is influenced by prognostic factors and therapeutic strategies. The aim of our work is to know how the Disease Free Time (DFT) is affected by these factors and to determine the best medical-surgical strategy to reduce the percentage of relapse.

Methods: A retrospective cohort study which includes 144 patients with ileo-cecal localization of CD, who underwent the first surgical intervention between years 2005–2016 in the HURS. We measured a total of 32 variables, which are grouped in sociodemographic, risk factors, disease characteristics, surgical aspects, therapeutic prophylaxis, DFT and recurrence; being these two last variables the principle ones. A descriptive univariate analysis of the variables was performed using the SPSS program, a bivariate correlation analysis using Pearson's analysis, cross-tables, Kaplan-Meier survival analysis and Cox regression.

Results: Recurrence correlates with smoking, since the 68.57% of recurrences are in smokers. The main surgical indication is the absence of response to treatment (31.25%), followed by obstruction (30%) and fistulas (14.58%). The inflammatory pattern is the most recurrent (44.28%) and the most typical location is ileal. The most frequent type of anastomosis is the side-to-side handsewn (75.7%), increasing the risk of recurrence when end-to-end or and end-to-side

are carried out. 14.5% of patients present post-surgical complications, with dehiscence being the most frequent.

Recurrence occurs in 48.61% of patients after 88 months (range 1–170). 84.72% received preventive treatment and the 41% of those ones relapsed, versus the 91% of relapse without treatment. Salicylates, antibiotics and corticosteroids do not imply an increase in DFT or decrease in recurrence, while these differences are found when talking about immunomodulators (63.19%, most used) and anti-TNF used in 12.5% of patients. Anti-TNF reduce relapse to 22.2%, while immunomodulators only achieve 31.86%. In the survival analysis, preventive treatment with immunomodulators and/or biologicals demonstrates an increase in DFT ($p < 0.05$).

Conclusions: In our attempt to reduce recurrence and increase DFT we have determined a number of prognostic factors (tobacco, side-to-side anastomosis, inflammatory pattern, preventive treatment with immunosuppressants and biological) to help us to adopt the best strategy to increase DFT in our patients. The main limitation is the reliability of the information collected from a pre-existing database and covering an extended period of time.

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Recurrence of ulcerative colitis during pregnancy in patients who became pregnant during remission

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Background: Ulcerative Colitis (UC) has a marked influence on the lifestyle of patients, and its effects on pregnancy and childbirth can especially become a problem for women in their child-bearing years. Various studies have suggested that it is desirable for pregnant women with UC to give birth while remaining in a state of remission. The present study evaluated pregnant women with UC attending our hospital who became pregnant during remission, in order to examine the factors that contributed to recurrence of UC during pregnancy.

Methods: We investigated 40 pregnant patients in remission (44 cases) attending our hospital between January 2008 and June 2016 who had remained in remission for one year prior to pregnancy.

After becoming pregnant while in remission, patients who stayed in remission until delivery were classified into the ongoing remission group (35 cases) and patients with recurrence during pregnancy were classified into the recurrence group (9 cases). Items examined: Clinical characteristics, the CAI and whether or not patients continued treatment during pregnancy were examined and compared between the two groups. The reasons for discontinuation of treatment were also investigated.

Results: There were significant differences between the two groups with respect to the age of becoming pregnant, the CAI in the first, second, third trimester, and whether oral treatment was continued (continuation of treatment [yes:no] 30:5 in the ongoing remission group vs. 5:4 in the recurrence group). Regarding the discontinuation of oral treatment, two patients in the ongoing remission group and one patient in the recurrence group discontinued it on their own judgment, while two patients in the recurrence group discontinued it due to hyperemesis.

Conclusions: The present study revealed that factors influencing the recurrence of UC during pregnancy were the age of becoming pregnant and the continuation of oral treatment. As expected, discontinuing oral treatment was a factor that contributed to recurrence.

However, the reasons for discontinuing treatment during pregnancy differed from those for non-pregnant women. Some patients discontinued treatment on their own judgment because they were concerned about adverse effects on the fetus, while others had difficulty with continuing treatment due to hyperemesis.

With regard to the effects of medications on the fetus, medical staff should provide an explanation about the safety of treatment and should be aware that patients may have various concerns about drug therapy. If patients have difficulty continuing oral treatment due to severe hyperemesis, administration of local therapy should be considered. During pregnancy, it is important to continue treatment for UC so that patients can give birth while remaining in remission.

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Efficacy of ustekinumab for induction and maintenance of histological healing in patients with Crohn's disease

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Background: Ustekinumab (UST) has been shown to induce & maintain clinical response & remission & to produce clinically meaningful endoscopic improvement in patients (pts) with moderate-severe Crohn's disease (CD). Effects of UST on histologic CD activity were evaluated in a substudy of the induction (UNITI-1&2) & maintenance (IM-UNITI) Phase 3 studies.

Methods: At endoscopy, 2 biopsies were collected at induction baseline (I-Wk0), Wk8 (I-Wk8), & maintenance Wk44 (M-Wk44) from 3 anatomical regions (ileum, splenic flexure, rectum). One expert GI pathologist (GDH) blindly scored all biopsies using the Global Histology Activity Score (GHAS [1] for each region. At I-Wk0, pts received a single IV dose (UST 130 mg, UST ~6 mg/kg, or PBO). At maintenance Wk0 (i.e. I-Wk8), UST induction responders (R, CDAI decrease ≥ 100 [CR]) were re-randomized to SC PBO, UST 90mg q12w or UST 90mg q8w; UST induction non-responders (NR) received SC UST 90mg → SC UST 90mg q8w if in CR after 8wks; PBO induction NR received UST IV 130mg → SC UST 90mg q12w if in CR after 8wks; and PBO induction R received PBO. Histology data from 251 substudy pts with simple endoscopic score for CD (SES-CD) ≥ 3 (i.e. ulceration in any segment) at I-Wk0 were eligible for analysis. The relationship between GHAS & SES-CD was evaluated by Spearman correlation. Histologic improvements (i.e. change in GHAS from I-Wk0 at I-Wk8, M-Wk44) were assessed within each group (UST, PBO) & between groups (UST vs PBO, among pts with evaluable data at both I-Wk0 & I-Wk8, M-Wk44).

Results: Regional & overall GHAS were moderately correlated with SES-CD at all timepoints ($r=0.6$, $p < 0.001$). GHAS was significantly reduced at I-Wk8 in pts treated with UST (from 10.4 to 7.1, $p < 0.001$) but not PBO (from 9.2 to 7.8). At M-Wk44 in the randomized maintenance population, a continued reduction in GHAS from I-Wk8 was observed with UST 90mg SC q8w (from 7.39 to 6.07, $p=0.07$) but not UST 90mg SC q12w (from 5.29 to 8.67) or PBO (from 9.19 to 10.85). In the pooled maintenance population (randomized & non-randomized), continued histologic im-

provement from I-Wk8 was observed with UST 90mg q8w (7.14 to 5.19, p<0.0001), but not UST 90mg q12w (from 6.14 to 7.18) or PBO (from 8.19 to 8.85). Consistent results are observed in between-group (UST vs. PBO) analyses, numerically greater GHAS reduction was observed for UST.

Conclusions: Histologic & endoscopic disease activities were moderately correlated. Consistent with previously reported endoscopic results, statistically significant histologic improvements were observed in pts induced with UST, but not PBO. Trends for greater & continued histologic improvement were observed in pts who received UST 90mg q8w maintenance.

References:

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P466
Real world effectiveness of vedolizumab over one year in inflammatory bowel disease: a meta-analysis

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Background: A growing number of real-world studies document the effectiveness of Vedolizumab (VDZ), a gut-selective monoclonal anti-α4β7-integrin antibody approved for treatment of Crohn’s disease (CD) and ulcerative colitis (UC). A systematic meta-analysis on clinical response, remission, and steroid-free remission real-world outcomes (6 and 14 weeks, 6 [26–30 weeks] and 12 months [46–54 weeks]) was conducted.

Methods: MEDLINE-, Cochrane-, Embase-indexed publications and conference abstracts (n≥10) were searched from 1 May 2014–31 October 2016 for studies reporting real-world VDZ effectiveness. Reports for patients <18 years of age or for off-label VDZ use were excluded. A meta-analysis was conducted using the DerSimonian-Laird random-effects method to obtain a weighted mean (95% confidence interval) for each outcome.

Results: A total of 98 studies were identified with 20 cohorts reporting response and/or remission rates on 1,714 (UC: 704; CD: 1,010) VDZ patients over a one-year treatment period. Amongst included studies, average age of patients ranged from 34 to 49 years and median disease duration ranged from 6 to 11 years. Most VDZ patients (≥71%) had prior exposure to ≥1 anti-tumour necrosis factor (TNF) therapy. Outcome measures included partial Mayo score, Simple Clinical Colitis Activity Index, Harvey-Bradshaw index, Crohn’s Disease Activity Index and Physician Global Assessment. In UC, pooled clinical remission rates at week 14, 6 months and 12 months were 32%, 31% and 51%, respectively (Table 1). In CD, pooled clinical remission rates at week 14, 6 months and 12 months were 30%, 23% and 30%, respectively (Table 1). Pooled steroid-free remission rates at 6 and 12 months were 31% and 48%, respectively, in UC, and 23% and 25%, respectively, in CD (Table 1). The most common adverse events (AEs) reported were fatigue (<1–16%), arthralgia (<1–14%), fever (1–13%) and upper respiratory tract infections (1–14%); serious AEs occurred in 7–8% of VDZ patients.

Conclusions: Pooled real-world clinical response and remission rates and safety data support the positive benefit-risk profile of VDZ over at least one year. Results exceed efficacy reported from the GEMINI clinical trials, despite the selection of complex patients failing previous immunosuppressive or biologic therapies. Real-world data are an important supplement to randomized controlled trials; future studies should look to pool clinical outcomes in biologic-naive VDZ patients.

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Maintenance of quality of life improvement in a phase 3 study of tofacitinib for patients with moderately to severely active ulcerative colitis

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Abstract P466 – Table 1. Pooled VDZ real-world clinical outcomes over one year in UC and CD

	Week 6						Week 14					
	n	Clinical Response	n	Clinical Remission	n	SF-Remission	n	Clinical Response	n	Clinical Remission	n	SF-Remission
		%		%		%		%		%		%
Ulcerative Colitis	288	43 [38-49]	308	24 [13-41]	236	14 [6-30]	416	59 [53-65]	495	32 [26-39]	351	26 [19-35]
Crohn’s Disease	602	56 [46-65]	598	24 [16-34]	387	13 [8-21]	587	61 [54-67]	740	30 [25-35]	441	25 [19-31]
	6 Months						12 Months					
	n	Clinical Response	n	Clinical Remission	n	SF-Remission	n	Clinical Response	n	Clinical Remission	n	SF-Remission
		%		%		%		%		%		%
Ulcerative Colitis	200	43 [33-54]	145	31 [19-46]	265	31 [20-45]	174	64 [19-93]	186	51 [20-82]	146	48 [18-79]
Crohn’s Disease	338	34 [27-41]	332	23 [17-32]	364	23 [14-35]	279	41 [15-73]	289	30 [20-43]	194	25 [13-43]

95% CI: 95% Confidence Intervals; SF: steroid-free

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Background: Tofacitinib is an oral, small molecule Janus kinase inhibitor that is being investigated for ulcerative colitis (UC). Tofacitinib 10 mg twice daily (BID) improved quality of life (QoL) in two Phase 3 induction studies of patients with moderately to severely active UC (OCTAVE Induction 1 & 2) [1].

Methods: OCTAVE Sustain (NCT01458574) was a Phase 3, ran-

domised, double-blind, placebo-controlled study that enrolled patients who completed OCTAVE Induction 1 or 2 with clinical response (≥ 3 points and $\geq 30\%$ decrease from baseline (BL) Mayo score plus decrease in rectal bleeding subscore of ≥ 1 or rectal bleeding subscore ≤ 1). Patients were re-randomised (1:1:1) to placebo, tofacitinib 5 or 10 mg BID for 52 weeks. QoL was assessed at Weeks 24 and 52 using the 32-item Inflammatory Bowel Disease Questionnaire (IBDQ) and the Short Form-36 (SF-36; version 2, 1-week recall; 8 domain scores summarised as Physical and Mental Component Summaries [PCS and MCS]). Clinically relevant endpoints including IBDQ Remission (IBDQ Score ≥ 170) and Response (≥ 16 -point improvement from induction study BL IBDQ Score), were compared by Cochran-Mantel-Haenszel chi-square test. Continuous endpoints were analysed using a linear mixed-effects model.

Results: OCTAVE Sustain randomised 593 patients (placebo: n=198; 5 mg BID: n=198; 10 mg BID: n=197). At Sustain BL, across treatment groups, mean IBDQ total score ranged from 166.7–167.7, and mean SF-36 PCS and MCS ranged from 49.3–50.5 and 47.8–49.0, respectively. IBDQ and SF-36 endpoints at Weeks 24 and 52 are shown in Table 1. There was no significant change from Sustain BL

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Table 1 Summary of PRO endpoints in OCTAVE Sustain

	Placebo N=198	Tofacitinib 5 mg BID N=198	Difference From placebo (95% CI)	Tofacitinib 10 mg BID N=197	Difference From placebo (95% CI)
Change from OCTAVE Sustain baseline in IBDQ total score, mean (SE)					
Week 24	-22.7 (2.4)	-2.4 (2.2)***	20.3 (14.6, 26.0)	0.6 (2.2)***	23.2 (17.6, 28.9)
Week 52	-20.2 (2.9)	-1.3 (2.3)***	18.9 (12.2, 25.5)	0.6 (2.3)***	20.8 (14.2, 27.3)
Patients achieving IBDQ Remission,^a %					
Baseline	58.1	61.1	-	61.9	-
Week 24	22.7	50.0***	27.3 (18.2, 36.4)	51.3***	28.5 (19.4, 37.6)
Week 52	14.6	38.4***	23.7 (15.4, 32.1)	48.2***	33.6 (25.0, 42.1)
Patients achieving IBDQ Response,^b %					
Baseline	81.3	82.3	-	84.3	-
Week 24	31.8	59.6***	27.8 (18.4, 37.2)	66.0***	34.2 (24.9, 43.4)
Week 52	19.2	46.5***	27.3 (18.4, 36.1)	53.8***	34.6 (25.8, 43.5)
Change from OCTAVE Sustain baseline in SF-36 PCS, mean (SE)					
Week 24	-5.0 (0.7)	-0.3 (0.7)***	4.8 (3.2, 6.4)	0.4 (0.7)***	5.4 (3.8, 7.0)
Week 52	-5.2 (0.9)	-0.0 (0.8)***	5.1 (3.1, 7.2)	0.3 (0.7)***	5.5 (3.4, 7.5)
Change from OCTAVE Sustain baseline in SF-36 MCS, mean (SE)					
Week 24	-7.3 (0.9)	-1.1 (0.9)***	6.3 (4.2, 8.3)	-0.4 (0.9)***	6.9 (4.8, 9.0)
Week 52	-6.7 (1.2)	-1.0 (1.0)***	5.8 (3.1, 8.4)	0.1 (1.0)***	6.8 (4.2, 9.4)

***p<0.001 vs placebo

Change from baseline data are full analysis set, observed case; IBDQ Remission and Response are full analysis set with non-responder imputation

All baseline data reported are from Visit 1 of OCTAVE Sustain

^aIBDQ Total Score ≥ 170 ; ^b ≥ 16 -point increase from induction study baseline IBDQ Total Score

BID, twice daily; CI, confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, mental component score; PCS, physical component score; PRO, patient-reported outcome; SE, standard error; SF-36, Short-Form 36

in total IBDQ scores at Weeks 24 and 52 with tofacitinib (Table 1). In contrast, IBDQ total score decreased with placebo ($p < 0.001$ for all comparisons of tofacitinib vs placebo). Significantly more patients achieved IBDQ remission and response with both tofacitinib doses vs placebo at all time points ($p < 0.001$ for all comparisons). Mean changes from Sustain BL in SF-36 PCS and MCS and all individual domain scores showed similar benefit with both tofacitinib doses vs placebo at Weeks 24 and 52 ($p < 0.001$ for all comparisons).

Conclusions: For patients with moderate to severe UC and clinical response to tofacitinib induction therapy, significant and clinically meaningful improvements in QoL (assessed by IBDQ and SF-36) were maintained with tofacitinib 5 and 10 mg BID vs placebo through 52 weeks of maintenance therapy.

References:

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Etolizumab treatment improves histological activity as assessed by the Robarts histopathology index

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Background: Etolizumab, an anti-β7 mAb targeting α4β7 and αEβ7 integrins, showed efficacy and safety vs placebo (PBO) during 10 weeks of induction in patients with moderate-to-severe UC in the phase 2 trial, EUCALYPTUS. Because a reduction in histological inflammation has been linked with improved long-term clinical outcome (Bryant et al. *Gut* 2016), and the FDA recommends using both histological assessments and endoscopy to evaluate efficacy, we assessed the effect of etolizumab on histological inflammation in mucosal biopsies from EUCALYPTUS patients using the Robarts histopathology index (RHI).

Methods: Patients were randomly assigned (1:1:1) to subcutaneous etolizumab (100 mg at weeks 0, 4 and 8, with PBO at week 2, or 420-mg loading dose at week 0, followed by 300 mg at weeks 2, 4 and 8), or matching PBO. Biopsies were taken using flexible sigmoidoscopy/full colonoscopy from the most inflamed colonic area within 10–40 cm from the anal verge at baseline (BL) and at week 10. Batched H&E stained slides were scored by a single pathologist using the Geboes scale and converted to RHI (Mosli et al. *Gut* 2015). At week 10, mean change from BL RHI score and mean difference between pooled etolizumab and PBO were calculated. Subanalyses explored histological improvement (defined as categorical reductions in RHI of ≥6 points or ≥50% improvement from BL RHI score) and the relationship with endoscopic improvement.

Results: Analysis included 89 (of 119 efficacy-evaluable) patients with BL histological data and BL RHI >1. Mean week 10 RHI re-

duction was greater for etolizumab- compared with PBO-treated patients regardless of previous aTNF experience, and a greater proportion of patients receiving etolizumab achieved histological improvement compared with PBO. Of patients with an endoscopic subscore (ES) ≤1 at week 10, 89% experienced histological improvement. Mean (SD) RHI change was -14.2 (5.5) in patients with an ES ≤1 at week 10 versus -2.5 (9.5) in patients with an ES >1.

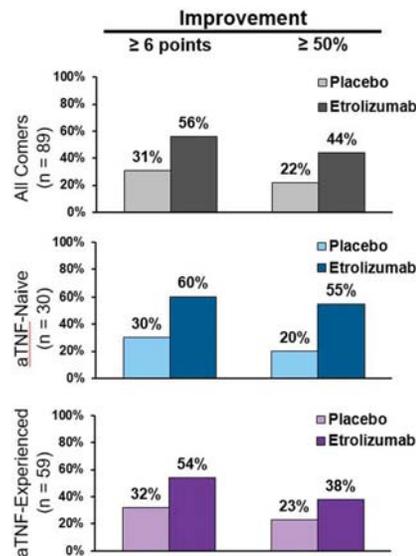


Figure 1

Conclusions: RHI-measured histological activity improved after 10 weeks of etolizumab treatment. Consistent with the clinical remission rates observed in EUCALYPTUS, the magnitude of histological improvement was greater in the aTNF-naive vs aTNF-IR subgroup. RHI reductions are associated with improved ES at week 10.

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Safety, tolerability, and pharmacokinetics of the intestine-restricted oral pan-Janus kinase inhibitor TD-1473 after single and multiple oral doses in healthy subjects

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Background: TD-1473 is a novel, intestine-restricted, pan-Janus kinase (JAK) inhibitor being developed for the treatment of inflammatory bowel diseases (IBD), including ulcerative colitis (UC). JAK inhibition has demonstrated efficacy for inducing remission in UC patients using a systemically active oral agent (tofacitinib), but its use is associated with a risk of serious systemic adverse effects. TD-1473 was designed to inhibit JAK in the gastrointestinal tract following oral dosing while minimizing systemic exposure and associated adverse events. This double-blind, placebo-controlled, dose-escalation study in healthy subjects was conducted to evaluate the safety, tolerability, and PK after single and multiple oral doses of TD-1473.

Methods: Healthy male and female subjects (n=8 per cohort) were randomized to receive TD-1473 or placebo (3:1 ratio) for each cohort in the single ascending dose (SAD, 10 to 1000mg) or the 14-day multiple ascending dose (MAD, 10 to 300mg) parts of the

Table 1

	Mean (SD) Change From BL in RHI at Week 10		
	aTNF-Naive (n = 30)	aTNF-Experienced (n = 59)	All Comers (n = 89)
Etolizumab (100 mg and 300 mg pooled)	-8.8 (9.1)	-6.0 (9.8)	-6.9 (10.0)
PBO	0.4 (13.0)	-2.3 (8.5)	-1.5 (9.6)
Effect (95% CI)	-9.2 (-19.1 to 0.7)	-3.6 (-8.5 to 1.3)	-5.5 (-9.8 to -1.1)
P value	0.066	0.14	0.015

study. Safety and tolerability were assessed by monitoring treatment-emergent adverse events (TEAEs), electrocardiograms (ECGs), vital signs, and laboratory parameters. PK was assessed in plasma and urine.

Results: No moderate, severe, or serious TEAEs were reported in subjects administered TD-1473; no TEAEs led to study discontinuation. TEAEs incidence in the SAD was 33% (10/30) for TD-1473 and 40% (4/10) for placebo. TEAEs incidence in the MAD was 58% (14/24) for TD-1473 and 88% (7/8) for placebo. No clinically meaningful treatment-related effects on vital signs, clinical laboratory, or ECG parameters were observed.

TD-1473 was eliminated in a multiphasic manner with mean terminal elimination half-life values ranging from 4.40 to 43.88 hrs. Median T_{max} values ranged between 0.51 to 2.00 hrs. Systemic TD-1473 exposures were low; C_{max} and AUC_{0-24} increased in a dose-proportional manner with minimal accumulation as assessed on Day 14 (C_{max} and AUC_{0-24} accumulation ratios from Day 1 to Day 14 ranged from 0.52 to 2.27 and 1.36 to 1.63, respectively). Steady-state was achieved after 7 to 9 days of dosing. Mean steady-state apparent clearance (CL/F) and volume of distribution (V/F) ranged between 5519 to 8662 L/hr and 113500 to 571300 L, respectively. The fraction of the dose excreted as unchanged TD-1473 in urine through 24 hours after single and multiple doses of TD-1473 was <0.500%.

Conclusions: TD-1473 exhibits low systemic concentrations (consistent with intestine restriction) with dose-proportional PK following single (up to 1000mg) and multiple doses (up to 300 mg). TD-1473 was generally well tolerated in this study. Results are supportive of further development of TD-1473 for the treatment of IBD, including UC.

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Comparative effectiveness analysis of flares, hospitalisations, and corticosteroid use among biologic naïve patients with inflammatory bowel disease within 12 months of initiation of vedolizumab or infliximab

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Background: This study aimed to compare IBD-related flare, hospitalisations, and corticosteroid use within one year of initiation of vedolizumab (VDZ) versus infliximab (IFX) among biologic-naïve IBD patients in a real-world setting.

Methods: We undertook retrospective analysis of data from 01/05/2014 to 27/07/2016 in the US Explorys Universe electronic medical records database. Inclusion criteria included: diagnosis with UC (ICD-9 556.xx) or CD (ICD-9 555.xx); initiation of VDZ or IFX as 1st-line biologic therapy; age ≥ 18 years; ≥ 12 months of medical history, and; ≥ 12 months of follow-up. Patients commencing concomitant biologic therapies were excluded. Propensity scores were used to match VDZ initiators to IFX initiators (1:2). IBD-related flare was defined as ≥ 1 of: prescription for IV corticosteroids; IBD-related hospitalization; or IBD-related surgery. The percentage of patients experiencing ≥ 1 flare in the first 12 months of follow-up was reported, with focus on the proportion of patients admitted for an IBD-related hospitalization (and annual rate). The proportion of patients who received ≥ 1 oral/IV/rectal corticosteroid prescription,

during induction (0–98 days follow-up), and post-induction (99–365 days follow-up) were also reported.

Results: 81 VDZ initiators were matched to 162 IFX initiators. Among VDZ patients, median age was 44 years (interquartile range, IQR: 30, 56), 63.0% (n=51) had CD, 51.9% (n=42) were female, and median time since diagnosis was 3.6 years (IQR: 1.2, 6.2). No significant differences were observed in baseline characteristics between VDZ and IFX patients. Within 12 months of treatment initiation, 30.9% (95% CI: 21.9, 41.6) VDZ and 31.5% (95% CI: 24.8, 39.0) IFX patients experienced flare. In particular, 12.3% (95% CI: 6.8, 21.3) of the VDZ patients experienced IBD-related hospitalisation, and the associated annual rate was 0.2 (95% CI: 0.1, 0.4); among IFX patients the percentage was 17.9% (95% CI: 12.8, 24.5), and annual rate 0.4 (95% CI: 0.3, 0.5). During induction 28.4% (95% CI: 19.7, 39.0) VDZ patients and 33.3% (95% CI: 26.5, 40.9) IFX patients were treated with corticosteroids; during maintenance these proportions were 35.8% (95% CI: 26.2, 46.7) and 39.5% (95% CI: 32.3, 47.2), respectively.

Conclusions: In a real-world setting, within one year of biologic treatment initiation, IBD patients receiving VDZ as 1st-line biologic therapy experienced numerically lower rates of flares compared with IFX. Similarly, a smaller proportion of VDZ patients experienced hospitalisation or received steroid treatment. Further studies in larger cohorts are required to confirm these trends.

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Efficacy and safety of switching from reference infliximab to biosimilar infliximab in patients with inflammatory bowel disease: first French experience

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Background: Infliximab is widely used for induction and maintenance therapy in inflammatory bowel diseases (IBD). Reference infliximab (Remicade®) was the first anti-TNF available, but its costs are high, placing a strain on healthcare system. CT-P13 is a biosimilar of Remicade® with expected savings of 30%. No data is available in France regarding switching from reference infliximab to CT-P13. We aimed to assess efficacy and safety of switching from reference infliximab to CT-P13 in IBD.

Methods: From September 30, 2015 to March 30, 2016, a switch to CT-P13 (Inflectra®) and inclusion in a prospective observational study were proposed to all Remicade®-treated patients in our hospital (IBD, rheumatologic diseases, uveitis). Patients had to be on maintenance therapy (>3 Remicade® infusions) with stable treatment. Information was given and non-opposition was required. Data were collected in a anonymous questionnaire at baseline (2 infusions before the switch) and at each biosimilar infusion. Primary endpoint was the rate of patients still treated with Inflectra® after 3 infusions. Secondary endpoints were clinical activity, infliximab trough levels (ITL), anti-infliximab antibodies changes. A closeout visit was performed in July 2016. IBD activity was assessed with Mayo score [ul-

cerative colitis (UC)] or Harvey-Bradshaw [Crohn's disease (CD)]. ITL and anti-infliximab antibodies were measured before the first and the third CT-P13 infusion. Changes from baseline were analyzed with univariate analysis (Fisher or Mann-Whitney).

Results: Overall, 268 consecutive patients were enrolled. Among them, 64 had IBD: one patient refused the switch and 63 [33 women, aged 34.5 (29–44), 42 CD, 21 UC] were included. At inclusion, duration of Remicade[®] therapy was 34.8 (14–74) months. Three infusions after the switch, 60 (95.2%) were still on Inflectra[®]. One patient stopped Inflectra[®] for pregnancy and 2 had IBD relapse: one was switched back to Remicade[®] and one to adalimumab. In July 2016, 8.4 (7.9–8.9) months after the switch, 2 more patients had stopped CT-P13 for suspected adverse event (purpura) while 55 (87.3%) remained treated with CT-P13. No allergic infusion reaction was reported. Changes from baseline were not significant: Mayo score (p=0.95), Harvey-Bradshaw (p=0.14), infliximab dose (p=0.71) and ITL [baseline (5.9±5 µg/mL); 3rd infusion (7.8±6µg/mL) (p=0.09)]. No patient developed anti-infliximab antibodies after the switch.

Conclusions: This prospective observational study suggests that the switch from reference infliximab to CT-P13 does not change IBD evolution. After 3 infusions, 95.2% patients remained on CT-P13 treatment. No changes in clinical activity, infliximab doses and ITL were observed. No anti-infliximab antibodies appeared.

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Original and biosimilar infliximab: Are they two faces of the same coin? The experience from a pioneer European center

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Background: The use of anti-TNF antibodies has dramatically changed the management of patients with inflammatory bowel disease (IBD). While several biosimilar versions of the original drugs have already been developed, confidence regarding their efficacy and safety is not yet worldwide accepted. This study aimed to compare the efficacy and safety profile between the original infliximab (Remicade[®]) and a biosimilar infliximab (Remsima[®]) in IBD patients from a Portuguese center.

Methods: Comparative single-center retrospective study including patients with ulcerative colitis (UC) or Crohn's Disease (CD) treated with either Remicade[®] or Remsima[®]. Demographic, clinical, biochemical and endoscopic data were collected. Harvey-Bradshaw Index and Mayo Score were used to define clinical remission in CD and UC patients, respectively, according to prevailing guidelines. Endoscopic remission was defined as Simple Endoscopic Score for Crohn's Disease 0, Rutgeerts score i0-i1 or Mayo Endoscopic Subscore 0–1. Qui-square, Fisher's exact and t-student tests were used for statistical analysis.

Results: From the 90 consecutive included patients, 61 had CD and 29 had UC, from whom 60 were treated with Remicade[®] and 30 with Remsima[®]. The indications for infliximab were steroid-dependence in 36, active disease despite immunosuppressors in 22, perianal disease in 11, acute severe UC in 6, presence of several poor prognosis factors in 6, postoperative recurrence in 5, and steroid-refractoriness in 4 patients. Clinical remission was observed in 32, 54

and 64 patients, at weeks 12, 24 and 52, respectively. There were no significant differences in achieving clinical remission in any of these time points between Remicade[®] and Remsima[®] (p=0.755; p=0.361; p=0.511, respectively). From the 78 patients who had endoscopic re-evaluation 6–12 months after the initiation of infliximab, 44 (56.4%) had endoscopic remission of the disease, and no differences were found between Remicade[®] and Remsima[®] (p=0.474). The mean CRP level significantly decreased one year after infliximab (20.1 vs. 8.1 mg/L; p=0.001) and this was independent of the used agent. No differences were found between Remicade[®] and Remsima[®] regarding adverse events (7 vs. 3; p=1.000), number of patients discontinuing the drug during the follow-up (12 vs. 4; p=0.564), need of hospitalization because of disease flare (8 vs. 2; p=0.486), need of steroids during the follow-up (4 vs. 2; p=1.000), or secondary loss of response (21 vs. 8; p=0.425).

Conclusions: The biosimilar infliximab seems as effective as the original infliximab in achieving clinical and endoscopic remission in patients with IBD. No significant differences regarding adverse events, need to discontinue the drug, or loss of response were observed between Remicade[®] and Remsima[®].

P473

How to monitor the withdrawal of maintenance treatment with azathioprine in IBD patients with deep remission: results from a prospective study on multiple non invasive tests

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Background: There is uncertainty regarding the optimal duration of maintenance treatment with azathioprine (AZA) in Crohn's disease (CD) and ulcerative colitis (UC), with some studies suggesting durations up to 4–5 years and others supporting long-term indefinite use. More recent guidelines state that for patients in long term remission, cessation of treatment may be considered in the absence of objective signs of inflammation, but no data are available on how to monitor these patients after AZA withdrawal.

Methods: A prospective observational study was performed on consecutive patients with CD or UC who stopped their maintenance treatment with AZA while being in steroid-free, deep remission, defined as normal clinical and endoscopic indexes, normal C-reactive protein (CRP) and normal fecal calprotectin. After AZA withdrawal, all patients received maintenance treatment with salicylates. Every 3 months, blood samples were collected for standard biochemical tests (including CRP, full blood count and protein electrophoresis), as well as stool samples for fecal calprotectin dosage. Bowel ultrasonography and ileocolonoscopy were performed every 6 and 12 months, respectively, as well as in case of clinical relapse. Multiple logistic regression and Cox proportional-hazards models were used to assess the predictors of disease relapse.

Results: 41 patients (23 males, median age 45 years) who stopped AZA after median 7 years (range 5–14) were enrolled. After a mean follow-up of 24 months (range 5–48), 19 patients (46%; 7/19 CD, 12/22 UC) relapsed, within median 13 months (range 2–35). Predictors of clinical relapse at the time of AZA withdrawal were female gender (p=0.045) and age ≤45 years (p=0.035) only for UC. Fecal calprotectin was the only predictor of clinical relapse during the non invasive monitoring performed after AZA withdrawal, both in UC

($p=0.019$) and in CD ($p=0.017$). Moreover, fecal calprotectin was positive in all patients with UC and in 57% of CD patients at the time of relapse.

Conclusions: Up to half of patients with IBD relapses after AZA withdrawal at different times. Fecal calprotectin can predict subsequent clinical relapse after AZA withdrawal. This can be useful in the non invasive monitoring of patients to detect preclinical relapse and to early correct our therapeutic strategy after AZA withdrawal. Prospective randomized studies are needed to validate such strategy.

P474

An enzyme-linked immunosorbent assay for therapeutic drug monitoring of vedolizumab

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Background: Vedolizumab (VLZ), an $\alpha 4\beta 7$ integrin antagonist, is a therapeutic monoclonal antibody recently approved for use in moderate to severe ulcerative colitis (UC) and Crohn's disease (CD). Part of the interindividual differences in response to VLZ treatment may be explained by interindividual variability in pharmacokinetics.

Methods: Microtiter plates were coated with anti-VLZ specific monoclonal antibody. Samples diluted 1:200 were added on a microtiter plate for specific binding, and bound VLZ was detected using mouse anti-human immunoglobulin G1 (HRP-anti h IgG1). Trough serum concentrations of VLZ were analyzed in 86 samples of 21 adult UC patients and compared to concentrations measured by in-house developed LC-MS/MS assay (Christ et al., J Crohn's Colitis 2016, S1).

Results: The limit of quantification (LoQ) for VLZ determination in human serum samples was 0.0071 $\mu\text{g/mL}$. The intra-assay variation ($n=20$) was 8.57% for 9.55 $\mu\text{g/mL}$ and 6.54% for 18.9 $\mu\text{g/mL}$. The inter-assay variation ($n=40$) was 7.10% for 28.5 $\mu\text{g/mL}$ and 8.33% for 35.7 $\mu\text{g/mL}$. Linearity testing of the ELISA was performed by analysis of two serially diluted patient samples; the coefficients of variation (CV%) were below 8%. No false positive signals were detected in samples spiked with TNF α blockers (infliximab, adalimumab, golimumab). In the samples of patients treated with VLZ the trough level ranged from 0.02 to 71.01 $\mu\text{g/mL}$. VLZ results of ELISA and an in-house developed LC-MS/MS assay showed a correlation coefficient (r) of 0.96 (Fig. 1).

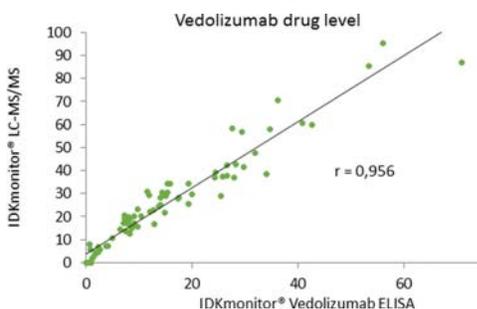


Figure 1

Conclusions: This newly developed ELISA method is rapid, accurate and reproducible, and may be useful for pharmacokinetic-pharmacodynamic studies, as well as in therapeutic drug monitoring of vedolizumab.

P475

Switching from infliximab originator to CT-P13 is not related to increased immunogenicity in IBD patients: a prospective case-control study

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Background: Switching from infliximab originator (Remicade[®], RMC) to CT-P13 has been shown to be safe in patients with inflammatory bowel disease (IBD). There are few data confirming that switching is not related to higher immunogenicity than continuing RMC, and the role of anti-infliximab antibodies (ADA) formation in IBD patient clinical outcomes.

Methods: We prospectively analysed 3 cohorts of consecutive IBD patients (43 Crohn's disease, 43 ulcerative colitis, 15 unclassified colitis) treated with RMC, CT-P13, or switchers from RMC to CT-P13. A total of 564 consecutive trough sera were collected just before the infusion to all patients. All samples were frozen for subsequent testing with ELISA Promonitor[®]-IFX and Promonitor[®] Anti-IFX (Progenika, Spain). The ADA positivity rate (presence of stable ADA in at least two consecutive samples), trough IFX levels (TL), and the correlation between ADA and infusion reactions (IR) and secondary loss of response (sLoR) was analysed with survival curves and log-rank test, and logistic regression, and compared in the three groups. Statistical significance was set as $p < 0.05$.

Results: One-hundred IBD patients treated with infliximab (RMC ($n=30$), CT-P13 ($n=52$), or switchers from RMC to CT-P13 ($n=18$)) were enrolled. In the entire population, 34 patients developed ADA in the follow-up (FU) time (13 RMC, 9 CT-P13 and 12 switchers, $p=0.5$). Forty-nine patients (49%) had suboptimal levels of IFX TL in the FU time without differences between the three groups (19% RMC, 18% CT-P13, 12% switchers, $p=0.14$). Fifteen patients (15%) had sLoR (4% RMC, 9% CT-P13, 2% switchers, $p=0.19$) in the FU time. Seven patients (7%) had IR in the FU time (1% RMC, 5% CT-P13, 1% switchers, $p=0.15$). There was significant difference ($p < 0.001$) in the ADA levels between patients having IR (median ATI=37 AU/mL) and those without IR (median ATI = 0.0 AU/mL), regardless of the cohort ($p=0.003$).

Conclusions: Patients switching from RMC to CT-P13 are not at higher risk for immunogenicity compared to those exposed to RMC or CT-P13 alone. Although ADA formation was related to IR, no significant increase in ADA formation was found in patients who were switched. Switching from RMC to CT-P13 is safe in IBD patients.

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Sigmoidostomy or Hartman's procedure during laparoscopic subtotal colectomy for acute colitis complicating inflammatory bowel disease? A comparative study in 129 consecutive patients

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Background: Today, there is no consensus about the best management of the remaining rectum following subtotal colectomy for acute

colitis complicating inflammatory bowel disease. There are three options: intra-peritoneal rectal stump closure (Hartmann's pouch with closed stapled rectal stump), creation of a mucous fistula by exteriorizing the recto-sigmoid remnant in the left iliac fossa, suprapubic or in the same opening as the ileostomy (stoma rectal stump) or to position the closed recto-sigmoid remnant in the subcutaneous tissue. Results from retrospective studies are conflicting. The objective was thus to evaluate the impact of rectal stump management during laparoscopic subtotal colectomy for acute colitis.

Methods: All the patients who underwent laparoscopic subtotal colectomy for inflammatory bowel disease in 2 expert centres were included and divided into 2 groups: Hartman's with stapled rectal stump (Group A) and sigmoidostomy at the same site than ileostomy, in the right iliac fossa (Group B). Comparisons were performed between groups for the following findings: demographic features, inflammatory bowel disease characteristics, preoperative treatment in the three last months, intraoperative features, postoperative outcomes, characteristics of completion proctectomy with IPAA, and long-term results.

Results: From 2005 to 2015, 129 patients (71 males, median age =37 [13–78] years) were divided into Groups A (n=52) and B (n=77). Patients in Gr. A were more frequently under steroids before subtotal colectomy (83% vs 58%, p=0.004), but less frequently under anti-TNF (38% vs 74%, p=0.0001) than those from Gr. B. Operative time for subtotal colectomy was longer in Gr. A than Gr. B (210 [139–396] vs 180 [150–310] minutes, p=0.002). Overall, surgical, medical and major morbidity was similar between groups. Completion proctectomy with ileal pouch-anal anastomosis (IPAA) was more frequently performed through an open approach in Gr. A than in Gr. B (88 vs 0%, p<0.0001). Postoperative and long-term results after the second surgical stage were similar between groups.

Conclusions: This study suggests that the management of the remaining rectum after subtotal colectomy has no impact on operative and long-term results. Thus, the choice of the most appropriate option can depend on surgeon's discretion.

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Abstract has been withdrawn

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The current place of probiotics in treatment of pouchitis: systematic review

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Background: Pouchitis is a common complication in patients undergoing restorative proctocolectomy for ulcerative colitis. Therapeutic attempts include manipulations of pouch flora composition. In this systematic review, we aimed to score the evidence supporting the use of probiotics and prebiotics in pouchitis patients, to clarify the place of these treatments in current therapeutic regimens.

Methods: We conducted extensive electronic searches of the PubMed and SCOPUS databases, from their earliest records through Nov 2016, for MESH terms “probiotics” and “pouchitis”.

Results: The electronic search retrieved 20 citations [1–20]. Six published RCTs [2,3,9,10,13,14] and a RCT presented as an abstract [12] evaluated clinical, endoscopic end/or histological effect of probiotics as a primary outcome; other reports ranged in level of evidence between meta-analyses [16–19] (4), open-labeled trials [1,4–8,11,15] (8) and letters [20] (1).

Conclusions: *Prevention of onset of pouchitis/Primary prevention.* Three studies examined the ability of various probiotic regimens to prevent the onset of pouchitis after the restorative proctocolectomy [1–3]. Primary preventive effect of VSL#3 was indicated by a single RCT, with calculated effect ratio of 1.50 [1.02, 2.21] [16].

Treatment of acute episode. Seven – mostly open-labeled and uncontrolled – trials examined the use of probiotics for treatment of acute pouchitis episode [4–10]. Efficacy of probiotics in acute episodes of pouchitis needs to be proved in randomized controlled trials.

Seven studies aimed to determine the efficacy of probiotic strains in preventing recurrences in patients with previous episode/s of pouchitis [4,9,11–15]. Probiotic mixture VSL#3 effectively prevents relapses after successful antibiotic treatment of active inflammation, with calculated effect ratio of 20.24 [4.28, 95.81] [16]. Side effects may affect the adherence of the patients with the long-term treatment [15,16].

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Abstract P478 – Table 1. Use of probiotics for prevention of onset of pouchitis

Study	No. of patients	Duration (months)	probiotic strain	Strain	Control	Pouchitis-free survival
Gosselink (2004)	117	36		LGG	No treatment (historical control)	93% vs. 71% (p=0.011)
Gionchetti (2003) [2]	40	12		VSL#3	Placebo	90% vs. 60% (p<0.05)
Yasueda (2015) [3]	17	24		<i>Clostridium butyricum</i>	Placebo	89% vs. 50% (NS)

Abstract P478 – Table 2. Use of probiotics for treatment of active pouchitis

Study	No. of patients	Duration (months)	Strain	Control	Outcome
Gionchetti et al. (2007) [4]	23	1	VSL#3	Open-labeled; uncontrolled	69% remission rate
Laake et al. (2005) [5]	51 (10 with active disease)	1	Cultura [®] fermented milk product	Open-labeled; uncontrolled	Symptomatic and endoscopic improvement in patients with active disease
Laake et al. (1999) [21]			Cultura [®] fermented milk product	Open-labeled; uncontrolled	Symptomatic improvement
Laake et al. (2003) [7]	10	1/2 month	Cultura [®] fermented milk product	Open-labeled; uncontrolled	Endoscopic improvement
Laake et al. (2004) [8]	41 UC + 10 FAP	1	Cultura [®] fermented milk product	Open-labeled; uncontrolled	Symptomatic remission and endoscopic improvement
Tomasz et al. (2014) [9]	43 (14 with active disease)	9	<i>Lactobacillus acidophilus</i> , <i>Lactobacillus delbrueckii</i> subsp. <i>Bulgarius</i> , <i>Bifidobacterium bifidus</i>	Placebo	43% remission rate vs 0% on placebo
Kuisma (2003) [10]	20	3	LGG	Placebo	No benefit

Abstract P478 – Table 3. Use of probiotics for prevention of recurrences of pouchitis

Study	No. of patients	Duration (months)	Probiotic strain	Control	Outcome
Pronio (2008) [11]	31	12	VSL#3	No treatment	Small reduction of PDAI scores
Brown (2004) [12] (abstract)	17	6	Bifidobacterium longum BB-536	Placebo	Pouchitis-free survival 86% vs. 60% on placebo (NS); small reduction of PDAI scores
Tomasz et al. (2014) [9]	43	9	Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. Bulgaricus, Bifidobacterium bifidus	Placebo	43% in remission vs 0% on placebo
Gionchetti et al. (2007) [4]	16	6	VSL#3	Open-labeled; uncontrolled	69% remission rate
Gionchetti (2000) [13]	40	9	VSL#3	Placebo	Pouchitis-free survival 85% vs. 0% on placebo (P<0.001)
Mimura (2004) [14]	36	12	VSL#3	Placebo	Pouchitis-free survival 85% vs. 6% on placebo (P<0.0001)
Shen (2005) [15]	31	8	VLS#3 (self administration)	Open-labeled compliance trial	80% non-adherence; 74% self-reported recurrence of symptoms

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Shifting the shunters in a paediatric inflammatory bowel disease population: thiopurine dose splitting versus allopurinol and thiopurine co-therapy

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Background: The use of 6-Thioguanine nucleotide (6-TGN) levels as a method of adjusting Thiopurine dosing, thus optimizing therapeutic effects, have dramatically improved the safety of their use in Paediatric Inflammatory Bowel Disease (pIBD). The study aim was to evaluate the therapeutic outcomes of pIBD patients treated with either Thiopurine dose splitting (Group 1) or Allopurinol and Thiopurine Co-Therapy (Group 2) (Thiopurine dose reduced to 25% of 2mg/kg, Allopurinol 50mg <30kg weight, 100mg >30kg) for either abnormal level outside the therapeutic range of 235 to 450 pmol/8×10E8 RBC and/or abnormal 6-TGN/MeMP ratios (>11).

Both are effective treatment options and although data is available in adult IBD on either regimen, there is paucity of data in pIBD patients.

Methods: 136 patients (male n=81, age range 4 years 10 months–16 years 8 months, median 13 years) on Thiopurines with recorded metabolites were retrospectively identified over a 26 month period from a database.

101 (74%) of patients had levels within the therapeutic range with normal ratios. The two regimens above were implemented on those with abnormal result, n=35 (26%).

Results: In Group 1, n=22 patients were identified; the pre-intervention 6-TGN levels had a median of 199, range 75–521; post-intervention 245, range 123–577. The pre-intervention ratio had a median of 14.5, range 2–32; post-intervention 5, range 0–18. 18 patients had a ratio of >11, in n=17 (77%) the ratio median drop was 11, range 4–31, the biggest drops were with pre-intervention ratios of >18, with 19/22 (86%) patients returning to ratios <11. The pre-intervention MeMP levels had a median of 3179, range 219–5902, post intervention 1496, range 143–3805.

In Group 2, n=13 patients were identified; the pre-intervention 6-TGN levels had a median of 186, range 75–387; post-intervention 309, range 156–578. The pre-intervention ratio had a median of 15, range 8–34; post-intervention 1, range 0–6; 12/13 (92%) patients had a ratio of >11, in those the ratio median drop was 14, range 6–34 with 11/12 having median ratio of 1, range 0–2; The pre-intervention MeMP levels had a median of 2539, range 648–6333, post intervention 246, range 116–2306. There was a statistically significant difference regarding 6-TGN levels in the slit dose versus Co-therapy (0.04) and in the drop in ratio (0.013) favoring the Co-therapy treatment. There was no statistically significant difference in the MeMP levels (0.073)

Conclusions: Although both groups lowered the abnormal levels/ratios, Co-therapy was superior to split dose in our patient cohort. Low-dose Thiopurines and Allopurinol co-therapy is a safe and effective treatment option in pIBD, however needs close monitoring to avoid myelotoxicity. Larger patient numbers are needed to confirm our data.

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Characteristics of drug-induced lupus 2° to anti-TNF agents in inflammatory bowel disease patients and evolution after switch to a second anti-TNF

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Background: Anti-TNF agents can induce the formation of antinuclear antibodies (ANA), anti-DNA, and can facilitate the development of drug-induced lupus (DILE). DILE treatment could require anti-TNF withdrawal and use of steroids, antimalarials and immuno-

suppressants to control DILE symptoms. Little is known if it is a class effect or drug dependent, and there is no information about the safety of switching to another anti-TNF.

Objectives: To describe the characteristics of DILE due to anti-TNF in patients with inflammatory bowel disease (IBD) and evaluate their progress after switch to another anti-TNF.

Methods: A retrospective, multicenter descriptive study. We identified all cases of DILE from the participating centres, which meet with the following criteria: 1) temporal relationship between the administration of anti-TNF and the development of symptoms and autoantibodies and 2) at least 4 systemic lupus criteria or the presence of nephritis in the presence of ANA or anti-DNAs. Evolution was recorded in case of beginning a second anti-TNF.

Results: We identified 38 patients with DILE due to anti-TNF (76% women, 73% Crohn's disease and 27% ulcerative colitis) with a mean age of 38 (±11) years at the time of DILE. The mean time under treatment with anti-TNF to DILE diagnosis was 14 (±12) months. Regarding anti-TNF agents, 70% cases of DILE were associated with IFX and 30% with adalimumab, 66% of patients were concomitant treated with IMS and 34% with mesalazine. Most common feature of DILE were: arthritis (91%), rash (64%), oral ulcers (20%). Serologically, 91% ANA+, 20% anti DNAs+, 9% low levels complement. Anti-TNF agents was retired in 94% of cases and 77% required specific treatment (14% hydroxychloroquine, steroids 43%, methotrexate 17%). 60% of patients started a second anti-TNF, with recurrence of symptoms in 21% of them.

Conclusions: DILE secondary to anti-TNF is a rare phenomenon that requires specific treatment in most cases despite the withdrawal of the anti-TNF. Switching to another anti-TNF is seldom associated with the recurrence of DILE.

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Serum levels of infliximab associate with early mucosal healing in Crohn's disease: different "therapeutic window" between post-induction and maintenance treatment

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Background: Serum levels of Infliximab (IFX) was reported be associated with mucosal healing (MH) in Crohn's disease (CD) in some studies. However, association between pharmacokinetics of IFX and early MH remains unknown. We aimed to analyze the association between serum trough IFX level and MH at week 14 (post induction) and week 30 (maintenance) in CD patients, respectively.

Methods: CD patients with scheduled IFX therapy in The First Affiliated Hospital of Sun Yat-sen University between January 2012 and April 2016 were retrospectively screened for complete follow-up data, especially availability of both serum and endoscopy at week 14 or 30. Serum trough IFX level was measured using enzyme-linked immunosorbent assay. Correlations between IFX level and MH were investigated at week 14 and 30, respectively.

Results: At week 14, 74 CD patients (median age: 19.0 (16.0, 26.0) years, male: 53%) were included and 50 patients achieved MH. Median serum IFX level was significantly higher in patients with MH than those without (4.3 (1.5, 7.1) vs 1.1 (0.3, 2.6) ug/mL, p=0.002). IFX level was negatively correlated with CRP (r=-0.628, p<0.001). Multivariate logistic regression analysis showed that IFX level was an independent risk factor for MH (OR 1.430, 95% CI: 1.125–1.816,

$p=0.003$). IFX level above 4.5 ug/mL identified patients with MH with 50.0% sensitivity and 95.8% specificity (area under the curve = 0.725, $p=0.002$). Increasing levels of IFX above 8 ug/mL had minimal impact on the achievement of MH. At week 30, 80 CD patients (median age: 19.5 (16.0, 25.0) years, male: 56%) were eligible for analysis and 42 patients obtained MH. Multivariate logistic regression analysis identified IFX level as an independent risk factor for MH (OR 1.337, 95% CI: 1.032–1.731, $p=0.028$). The optimal cutoff value of IFX level for predicting MH was 2.7 ug/mL (area under the curve=0.793, sensitivity 73.8%, specificity 89.5%, $p<0.001$). The association between IFX level and increase of MH reached a plateau at 12 ug/mL.

Conclusions: Serum IFX level positively correlated with early mucosal healing in CD patients. We propose that serum IFX levels of 6–10 ug/mL at week 14 and 10–14 ug/mL at week 30 are required to achieve MH in >80% of patients with CD, respectively, and that this could be considered as “therapeutic window”.

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Early anti-TNF/immunomodulator therapy is associated with better clinical outcomes in Asian patients with Crohn’s disease with poor prognostic factors

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Background: Although the use of anti-TNFs or immunomodulators (IMs) in the early course of disease is believed to be effective in improving long-term outcomes of patients with Crohn’s disease (CD), especially those with poor prognostic factors, this concept was not clearly proved in Asian patients.

Methods: We retrospectively analyzed clinical data of Korean patients with CD who were treated at the Asan Medical Center between January 1997 and August 2016. Patients with two or more among the following risk factors for progression; diagnosis at age of under 40, need for systemic corticosteroids within three months after diagnosis, and perianal fistula at diagnosis were included. Patients who already experienced intestinal surgery and/or intestinal complications before or at diagnosis of CD were excluded. A total of 670 patients were enrolled and the probabilities of intestinal surgery and intestinal complications were compared between the following three groups; the early anti-TNF group ($n=79$, starting anti-TNFs within 2 years after diagnosis), the early IM group ($n=286$, starting IMs, but not anti-TNFs within 2 years after diagnosis), and the late therapy group ($n=305$, starting anti-TNFs and/or IMs 2 years after diagnosis).

Results: The chi-squared test showed that lower proportion of patients in the early anti-TNF/IM groups suffered from intestinal surgery ($p<0.001$), stricturing complication ($p=0.001$), and penetrating complication ($p<0.001$) than the late therapy group. However, there were no significant differences between the early anti-TNF

group and the early IM group in terms of intestinal surgery and intestinal complications. The Kaplan-Meier analysis with the log-rank test showed the superiority of the early anti-TNF/IM groups in terms of delaying intestinal surgery ($p<0.001$), stricturing complication ($p=0.002$), and penetrating complication ($p<0.001$) compared with the late therapy group, but not identifying the superiority of the early anti-TNF group compared with the early IM group. In the multivariate Cox regression analysis, the late anti-TNF/IM therapy was independently associated with a higher risk of intestinal surgery (adjusted hazard ratio [aHR] 2.321, 95% confidence interval [CI] 1.503–3.584, $p<0.001$), behavioral progression (aHR 2.001, 95% CI 1.449–2.763, $p<0.001$), stricturing complication (aHR 1.736, 95% CI 1.209–2.493, $p=0.003$) and penetrating complication (aHR 3.315, 95% CI 2.094–5.249, $p<0.001$).

Conclusions: In Asian CD patients with poor prognostic factors and who are naïve to both intestinal surgery and intestinal complications, use of anti-TNFs or IMs within 2 years after diagnosis of CD is associated with better outcomes than the late use of the drugs in terms of intestinal surgery and intestinal complication.

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Relapse after discontinuation of the maintenance drug in patients with Ulcerative proctosigmoiditis: preliminary result of a prospective randomized trial

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Background: The drug maintenance in patients with ulcerative colitis (UC) is essential. But the adherence with drug maintenance in quiescent UC is low and it is not well established how long the drug maintenance must be continued. Although discontinuation of medication may be reasonable for those with distal disease who have been in remission for 2 years and are averse to such medication according to European guideline, there were few prospective studies. We evaluated the relapse rate after discontinuation of the maintenance drug in patients with ulcerative proctosigmoiditis, prospectively.

Methods: The patients with UC who initially diagnosed and had been maintained the clinical, endoscopic, and histological remission more than 2 years were randomized two groups. Maintenance drug was continued in C group and discontinued in D group. The patients with active disease, steroid-dependency, history of biologics use, and pregnancy were excluded. Partial Mayo score and compliance were checked every 3 months for 1 year of follow-up period. Primary end point was the clinical, endoscopic, and histological relapse rate at 1 year and secondary end point was to evaluate the cumulative relapse rate over 1 year and risk factors related to relapse.

Results: Total 55 patients were enrolled and one patient in C group was dropped out because of non-adherence to drug. The age at diagnosis, gender, disease extent, frequency of relapse before enrollment, duration of remission, Mayo score at diagnosis, initial laboratory findings, and drug usage were not different in two groups. Compliance was over 90% in all patients. Nine patients (7.4%, 2/27 in C group and 25.9%, 7/27 in D group) were relapsed within 1 year but the cumulative relapse rate at 1 year was not statistically different between two groups ($p=0.068$). The risk factors related to relapse were initial CRP level, extent of disease, Mayo score at diagnosis and history of oral steroid use. Duration of remission and was not predictive factor for relapse.

Conclusions: Although this study was preliminary, discontinuation

of maintenance drug maybe increase the relapse at 1 year, especially in patient who had abnormal initial CRP level, sigmoid involvement, or used oral steroid. Initially mild ulcerative proctitis patients who have been maintained remission more than 2 years can be withdrawn maintenance drug.

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Dietary therapy using the Crohn's disease exclusion diet is a successful strategy for induction of remission in children and adults failing biological therapy

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Background: Loss of response (LoR) to biologics in Crohn's disease (CD) is a significant clinical problem. Dietary therapy as a treatment strategy in this setting has not been previously reported. We report the use of dietary strategies using enteral nutrition coupled with the Crohn's Disease Exclusion Diet (CDED) for LoR.

Methods: We have used dietary therapy as a salvage therapy for patients with biologic refractory disease or LoR. All cases of LoR to a biologic treated with dietary therapy as the sole salvage therapy in our unit. Patients with severe flares received 14 days of exclusive enteral nutrition followed by 6 weeks of CDED with Partial Enteral Nutrition (PEN) providing 50% of calories. Patients with non-severe disease received only CDED + PEN 50% for 12 weeks. Current and prior treatment, Harvey Bradshaw Index (HBI), CRP and albumin were recorded. All patients were seen at week 6 & 12 for follow up. Remission was defined as HBI <5 at week 6.

Results: Twenty one patients, mean age 22.1±8.9 years. (11 adults and 10 children) met study criteria. Seventeen patients (81%) had used combination therapy, 10/21 (47.6%) were failing a second biologic. Dose escalation had failed in 13/21 (62%) patients. Clinical remission after 6 weeks was obtained in 13/21 (61.9%). Mean HBI decreased from 9.14±4.05 to 2.5±3.7 (p<0.001), mean CRP decreased from 3.2±3.4 to 1.1±2 (p=0.033) and mean albumin increased from 3.5±0.6 to 3.8±0.5 (p=0.06).

Conclusions: Dietary therapy combining enteral therapy with the CDED may be a useful salvage therapy for patients failing biological therapy despite dose escalation.

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Dosing infliximab in Crohn's disease: Is adjustment for body size justified?

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Background: Infliximab (IFX), an anti-TNF monoclonal antibody approved for the treatment of inflammatory bowel disease, is dosed per kg body weight (BW). However, the rationale for body size adjustment has not been unequivocally demonstrated [1], and first attempts to improve IFX therapy have been undertaken [2]. The aim of our study was to assess the impact of different dosing strategies (i.e. body size-adjusted and fixed dosing) on drug exposure and pharmacokinetic (PK) target attainment. For this purpose, a comprehensive simulation study was performed, using patient characteristics (n=116) from an in-house clinical database.

Methods: IFX concentration-time profiles of 1000 virtual, clinically representative patients were generated using a previously published PK model for IFX in patients with Crohn's disease [3]. For each patient 1000 profiles accounting for PK variability were considered. The IFX exposure during maintenance treatment after the following dosing strategies was compared: i) fixed dose, and per ii) BW, iii) lean BW (LBW), iv) body surface area (BSA), v) height (HT), vi) body mass index (BMI) and vii) fat-free mass (FFM)). For each dosing strategy the variability in maximum concentration C_{max} , minimum concentration C_{min} ($= C_{8weeks}$) and area under the concentration-time curve (AUC), as well as percent of patients achieving the PK target, $C_{min}=3 \mu\text{g/mL}$ [4] were assessed.

Results: For all dosing strategies the variability of C_{min} (CV ≈110%) was highest, compared to C_{max} and AUC, and was of similar extent regardless of dosing strategy. The proportion of patients reaching the PK target (≈1/3) was approximately equal for all dosing strategies.

Conclusions: By using a simulation approach different dosing regimens of IFX revealed the highest variability for C_{min} , the most commonly used PK parameter guiding treatment, independent upon dosing regimen. The variability of AUC and C_{max} was lowest with BSA-based and BW-based dosing, respectively. According to the results of the study, and taking into account simplicity and pharmacoeconomic reasons the fixed dosing of IFX could be a better alternative to currently recommended BW-based dosing, especially for lighter patients, with 33% more patients benefiting.

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Dosing regimen	Per BW (5 mg/kg)	Fixed (364 mg)	Per LBW (6.91 mg/kg)	Per BSA (198 mg/m ²)	Per HT (2.13 mg/cm)	Per BMI (14.8 mg/kg/m ²)	Per FFM (7.33 mg/kg)
Variability in AUC (CV%)	34.9	36.6	35.2	34.7	36.8	36.1	36.2
Variability in C_{max} (CV%)	13.0	18.7	14.8	14.1	19.1	15.6	17.0
Variability in C_{min} (CV%)	110.2	110.9	110.2	109.9	111.1	110.9	110.9
PK target (3 $\mu\text{g/mL}$) attainment (%)	29.5	30.0	30.0	29.9	30.2	29.8	29.9

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Immunization status of children and adolescents with inflammatory bowel disease or autoimmune hepatitis in Germany

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Background: Long-term immunosuppressed patients with inflammatory bowel disease (IBD) and autoimmune hepatitis (AIH) are at risk of severe infections with vaccination preventable diseases. Several recent studies demonstrated insufficient immunization coverage in children and adolescents with IBD. Therefore, we evaluated the vaccination rate of children and adolescents with IBD and AIH in Germany.

Methods: As part of the German multicentre clinical trial called "VARICED", the immunization rate of patients with IBD and AIH below 18 years of age was assessed from the certificate of vaccination, medical history of chicken pox and by analysing varicella zoster virus (VZV) IgG and measles virus IgG antibody titres by ELISA.

Results: To date 229 patients (51% female, mean age at diagnosis 9.9 years) are registered: 137 have Crohn's disease (CD), 53 ulcerative colitis (UC), 19 IBD-unclassified (IBD-U) and 20 AIH. The majority of the patients (n=190, 83%) are on immunosuppressive therapy (AIH 100%, CD 89%, UC 68%). A complete basic immunisation consisting of 4 doses of a hexavalent vaccine were given to 89% of the total cohort. A combined inoculation for measles, mumps, and rubella (MMR) was documented in 225 (98%) patients, 208 (92%) received two doses.

VZV vaccination was introduced in 2004 to the vaccination schedule from the German Standing Committee on Vaccination (STIKO). A good implementation with 90% was found in the birth cohorts from 2005 onwards. In children born before 2005 (n=190) only 22% received VZV vaccination catch up. VZV vaccination was documented in only 77 (34%) patients, but 17 patients (22%) did not display sufficient VZV IgG titres. Already 144 (63%) patients had a medical history of chicken pox. However, three of them did not have verifiable VZV IgG antibodies. In addition, 37 patients had neither a history of a chicken pox infection nor VZV inoculation, but 11 out of them were found to have sufficient VZV IgG titres.

Conclusions: There is a good implementation of the vaccination schedule from the German Standing Committee on Vaccination (STIKO) in the group of children and adolescents with IBD and AIH. Our data suggests a gap in VZV immunity in birth cohorts before 2005 in Germany. Moreover, neither the certificate of vaccination nor the medical history of chicken pox infection is reliable for assessing VZV immunity. Serologic investigations demonstrated that some non-immunized patients may undergo occult immunization, and immunized patients did not present sufficient VZV-IgG titres. Thus, we recommend VZV IgG serology within the check-up in newly diagnosed IBD or AIH and VZV vaccination before initiating immunosuppressive therapy, if applicable.

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Effectiveness and safety of CT-P13 under routine care in paediatric patients with inflammatory bowel disease

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Background: Biosimilar to innovator infliximab (INX), CT-P13, has been approved for all indications including paediatric patients with inflammatory bowel disease (IBD) by the European Medicines Agency in 2013 and Food and Drug Administration in 2016. Observational study has been conducted for paediatric patients with Crohn's disease (CD) or Ulcerative colitis (UC) at 10 study centres in South Korea.

Methods: Paediatric CD and UC patients were classified as naïve patients or switch patients defined by history of treatment with anti-TNF agents prior to receiving CT-P13. For CD patients, remission was defined by Paediatric Crohn's Disease Activity Index (PCDAI) score of less than 10 (Hyams et al. 2005 [1]). For UC patients, remission was defined by Paediatric Ulcerative Colitis Activity Index (PUCAI) score of less than 10 (Turner et al. 2012 [2]). Effectiveness was considered as post-baseline remission if at least one remission was achieved throughout Week 2 to 30.

Results: A total of 51 paediatric patients with CD (26 naïve patients and 25 switch patients) and 23 paediatric patients with UC (16 naïve and 7 switch patients) were included. Paediatric CD population consisted of 25 male and 26 female patients with mean age of 14.3±2.4 years. For paediatric UC, 11 male and 12 female patients were included with mean age of 13.6±3.0 years. At baseline, disease status of naïve patients was 4 times higher than switch patients when comparing baseline PCDAI or PUCAI score. The proportion of patients achieving post-baseline remission was 87.5% (21/24) and 80.0% (12/15) for naïve CD and UC patients, respectively. For switch group, post-baseline remission was achieved in 86.4% (19/22) and 100.0% (7/7) of CD and UC patients, respectively. Overall, 2 (6.3% [2/32])

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Table 1: Post-baseline Remission by PCDAI and PUCAI

	Naïve	Switch
CD	21/24 (87.5%)	19/22 (86.4%)
UC	12/15 (80.0%)	7/7 (100.0%)

switch patients experienced at least 1 related treatment-emergent adverse event (TEAE) (for CD, 4.0% [1/25]; for UC, 14.3% [1/7]). And no related TEAE was observed in naïve patients. There were total 4 (9.5% [4/42]) naïve patients and 1 (3.1% [1/32]) switch patient reported treatment-emergent serious adverse event (TESAE) but none of them were considered related to treatment by investigator. Infusion-related reaction was reported in 1 (3.1% [1/32]) switch patient and there were no cases from naïve patients.

Conclusions: CT-P13 in both naïve and switch paediatric patients with IBD was effective over 30 weeks. The safety of CT-P13 was favourable and product was well tolerated in paediatric IBD population.

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Does Statin use reduce the risk of J-pouch related complications in patients with inflammatory bowel disease?

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Background: Previous studies have shown a decreased risk of disease onset, steroid use and colorectal cancer in patients with IBD who use statins. We have investigated the effect of statins in preventing pouch-associated complications in patients with ulcerative colitis who have undergone total proctocolectomy and ileal pouch-anal anastomosis.

Methods: We designed a retrospective case-control study of UC patients who have undergone proctocolectomy and IPAA followed at the Johns Hopkins Meyerhoff IBD Center between 2003 and 2016. Patient characteristics including demographics, tobacco use, personal and family history, past and current medical therapy, surgeries and pouch related complications (acute pouchitis, chronic pouchitis, fistula, and stricture) were collected.

Cases were defined as patients who had used statins for at least 2 years prior to their last recorded encounter with a physician. Controls were patients who had never used statins, matched in a 1:2 ratio to controls, according to the duration of IPAA (years). Matched controls were randomly selected from a pool of eligible controls. At time of enrollment, all cases and controls were asymptomatic, had no history of chronic pouchitis, fistula or stricture and required one or none antibiotic course.

Pouch related complications registered during the 2 years of follow up were compared between cases and controls. The results were adjusted for steroid, antibiotic (ciprofloxacin or metronidazole) and anti-TNF use during the study.

Statistical analysis was performed using t-tests and Fisher's exact test. P values less than 0.05 were considered significant.

Results: A total of 17 cases were compared with 34 controls. Males predominated our cohort (54.9%) but no significant difference was noted in gender distribution among cases and controls. As expected, cases were older than controls. The average age was 63.5 vs 40.7 years old, $p < 0.0001$. The mean duration of IPAA was 7.75 ± 5.1 years (median=6 years).

Overall, cases were less likely to develop pouch related complications (6/17 (35.2%) vs 26/34 (76.5%), $p < 0.0062$) or need antibiotic therapy when compared to controls (29.4% vs 64.7%).

Table 1. Pouch-Related Complications			
Cases (with statins) versus Controls (without statins)			
	Cases (n=17)	Controls (n=34)	P value
Complication type (n)			
De novo Crohn's of the Pouch	0	5	< 0.3086
Non-CD related Fistula	0	0	<1
Non-CD related Stricture	0	5	< 0.3086
Acute Pouchitis	4	16	<0.1353
Chronic Pouchitis	5	9	<1
Any Complication	6	26	<0.0062
Antibiotic Course Use	5	22	<0.0357

Conclusions: Statin use was associated with a statistically significant reduced rate of pouch-related complications and antibiotic use. Further prospective studies are needed to confirm our findings.

P489

Double-dose infliximab therapy in Crohn's disease: appropriate time to evaluate the efficacy, long-term efficacy and safety

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Background: Loss of response (LOR) occurs in 60% of Crohn's disease (CD) patients by week 54 of receiving infliximab (IFX) at 5 mg/kg/8 week. Dose escalation and interval shortening are common approaches to treatment of CD patients with LOR to IFX. However, data are still lacking on the appropriate time to evaluate the efficacy of IFX dose escalation, and few studies have investigated long-term efficacy or predictors of response. The aim of this study was to investigate the long-term efficacy, safety, and appropriate time to evaluate the efficacy of double-dose infliximab therapy in active luminal CD.

Methods: We retrospectively reviewed the outcome of consecutive CD patients treated with infliximab dose doubling (to 10 mg/kg) for LOR between 2011 and 2016 in a single tertiary centre. Patients whose IFX infusion intervals had been shortened, whose dose had been escalated to a dose other than 10 mg/kg/8 week, or reduced to less than 10mg/kg during the follow-up period were excluded. Clinical response and remission were assessed, Cox regression analysis was performed to identify predictors of clinical response, and the cumulative rate of intestinal resection-free survival was calculated using Kaplan–Meier analysis. All adverse events were recorded.

Results: Fifty-five patients with active luminal CD were included. The median CDAI score was 255 at initiation of IFX dose-doubling. After IFX dose doubling, clinical response rates were 44% at week 8, 62% at week 32, and 44% at week 48, respectively. Clinical response

was associated with haemoglobin level ($p=0.067$) and serum albumin level ($p=0.047$) at initiation of IFX dose-doubling. The duration of intestinal resection-free survival was 95% at 1 year, and 83% at 3 years. The long-term intestinal resection-free survival was associated with efficacy at Week 8 (100% of the 8-week responders were free of intestinal resection at 3 years vs 51% of 8-week non-responders, $p=0.0051$). Adverse events were reported in four patients (7.3%); one patient had to discontinue IFX therapy because of an anaphylactic infusion reaction, and other patient was diagnosed with rectal cancer.

Conclusions: IFX dose doubling seems to be well-tolerated and may be effective in inducing clinical remission in patients with luminal CD with LOR to IFX. Appropriate time to evaluate the efficacy of double-dose infliximab therapy assumed to be 8–32 weeks. Response at 8-weeks was predictive of long-term prognosis of double-dose infliximab therapy.

P490

A pilot study of the electronic patient portal “Patient Knows Best” for monitoring biologic therapy in inflammatory bowel disease

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Background: The number of inflammatory bowel disease (IBD) patients on biologics in the UK is increasing [1]. This has contributed to delays in delivering treatment compounded by the expansion of available drugs [2]. e-Health applications such as “Patients Know Best” (PKB), have been shown to improve efficiency of patient management in stable IBD with significant financial benefits [3]. In this pilot study we aimed to explore the uptake, acceptability and outcome of PKB in the management of IBD patients starting biologics.

Methods: PKB is a personal online healthcare record developed to facilitate self-management. IBD patients prescribed biologics were invited to register and received online training. We measured the number of new starters, PKB registrants, demographic data, time intervals to treatment and the nature of online activity. Six months after enrolment all patients using the application received a “patient questionnaire” to capture engagement and satisfaction.

Results: 33 patients (out of 40 newly started on biologics) with mean [SD] age of 44.3 [13.3] years were included in the study. The mean time interval from decision to treat to the first drug administration was 82.7 days [44.0]. Ten patients raised at least one issue on the platform and in total 45 new issues were raised. Most of issues were relevant to active disease (18/45) adverse events of treatments (6/45) and the funding application process (5/45). 39 of 45 issues were resolved online. 16 patients answered the patient experience questionnaire and 11 of them found it at least somewhat helpful and more training was requested.

Conclusions: There were significant delays between time of treatment decision and drug administration. The use of PKB did not accelerate the process. However, a majority of patients engaged with the use of the platform, several issues were raised and most were resolved electronically. Regular refreshing training and individually tailored treatment plans for patients starting biologics may enhance uptake and improve outcomes for long-term monitoring.

References:

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P491

Comparison of the durability of response to subcutaneous anti-TNF therapy between ulcerative colitis and Crohn's disease

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Background: Subcutaneous anti-tumour necrosis factor alpha (TNF) therapies appear to have greater efficacy in Crohn's disease (CD) compared with ulcerative colitis (UC). We aimed to evaluate, in real world clinical practice, whether there was a difference in the outcome of subcutaneous anti-TNF therapy comparing UC and CD. We also assessed the association between blood inflammatory biomarkers and therapy outcome.

Methods: Consecutive patients commencing anti-TNF therapy for UC and CD between 2011 and 2016 were identified. Demographic and baseline biochemical data were collected. Date of initiation and discontinuation of anti-TNF therapy were determined. Time to discontinuation of anti-TNF therapy was used as an index of therapy outcome. Primary analysis compared time to discontinuation of anti-TNF therapy between UC and CD cohorts. Secondary analyses evaluated the associations between baseline CRP/Albumin ratio, CRP, Albumin and Week 8 CRP and time to discontinuation of subcutaneous anti-TNF therapy. P values less than 0.05 were considered statistically significant.

Results: The study cohort comprised 157 IBD patients [n=76 CD /n=81 UC; Age (median, range) 42.6 years (17–81); 49% Male; 87% Adalimumab (ADA)/13% Golimumab (GLB). UC colitis extent: 0% proctitis, 48% left-sided & 52% extensive. Crohn's disease classification: L1 24%, L2 50%, L3 26% & L4 1%; B1 41%, B2 30% & B3 29%. Proportion receiving immunomodulators and systemic corticosteroids, 45% and 44% respectively. Baseline CRP and Albumin (median [range]) were: 5 mg/L [1–88], and 42 [23–72] respectively. The median (95% CI) time to discontinuation of anti-TNF therapy comparing UC and CD cohorts was similar, 168.1 weeks (101.9–234.3) versus 96.2 weeks (51.0–141.5) respectively $p=0.60$. Neither baseline CRP, Albumin, CRP/Albumin ratio nor Week 8 CRP were associated with time to discontinuation of anti-TNF therapy $p=0.98$, $p=0.15$ and $p=0.89$ and $p=0.76$ respectively. There was a trend toward greater dose optimisation in UC compared with CD cohorts 37% versus 22%, $p=0.07$.

Conclusions: In real world clinical practice the durability of response to subcutaneous anti-TNF therapy, measured by time to discontinuation of drug, is similar comparing UC and CD cohorts. This finding may reflect improved understanding of subcutaneous anti-TNF dosing requirements in UC along with proactive dose optimisation. Non-invasive biomarkers of inflammatory burden did not demonstrate a clear association with therapy outcome and may be more important in patient subgroups with severe disease.

P492 Cumulative safety signal review confirmed the established safety profile of Asacol™[†] (mesalazine)

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Background: Asacol™ (mesalazine) is indicated for induction and maintenance of remission of Ulcerative colitis and maintenance of remission of Crohn's ileo-colitis (indication may vary upon formulation and country). Signal detection (for early identification of hazards associated with the drug) is part of routine safety activities within the pharmaceutical industry and can be performed either in a quantitative or qualitative manner.

Methods: A cumulative signal review was conducted querying the pharmacovigilance database aided by standardised MedDRA terms. Data from single cases arising from all sources of the concerned product were analysed applying GVP criteria (including strength of the association, consistency of data, exposure response relationship and biological plausibility). Potential signals were assessed for causal relationship with the use of Asacol™. Identified signals were validated/rejected by a steering committee and either closed without further action, included in the product's label, or kept under close monitoring.

Results: Overall 19 potential signals were detected from 1500 adverse events reports and considered relevant for further investigation. Of these, 8 (Anaemia, tinnitus, hypoaesthesia, acute hepatic failure, atrial septal defect, angioedema, organising pneumonia and bronchiectasis) were closed without further action; 8 (DRESS syndrome, PRES, severe cutaneous adverse reactions, sinus bradycardia, vasculitis, and benign intracranial hypertension) are being closely monitored; 3 (pleurisy, CRP-increased and exacerbation of symptoms of underlying disease) were included in the reference safety information.

Table 1

Potential signal	N of cases	N related cases	De-challenge positive	Re-challenge positive	Resolved spontaneously/with treatment
Pleurisy	19	18	9	2	4
CRP-increased	81	55	29	–	19
Exacerbation of the disease	54	43	13	13	8

N: number; De-challenge/Re-challenge positive: the AE disappears/recurs after stopping/restarting the drug.

A literature search revealed several reports of pleural disease associated to mesalazine therapy. Limited information is available on CRP-increased, however some studies suggest that CRP levels are significantly higher in patients with active disease. There is evidence that symptoms of intolerance to mesalazine can manifest itself as exacerbation of disease. It is therefore difficult to draw the line between exacerbation of underlying disease due to natural course of disease and exacerbation due to Asacol™.

Conclusions: With more than 30 years of experience and more than 2.9 million patient years of post-marketing exposure, the safety profile of Asacol™ is well established. The three new signals' assessment revealed no significant impact on the product's safety profile.

[†]Tillotts Pharma AG's Asacol™ is registered in 42 countries worldwide. Tillotts Pharma AG doesn't own rights to Asacol in CH, US, GB, CA, IT, BE, NL or LU.

P493 Efficacy of anti-TNF for internal fistula in Crohn's disease – results from a retrospective multicenter cohort study

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Background: Fistulizing Crohn's disease is considered as a refractory disease phenotype which could be resistant to anti-TNF treatment. Internal fistula is especially a condition likely to require surgery, while few reports showed successful conservative management with medical treatments such as anti-TNF. Therefore, we performed a multicenter retrospective cohort study to investigate the outcome of anti-TNF for internal fistula in Crohn's disease.

Methods: Data were retrospectively collected from all Crohn's disease patients diagnosed with internal fistula then treated with anti-TNF (infliximab or adalimumab) between January 2002 and November 2015 at 20 institutions. Surgery was defined as a primary endpoint, and secondary endpoints were fistula closure and physician's assessment (closed, improved, no change, or worsened). Cumulative rate of surgery was evaluated by Kaplan-Meier analysis. Prognostic factors associated with surgery, fistula closure, and physician's assessments were assessed.

Results: A total of 93 Crohn's disease cases were included in the study with mean follow-up period of 1452.8 days. Infliximab was used in 69 (74.2%) patients and 49 (52.7%) were on concomitant immunomodulators. Most had single (n=67, 72.0%), while the remainder (n=26, 28%) had complex draining fistulas. Of these fistulas, majority were entero-entero/colonic (n=69, 76.7%), and others were enterovesical (n=16, 17.8%) or enterovaginal (n=5, 5.6%). Coexisting stricture was present in 55 (59.1%) patients. Cumulative surgery rate was 17.7, 27.5, 37.3, and 47.2% at 1, 2, 3, and 5 years from induction of anti-TNF, respectively, and there was a trend for the increased risk of surgery by the increment of CDAI scores (univariate HR 1.41 (0.93–1.84); p=0.073 & multivariate HR 1.46 (0.99–2.13); p=0.055, by 100 points increase in CDAI) by Cox regression analysis. Fistula closure was confirmed in 27.0% in 5 years. Number of fistula (OR 0.21 (0.05–0.77)), enterovesical fistula (OR 4.4 (1.34–14.43)) and stricture (OR 0.38 (0.15–0.99)) were associated with closure of fistula by univariate logistic model but none of them was significant by multivariate analysis. Anal lesion, infliximab, and concomitant immunomodulator use independently reduced the risk of worsening defined by the physician's assessment.

Conclusions: Anti-TNF can be effective and surgical treatment may be avoided in selected patients with internal fistula. Further prospective trials with larger sample sizes are necessary to confirm our results.

P494 Multicentre cohort study to evaluate the need for re-intervention following multimodal treatment in Crohn's disease with perianal fistula

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Background: Treatment paradigms for Crohn's disease with perianal fistula (CD-PAF) are still evolving. We aimed to study the impact of multidisciplinary multimodality treatment approach in patients with CD-PAF on the recurrence rates of fistula and the need for re-interventions. We also aimed to study the predictive factors for the need for re-intervention

Methods: This was a multinational multicentre (11 centres) retrospective cohort study with data collected in CD patients with CD-PAF from 2010 to 2015. Multidisciplinary multimodality approach was defined as using a combination of medical treatments (antibiotics, immunomodulators, and biologics) along with surgical approach (examination under anaesthesia (EUA) +/- Seton drainage) at diagnosis. Univariate analysis was done for variables impacting fistula recurrence and re-intervention a logistic regression adjusting for age to identify significant predictors of re-intervention.

Results: 253 adult onset CD-PAF patients were included (161 M, 92 F). 53% had complex fistula. 70% of the patients had EUA at presentation with 136 patients (53.8%) needing a median of 1 Seton insertion (range 1–6.84% of the patients had anti TNF therapy. There was significant difference in fistula healing rates between simple and complex fistulae (complete healing 60% vs 41%, $p=0.015$). 52% of patients who received multimodality treatment had complete fistula healing. 27% of simple fistula and 40.3% of the complex patients had recurrent fistula needing re-intervention. There was a significant difference in the need for re-intervention based on fistula healing with 22% of those with complete healing needing repeat surgery compared to 49% with partial healing and 71% in those with no healing ($p\leq 0.001$). Only 26% of the 141 patients having multidisciplinary multimodal treatment needed surgical re-intervention when compared to 59% without this ($p\leq 0.001$). Univariate analysis showed complex ($p=0.008$), absence of multidisciplinary approach ($p\leq 0.001$, EUA ($p=0.005$), combined immunosuppression ($p=0.032$, presence of proctitis ($p\leq 0.001$) as factors impacting need for re-intervention but there was no impact of age, gender, smoking status, mode of presentation, Montreal class, presence of anal stenosis and thiopurine use alone. On logistic regression, absence of multi-disciplinary approach (OR 2.8, 95% CI: 1.4–5.6) and presence of proctitis (OR 2.2, 95% CI: 1.2, 3.9) were predictors for re-intervention.

Conclusions: This large multicentre cohort study describes outcomes in CD-PAF patients receiving multidisciplinary multimodality treat-

ment approach. In this cohort, complete fistula healing rates were higher and the recurrence rates lower than previously reported. Presence of proctitis and lack of multidisciplinary approach are predictors for recurrence and re-intervention for CD-PAF.

P495 Intensified infliximab rescue therapy for acute severe ulcerative colitis does not improve long term colectomy-free survival

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Background: Infliximab (IFX) is an effective rescue therapy for hospitalized steroid refractory acute ulcerative colitis (ASUC). Treatment response is associated with serum IFX trough levels. Intensified dosing regimens with escalated dose and/or shortened interval are increasingly used to compensate for the higher inflammatory burden and drug clearance. Our study aims to determine if intensified IFX induction regimen improves colectomy-free outcomes and identify predictors of long term outcomes.

Methods: A retrospective review was performed between July 2010 and May 2016 at McGill University hospitals. All hospitalized adult patients who received at least one infusion of IFX as rescue therapy for steroid refractory ASUC were identified through our pharmacy drug database. We compared standard inductions with 5mg/kg vs 10mg/kg as well as shortened induction interval (i.e. completion of induction within 4 weeks). The primary outcome was the colectomy rate at 2 years. Baseline clinical parameters and dosing regimen were explored with regression analysis.

Results: 72 patients (38% female, mean age 41) were identified. 37 patients (51%) received standard 5 mg/kg IFX induction and 35 received 10 mg/kg. 5 patients received shortened induction interval with IFX 10mg/kg. Baseline clinical parameters were well matched among various regimens. The 30-day and 2-year colectomy rate in our cohort was 6.9% and 15.2% respectively. 2-year colectomy-free survival was not significantly different between the standard (86.5%) and escalated (82.9%) dose IFX induction ($p=0.388$) whereas the shortened induction was associated with lower colectomy-free rate (40% versus standard induction 88.1%, $p<0.001$). Hemoglobin ≤ 90 g/L (OR 4.8 [95% CI: 1.2–19.1], $p=0.03$), albumin <30 g/L (OR 7.9 [95% CI: 1.5–40.1], $p=0.01$) and a short IFX induction reg-

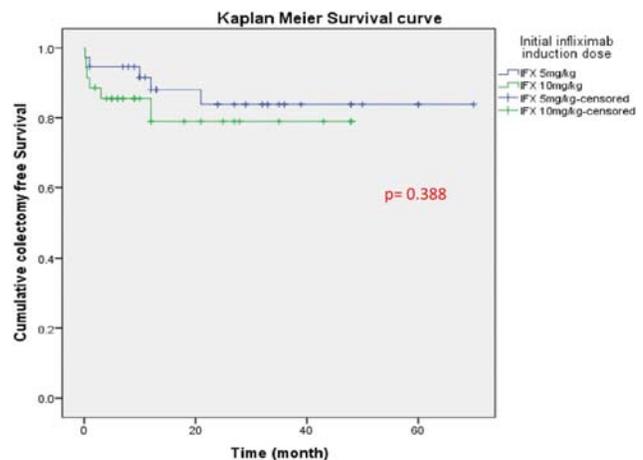


Figure 1. Colectomy free survival. Infliximab 5 versus 10 mg/kg induction.

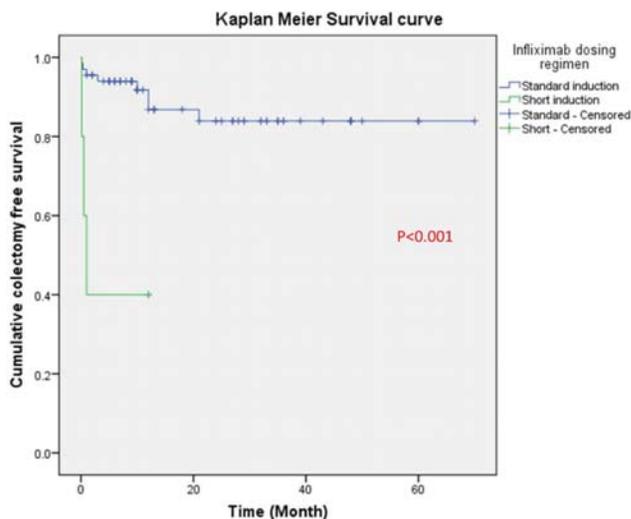


Figure 2. Colectomy free survival. Short versus standard interval induction.

imen (OR 11.1 [95% CI: 1.6–76.6], $p=0.015$) were all associated with increased risk of colectomy at 2 years in univariate regression analysis. Albumin <30 g/L remained significant in multivariate modelling ($p=0.03$).

Conclusions: Use of intensified infliximab rescue therapy did not improve 2-year colectomy-free survival in this cohort. Tailored use in high risk patients such as those with low albumin and hemoglobin may be beneficial although this needs to be validated in prospective clinical trials.

P496
Successful dose de-escalation to adalimumab 40mg every three weeks in patients with Crohn’s disease

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Background: Data on de-escalation of adalimumab (ADM) therapy in patients with Crohn’s disease (CD) in clinical remission are scarce.

However, dose de-escalation may not only have beneficial economic consequences, it might also decrease adverse events (AE). In this retrospective study, the outcome of dose de-escalation to ADM 40 mg every three weeks (ETW) in patients with CD was studied.

Methods: Out of 703 patients treated with ADM for CD in a tertiary referral center, we selected all patients who had received maintenance therapy with ADM 40 mg ETW with serum levels (SL) available before and after dose de-escalation. A sex- and age-matched control group consisted of patients continuing ADM 40mg EOW. ADM SL were measured using RIDASCREEN[®]. In addition, patient reported outcome (PRO2), C-reactive protein (CRP) and serum albumin were collected. Other baseline variables included disease behavior, disease location, smoking behavior, concomitant therapy, bodyweight, and body mass index. ROC curve analyses were performed to define cut off values for continuous variables. Mann-Whitney U, Wilcoxon Signed Rank test, and Cox regression were performed using SPSS 23.0

Results: We identified 40 patients (11 male, median age 37 years) who dose de-escalated to ADM 40 mg ETW for ADM-related AE ($n=1$), ADM SL $>7\mu\text{g/mL}$ ($n=8$), or both ($n=31$). Compared to the control population, ADM SL dropped significantly within four months, but without associated clinical or biochemical changes.

During a median follow-up of 24 months, 65% of patients maintained clinical response, but 35% needed dose escalation back to ADM 40mg EOW because of clinical relapse ($n=8$), ADM SL dropping to $<4\mu\text{g/mL}$ ($n=2$), or both ($n=4$). CRP $<3.5\text{mg/L}$ at dose de-escalation was independently associated with dose escalation free survival [Odds ratio 6.28 (95% CI 1.83–21.59), $p=0.004$]. We could not define a minimal ADM SL to consider or maintain dose de-escalation. In 53% of 32 patients with AE dose de-escalation was associated with a complete disappearance of AE after a median of 4 months (8/15 skin manifestation, 3/7 arthralgia, 5/7 frequent infectious episodes).

Conclusions: In this retrospective cohort analysis, 65% of patients were able to continue ADM therapy at a dose of 40 mg ETW for a median of 24 months. In half of the patients who experienced ADM related AE at baseline, the AE disappeared completely. Regardless of ADM serum levels, disease remission should be objectively assessed prior to dose de-escalation, since an elevated baseline CRP predicted clinical relapse and dose escalation back to 40mg EOW.

Abstract P496 – Table 1. Evolution of clinical and biochemical markers after dose de-escalation.

	Study population (n=40)		Control group (n=40)		p-value between groups ^o
	T0 T1	p-value within group*	T0 T1	p-value within group*	
Median (IQR) ADM serum level	12.0 (9.4-14.4) $\mu\text{g/mL}$ 7.9 (5.8-10.7) $\mu\text{g/mL}$	$p<0.001$	9.6 (8.1-11.1) $\mu\text{g/mL}$ 10.1 (8.0-11.7) $\mu\text{g/mL}$	$p=1.000$	T0: $p=0.002$ $\Delta\text{T0-T1}$: $p<0.001$
Median (IQR) body weight	58.6 (52.1-74.8) kg 59.2 (51.4-73.1) kg	$p=0.084$	61.8 (53.2-74.8) kg 61.5 (54.4-76.2) kg	$p=0.155$	T0: $p=0.603$ $\Delta\text{T0-T1}$: $p=0.034$
Median (IQR) body mass index	21.11 (19.98-24.95) kg/m^2 20.90 (19.83-24.34) kg/m^2	$p=0.098$	21.91 (19.17-25.23) kg/m^2 21.45 (19.66-25.03) kg/m^2	$p=0.135$	T0: $p=0.866$ $\Delta\text{T0-T1}$: $p=0.036$
Median (IQR) C-reactive protein	1.4 (0.6-3.5) mg/L 1.3 (0.6-5.1) mg/L	$p=0.188$	1.2 (0.4-3.0) mg/L 1.9 (1.0-3.6) mg/L	$p=0.020$	T0: $p=0.776$ $\Delta\text{T0-T1}$: $p=0.562$
Median (IQR) serum albumin	44.0 (42.2-46.9) g/L 43.7 (41.5-47.3) g/L	$p=0.533$	44.9 (43.0-47.1) g/L 45.3 (43.3-47.1) g/L	$p=0.876$	T0: $p=0.521$ $\Delta\text{T0-T1}$: $p=0.522$
Median (IQR) PRO2	0.0 (0.0-6.0) 2.0 (0.0-8.5)	$p=0.027$	0.0 (0.0-4.8) 2.0 (0.0-7.0)	$p=0.007$	T0: $p=0.918$ $\Delta\text{T0-T1}$: $p=0.752$

P497

Impacts of mucosal healing on clinical outcomes in patients with refractory ulcerative colitis on tacrolimus or biologics

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Background: The paradigm for treatment for inflammatory bowel disease (IBD) is shifting from resolving symptoms toward objective measures such as mucosal healing (MH). Several studies suggest that MH is associated with an increased rate of long-term clinical remission and a decreased rate of surgery. However, few studies investigated the impacts of MH on clinical outcomes in patients with refractory ulcerative colitis (UC) on tacrolimus or biologics. This retrospective study was to investigate the impacts of MH achieved during tacrolimus and biologic therapy for refractory UC on long-term clinical remission and need for surgery.

Methods: One hundred patients with moderately-to-severely active UC were studied. Fifty patients were treated with oral tacrolimus (TAC group). The other 50 patients were treated with anti-tumour necrosis factor (TNF) agents (anti-TNF group): infliximab 40, adalimumab 10. At baseline, endoscopic examination was performed in all patients. Endoscopic severity was assessed according to the mucosal appearance score in the UC-disease activity index (DAI). After the 12-week treatment, endoscopic examination was performed if patient condition permitted. MH was defined as endoscopic score of 0 or 1 in the UC-DAI, and endoscopic improvement (including MH) a decrease in the endoscopic score.

Results: At week 12, MH was achieved in 12/37 patients (32%) in the TAC group vs 10/36 patients (28%) in the anti-TNF group ($p=0.86$). Overall, 22/73 patients (30%) achieved MH in this study. Seventeen of the 22 patients (77%) who achieved MH at week 12 and 21 of 52 patients (41%) without MH maintained clinical remission during a 40-week follow-up after endoscopic evaluation ($p=0.005$). The colectomy-free rate was 95% in the MH group vs 82% in the non-MH group ($p=0.14$).

Conclusions: MH was associated with an increased rate of long-term clinical remission and a decreased rate of surgery during the subsequent 40 weeks. MH may therefore be a reasonable therapeutic target in the management of refractory UC.

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Emerging role of the IL-33/ST2 axis in predicting mucosal response to anti-TNF therapy in ulcerative colitis

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Background: Tumor necrosis factor (TNF) inhibitors (anti-TNF) are considered to be effective in inducing mucosal healing in patients with moderate-to-severe Ulcerative Colitis (UC). The role of IL-33 and its receptor, ST2, in intestinal inflammation is incompletely un-

derstood, with both pro-inflammatory and regulatory properties described. Recent evidence has shown that anti-TNF is able to modulate the IL-33/ST2 axis in inflammatory conditions. The aim of our study was to explore the potential role of the IL-33/ST2 axis in the mucosal healing process mediated by anti-TNF therapy in UC.

Methods: Endoscopic MAYO score was calculated before the first anti-TNF infusion (T0) and after 6 weeks (T2). 12 UC patients (MAYO score at T0 ≥ 2), grouped into 6 responders with mucosal healing (MAYO score ≤ 1) and 6 non-responders to anti-TNF at T2 (MAYO score ≥ 2) were enrolled. 10 healthy controls undergoing routine colonoscopy for tumor screening were also enrolled. At each time point, serum samples were collected and ELISA performed to assess IL-33/ST2 protein levels. Intestinal biopsies were also taken from the rectum and IHC was done to evaluate mucosal IL-33/ST2 expression and localization.

Results: IL-33 protein levels were significantly increased in responders vs. non-responders, both at T0 and T2. Among responders, IL-33 protein was slightly reduced at T2 vs. T0, while unchanged in non-responders. Interestingly, significantly higher levels of ST2 were found in responders vs. not responders at T0, while no differences between groups were found at T2. Among responders, ST2 levels were dramatically reduced at T2 vs. T0. No significant differences were found in non-responders at both time points. Healthy controls showed significantly lower levels of both IL-33 and ST2 compared with other groups. IHC confirmed these observations. In particular, IL-33 and ST2 staining was more intense within the inflamed and ulcerated mucosa of responders compared to non-responders at T0. After 6 weeks, ST2 staining was even more evident in responders, notably localized to the healed mucosa and in close proximity to areas of re-epithelialization. Little to no staining for both IL-33 and ST2 was present in healthy controls.

Conclusions: Our results suggest a possible role for IL-33/ST2 in predicting gut mucosal wound healing in patients with moderate-to-severe UC treated with anti-TNF. Further studies are underway to determine mechanisms of action that support these findings.

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Sexual dysfunction is frequent among inflammatory bowel disease patients: results of a prospective study

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Background: Quality of life improvement is a main goal in Inflammatory Bowel Disease (IBD) management. Sexuality is a major determinant of quality of life. Data on sexual dysfunction in IBD and its associated factors are scarce. This study aimed to compare the rate of sexual dysfunction between IBD patients and healthy adults and search for associated factors to sexual dysfunction.

Methods: A 53-item questionnaire was administered to all consecutive IBD patients in 2 University Hospitals from September to November 2015. Sexual function was assessed by two validated questionnaires: Female Sexual Index Function for women and International Index of Erectile Function for men. Healthy controls were recruited in occupational medicine and gynaecology clinics. Patients with Irritable Bowel Syndrome (IBS) were enrolled as a second control group. Age adjusted comparisons were performed.

Results: 358 IBD patients filled out the form (192 (53.6%) women;

median age: 38 y/o), 238 with Crohn’s disease (CD) and 120 with Ulcerative Colitis (UC). The response rate was 82%. 110 healthy controls (54 (49.1%) women; median age: 35 y/o) and 107 IBS patients (54 (50.5%) women; median age: 49.5 y/o) were included. In women, sexual dysfunction rates were 53.6% in IBD, 28% in healthy controls ($p<0.01$) and 77.5% in IBS ($p=0.10$); in men, figures were 16.9% in IBD, 7.4% in healthy controls ($p=0.64$) and 26.4% in IBS ($p=0.60$). An erectile dysfunction was identified in 43% of IBD patients, 13% of healthy controls ($p<0.01$) and 55% of IBS patients ($p=0.6$). IBD activity was not associated with sexual dysfunction. Twenty-eight per cent of IBD women and 15% of IBD men claimed that the disease had a negative impact on their sex life. Fifty-two per cent of women and 53% of men considered their gastroenterologist should address the subject of sexuality.

Conclusions: Impaired sexual function is more frequent among IBD patients than in general population, concerning half of women and 1 out of 6 men. Majority of patients considered that this aspect of their daily life should be taken into account by their gastroenterologist.

P500

Effectiveness and safety in Crohn’s disease patients who were treated with CT-P13

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Background: CT-P13 is a biosimilar to innovator infliximab (INX) and has been approved by the European Medicines Agency in 2013 and Food and Drug Administration in 2016. Here we present results from observational study in South Korea, which has been conducted at 24 study centres.

Methods: This observational study has been conducted from 2012 July to 2016 July. In patients with fistulizing Crohn’s disease (FCD) and moderate to severe active Crohn’s disease (CD) for 6 months of each patient and results were reported as either of naïve or switch groups defined by a history of treatment with anti-TNF agents prior to receiving CT-P13. In the naïve group, remission rate was evaluated at Week 14 and 30. In switch group, the remission rate was assessed during post-baseline visits and post-baseline remission was counted if at least one post-baseline result met remission criteria. Remission

was defined according to Sands BE, 2004 [1] and Hanauer SB, 2002 [2] in FCD and CD, respectively. The safety profiles were assessed throughout the study.

Results: A total of 204 patients consisting of 24 FCD patients and 180 CD patients were enrolled in the study. In the naïve group with FCD patients, remission rates were 40.0% (4/10) and 60.0% (6/10) at Week 14 and 30, respectively. In the case of CD patients in naïve group, remission rates were more than 72.0% both at Week 2 and 30. In the switch group, the proportion of patients who achieved clinical remission were 87.5% and 80.0% in FCD and CD patients, respectively during post-baseline visits.

Throughout 30 week safety follow-up, 3 (1.6%) patients were reported as infusion-related reaction in CD. Among FCD and CD patients, 1 (4.2%) and 11 (6.1%) patients have experienced at least one related treatment-emergent adverse event (TEAE). There were a few treatment-emergent serious adverse events (TESAE) cases reported in FCD and CD patients which were 6 (25.0%) and 11 (6.1%), respectively.

Conclusions: Remission rates treated with CT-P13 showed clinically consistent results to historical data [3–6]. The overall safety profile also revealed that CT-P13 is well-tolerated up to 6 months in each patient with FCD or CD under routine care.

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P501

Baseline characteristics of Crohn’s disease patients in the vedolizumab PASS study: a cohort study assessing the safety and effectiveness of vedolizumab compared to other biologic agents (02)

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Table 1. Remission rates in Naïve and Switch group

	Naïve		Switch
	Week 14	Week 30	Post-baseline
FCD	4/10 (40.0%)	6/10 (60.0%)	7/8 (87.5%)
CD	Week 2	Week 30	Post-baseline
	59/82 (72.0%)	35/43 (81.4%)	60/75 (80.0%)

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Background: The aim of this study is to quantify and compare the safety and effectiveness of vedolizumab (VDZ) with other biologic agents (OBAs) in ulcerative colitis and Crohn's disease (CD). The study is currently recruiting 5,000 IBD patients across 23 countries in North America and Europe, and will follow patients for up to 7 years. This interim analysis presents the baseline data of CD patients. **Methods:** The study is a multi-centre prospective observational cohort study. Inclusion criteria are that a patient has IBD, aged 18+, initiating or switching biologic agents, and no prior VDZ exposure. Those initiating VDZ enter the VDZ exposure cohort, while those initiating OBAs enter the OBAs exposure cohort, with each cohort enrolling 2,500 patients. Recruitment includes patients who are starting their first biologic and patients who are biologic experienced and changing to a new biologic agent.

Results: 237 of the 576 patients enrolled into the study as of 30 September 2016 had CD. 156 had CD and initiated VDZ, and 171 had CD and initiated an OBA. CD Patient age ranged from 18 to 75 years (mean=40y), 56% were female, and BMI ranged from 14 to 42 (mean=25). There was no difference between VDZ and Oba patients in disease location, history of fistula or proportion with active fistula and occurrence of all extra-intestinal manifestations and concurrent use of immunomodulators. There were also no baseline differences between cohorts in patient-reported quality of life as assessed using the Short IBD Questionnaire (SIBDQ).

CD patients who initiated VDZ were more likely than OBA patients to be female (63% vs. 50%, $p=0.017$), have a longer disease duration (15 vs. 10 years, $p<0.001$), to have had previously biologic therapy (87% vs. 28%, $p<0.001$), moderate or severe disease (43% vs. 25%; $p=0.013$) as measured by Harvey Bradshaw Index (mean HBI score 7.3 vs. 5.6, $p=0.004$), very poor general wellbeing (9% vs. 3%, $p=0.048$), more liquid stools per day (4.2 vs. 2.8, $p=0.002$) and to have had prior IBD surgery (55% vs. 37%, $p<0.001$). In addition, among biologic experienced CD patients, concurrent steroid use was more frequent in those initiating VDZ than OBA (43% vs. 23%, $p=0.015$).

Conclusions: At baseline, CD patients initiating or switching to VDZ compared to those initiating or switching to OBAs were more likely

to be female, have longer disease duration, more severe disease, poorer general wellbeing, more liquid stools per day and most had previously used a biologic therapy. These results demonstrate that at baseline, patients treated with VDZ are different to those treated with OBAs. The vedolizumab PASS Study will account for these patient differences at baseline when evaluating long-term safety and efficacy of VDZ.

P502

Ulcerative colitis patients on vedolizumab lacking response at induction phase continue to improve over the first 6 months of treatment

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Background: Vedolizumab, a gut-selective anti-integrin inhibitor, is a biologic agent indicated for ulcerative colitis (UC) treatment. We retrospectively assessed the real-world efficacy and safety of vedolizumab as induction and maintenance therapy in UC patients.

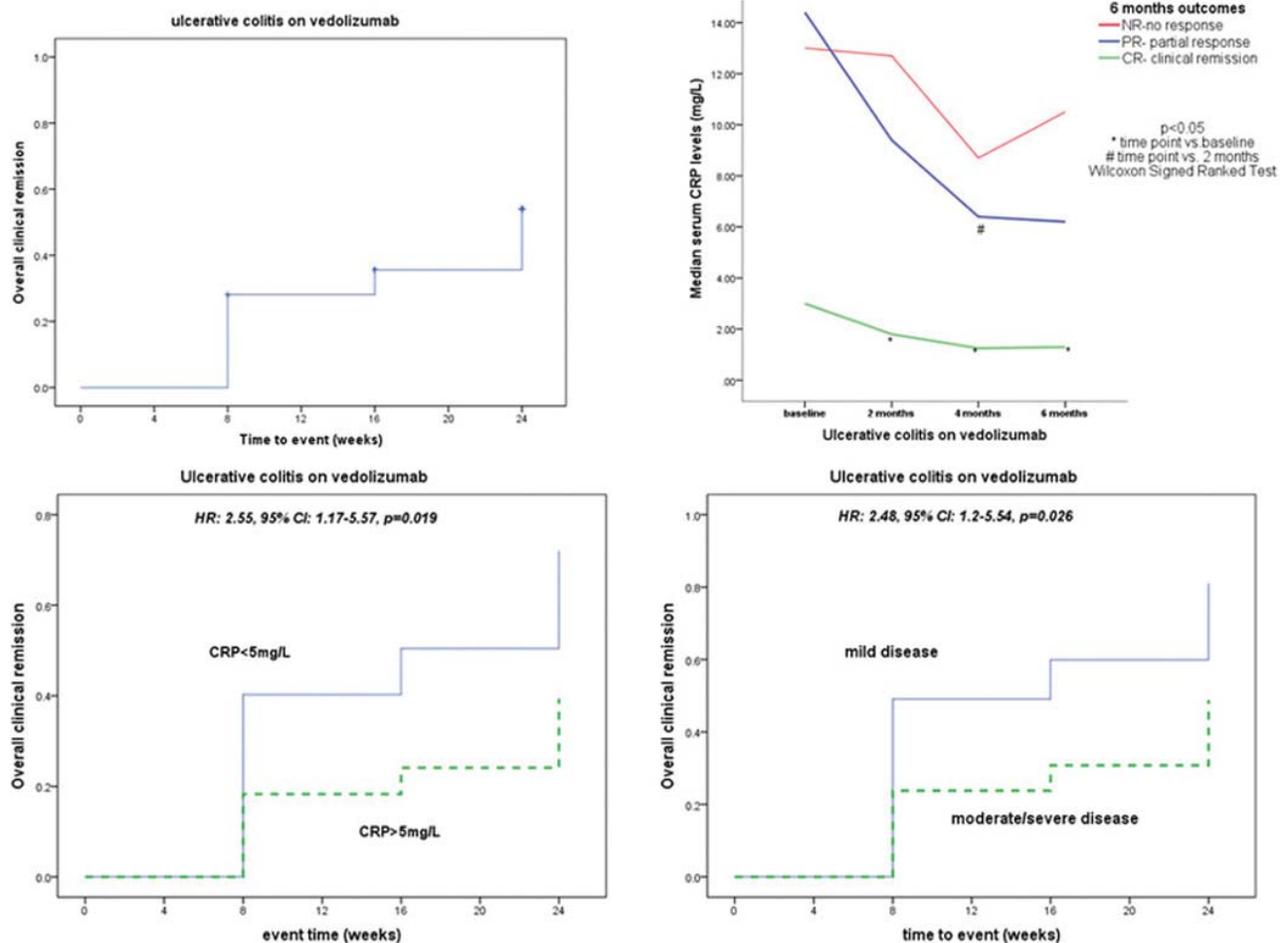
Methods: Adult UC patients followed at a tertiary IBD center and treated with vedolizumab were included. All patients received infusions at 0, 2, and 6 weeks and then every 8 weeks. Six-month cumulative rates of clinical remission (CR, partial Mayo score ≤ 2) and steroid-free clinical remission (SFCR) were assessed with Kaplan-Meier survival analyses. Univariate and multivariable Cox proportional hazard (PH) analyses were performed to identify among baseline variables independent predictors of clinical remission. Hospitalizations, surgeries and adverse events were recorded.

Results: Fifty-seven patients were analyzed (Table 1). At 2 months, CR and SFCR were 37% and 30%. At 6 months, the cumulative rates of CR and SFCR were 49% and 44% (Table 1, Fig. 1). Among patients who were not in CR after 3 infusions ($n=36$) the probability of remission with continuation of vedolizumab was 25% (9/36) at

Table 1. Ulcerative colitis patients: baseline characteristics and vedolizumab treatment outcomes

Patient characteristics	N=57
Male	68%
Age at start of vedolizumab, median [IQR], years	33 [26-41]
Disease duration, median [IQR], years	6 [4-10]
Disease extent	
Ulcerative proctitis (E1)	2%
Left-sided colitis (E2)	26%
Extensive colitis/Pancolitis (E3)	72%
Extraintestinal manifestations	16%
Prior immunomodulators	53%
Prior anti-TNF exposures	0=32%, 1=47%, 2=18%, 3=3%
Reason for anti-TNF discontinuation	
Primary none response	47%
Secondary loss of response	45%
Adverse events	8%
Vedolizumab monotherapy	47%
Concomitant corticosteroids (Cs)	46%
Concomitant immunomodulators (IMMs)	18%
Concomitant Cs & IMMs	11%
Treatment outcomes	N=57
Clinical remission, months 2, 4, 6	37%, 37%, 49%
Steroid-free clinical remission, months 2, 4, 6	30%, 33%, 44%
On steroids, baseline and months 2, 4, 6	46%, 33%, 21%, 12%
Median clinical Mayo Score, baseline and months 2, 4, 6	7, 4, 3, 5, 2
Median CRP (mg/L), baseline and months 2, 4, 6	9.9, 5, 2.8, 4
Adverse events (Side effects)	14%
	(3 headache/migraines, 2 transient rash, 1 folliculitis, 1 gastroenteritis, 1 pruritus)
Vedolizumab discontinuation	19% (primary none response)
Surgery (Colectomy)	14%

2 months= post 3rd infusion at week 6, 4 months= post 4th infusion at week 14, 6 months= post 5th infusion at week 22. Over the 6-month period drop out patients (surgery or VDZ discontinuation) were included and considered treatment failures



Abstract P502 – Figure 1. Clinical remission rates in UC patients on continuous vedolizumab for 6 months.

6 months. Pairwise analyses showed significant improvement in median partial Mayo scores and median CRP levels over the 6-month period compared to baseline (Fig. 1). Cox PH analysis revealed a 3-fold increase in the probability of clinical remission at 6 months among patients with baseline CRP levels less than 5mg/L (univariate analysis, hazard ratio [HR]: 2.55, 95% CI: 1.17–5.57, p=0.019; multivariate analysis, HR: 2.72, 95% CI: 1.24–5.97, p=0.012) and mild baseline disease (univariate analysis, HR: 2.48, 95% CI: 1.2–5.54, p=0.026; multivariate analysis, HR: 2.86, 95% CI: 1.27–6.44, p=0.011) compared with those who did not (Fig. 1). Cumulative rates of colectomy were 5%, 9%, and 14% at 2, 4 and 6 months respectively. The most common side effect was headache.

Conclusions: In our study, 35% of UC patients, most of whom were unresponsive to anti-TNFs, achieved CR after induction and 50% were in CR at six months with vedolizumab maintenance treatment. We did not observe severe adverse events. Our data would indicate that a significant proportion of patients who had not achieved response at 2 months may go on to achieve CR by 6 months of continuous therapy.

**P503
Rapid point-of-care monitoring of anti-infliximab antibodies in patients with inflammatory bowel disease treated with the reference infliximab or CT-P13 in routine clinical practice**

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Background: Loss of clinical response and infusion reactions to infliximab are associated to Anti-IFX antibodies (ATI). ATI detection is a key step of patient management algorithm [1]. However, current techniques require additional patient appointments for sample collection, processing and batching in centralised facilities. Test reporting usually takes several days or weeks impairing effective decision making. Here we validate the use of capillary blood in a real-life point-of-care (POC) setting where patients attend the infusion centre for Remicade® (RMC) or CT-P13 infusions.

Methods: PQ-EF2 is a prospective, observational study designed to evaluate the performance of a rapid POC test (Promonitor® Quick Anti-IFX, Progenika, Spain) to detect ATI in routine clinical practice in IBD and rheumatic patients treated with RMC or Inflectra® attending the infusion centre with the reference ELISA. The POC test is a qualitative immunochromatographic assay based on lateral flow technology to detect ATI (including biosimilar CT-P13) in either fingerprick or serum. Consecutive patients (initiating or under maintenance therapy) were recruited and tested with the rapid test in venous and capillary whole blood specimens immediately before the infusion. ATI test results were read visually with the POC test in

30 min, just before the patient started the infusion. Trough sera were also collected for subsequent analysis with the rapid test and benchmarked with Promonitor®-Anti-IFX ELISA. Follow-up time was 6 months. ELISA quantitative results were categorized as positive and negative to allow comparisons with the qualitative rapid test.

Results: Fifty four consecutive patients (21 IBD (13 Crohn's disease, 8 ulcerative colitis), and 33 with rheumatic diseases) were recruited (a total of 101 visits in the 6 months follow-up) accounting for a total of 101 sera, 101 fingerpricks and 35 venous whole blood samples. Overall, 4 (7.4%) patients developed ATI (1 CD, 1 UC, 2 ankylosing spondylitis). ATI were detected in 3 patients treated with RMC and 1 treated with Inflectra®. Overall agreements between fingerprick vs venous whole blood and fingerprick vs serum measured with the rapid POC test were 100% and 98%, respectively. Positive (PPA) and negative (NPA) agreements between the POC test and ELISA were 86% and 99%, respectively. PPA and NPA between the ELISA and the POC test in serum was 100% and 99%, respectively.

Conclusions: ATI can be reliably detected in either venous or capillary circulation. Results show an almost perfect agreement between specimens and with the reference ELISA technique. ATI measurement with the POC test allows the clinician to detect ATI in a quick and fully decentralized mode facilitating immediate POC decision making.

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P504

Differences between paediatric and adult inflammatory bowel disease presentation – analysis based on the data from multicenter, prospective cohort observational study assessing safety of anti-TNF therapy – Satimos study

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Background: Anti-TNF therapy is actually easy available for inflammatory bowel disease treatment. Even if biologics are commonly used for many years, surveillance, especially focusing at safety is needed. In that case, study to assess efficacy and prevalence of adverse events in Polish cohort adult and pediatric patients with Crohn's disease (CD) and ulcerative colitis (UC) has been started. In database were recorded information about demographic and medical history. The aim of actual assessment was to compare disease presentation between children and adults with inflammatory bowel disease qualified to anti-TNF therapy.

Methods: A multicenter, prospective cohort observational study was started at January 2014. To study were included all patients in every age who started anti-TNF treatment. From final assessment were excluded 74 patient due to lack of complete data. Data were recorded with use of electronic database. Demographical findings, collateral diseases, history of treatment were also collected. Finally, 667 patients were enrolled to the study. Group consist 397 adults (59.6%) and 270 patients aged below 18 years old (40.4%).

Results: Time from first symptoms to diagnosis varied between type of disease and age. Diagnosis was performed earlier for patients aged below 18 years. Mean time was 4 months for UC and 6.9 months for CD in pediatric population vs 7.8 months and 12 months in adults, respectively. At the moment of anti-TNF qualification, most UC patients presented high disease severity. 58,0% adults and 60.4% children were defined as E3 in Montreal classification. Among CD patients the most common disease localisation in children were colon (40.2%) and terminal ileum (38.3%) meanwhile terminal ileum in adults were affected only in 29.3%. The most common disease localisation in adults were large intestine (44.3%). Upper digestive tract were 4 times more common affected in children 27.1%; vs 7.2% in adults. Most patients were qualified to biological treatment due to luminal active disease. Nevertheless, young patients with CD earlier than adults needed biological therapy. Mean time from diagnosis to treatment with biologic therapy was 1.4 years for children with CD, and 5.8 years for adults. Mean time among UC patients were 2.0 years for children and 4.3 years for adults.

Conclusions: Analysis showed that pediatric patients mostly have more aggressive form of disease what lead to earlier disease diagnosis and earlier need of anti-TNF treatment. In comparison to adults, in children with CD, localisation is more common in terminal ileum and upper digestive track.

P505

Efficacy of MMX-mesalazine monotherapy for maintenance of remission in ulcerative colitis patients after mucosal healing

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Background: Mucosal healing has become a common endpoint in most ulcerative colitis (UC) clinical trials as well as an important

objective in clinical practice. Mucosal healing in UC patients is associated with high rates of clinical remission and a favorable prognosis. MMX-mesalamine is a drug that due to its pharmacokinetics characteristics reaches more distal segments of the colon. Thus, it could be used in patients with intolerance to topical therapy.

The aim of this study was to evaluate the efficacy of MMX-mesalamine for maintenance of remission in UC patients after mucosal healing.

Methods: A prospective, observational cohort study was designed. Consecutive UC patients with demonstrated mucosal healing at colonoscopy, and who were under monotherapy with MMX-mesalamine were included. Patients receiving additional topical therapy were excluded. Extension of the disease was classified according to the Montreal Classification. Mucosal healing was defined as endoscopic Mayo sub-score of 0 or 1. In order to avoid interpretation bias, all colonoscopies were performed and scored by the same endoscopist, who is an expert in IBD. Clinical relapse was defined as the need for remission induction treatment, any treatment escalation, hospitalization or colectomy. In order to assess the clinical course of UC, patients were followed-up and clinical relapses were evaluated at months 6 and 12 from initial colonoscopy. The influence of demographic and clinical variables (smoking, extension of disease and Mayo sub-score) in the clinical course of UC was also evaluated. Results are shown as percentages and analyzed by the chi-squared test and logistic regression.

Results: 57 UC patients fulfilled the inclusion criteria and were finally included. Mean age was 48 years (range 33–58), 58% women; 44% had never smoked, 19% were active smokers and 37% former smokers. 51% were E1, 26% were E2 and 23% were E3. Sixty-five percent had Mayo 1 and 35% had Mayo 0. During the first six months of follow-up 79.1% of patients remained in remission and 20.9% relapsed (mean time to relapse 14 weeks). Over the second semester, an additional 7% of patients relapsed. 10 out of the 12 patients who relapsed had a Mayo 1 sub-score. Frequency of relapses was not different in the different Montreal groups ($p=0.78$). 83% of former smokers patients presented a relapse compared to 17% of non-smokers ($p=0.06$).

Conclusions: MMX-mesalamine appears to be effective to maintain endoscopic remission in UC patients. Neither the extension of the disease nor the Mayo sub-score seem to influence the efficacy of the therapy in this study. Further studies including larger numbers of patients are required to confirm these data.

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Psychological factors and quality of life in inflammatory bowel diseases patients: the Psycho study

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Background: Psychological disorders are more frequent in patients with inflammatory bowel diseases (IBD) than in general population, and they are usually more severe during IBD relapse, with a huge

impact on quality of life (QoL). The role and the characterization of psychological factors in IBD is not well documented.

Methods: This was a single-center, observational, transversal study. Consecutive adult IBD patients were enrolled and stratified according to disease activity (active/remission). Socio-demographic and clinical data were collected and specific validated questionnaires Symptom Checklist-90-R (SCL-90-R) for psychological distress, Defense Mechanism Inventory (DMI) for psychological defense mechanisms, and Inflammatory Bowel Disease Questionnaire (IBDQ) for QoL were administered. We aimed to analyse the frequency of specific psychological factors in IBD subjects, to compare psychological and behavioral factors between patients with active disease or in remission, and to correlate those factors with socio-demographic and clinical data.

Results: 201 IBD patients (CD=47%; UC=53%) were prospectively enrolled, half of them had active disease (HBI>5 or PMS>2). Median IBD-Q (cut-off>209) was significantly lower in patients with active disease compared to those in remission (136.5 vs. 177.5, $p<0.001$). No patients had psychological scores above the cut-off for normality, but scores slightly below the cut-off were found for somatization, depression, anxiety, Global severity Index (GSI), and Positive Symptom Total (PST). Statistically significant differences were found in active IBD patients for obsessive-compulsive ($p=0.026$), depression ($p=0.013$), anxiety ($p=0.013$), phobic anxiety ($p=0.002$), psychoticism ($p=0.007$), GSI ($p=0.005$), PST ($p=0.001$) compared to those in remission. Crohn's disease and disease activity were associated with higher probability to have an increased GSI, PST and Positive Symptom Distress Index (PSDI). No significant differences were found for defense mechanisms.

Conclusions: IBD patients suffer from psychological distress and are characterized by impaired QoL, independently from disease activity. Psychological status is significantly impaired in patients with active disease. Psychological support may play a key role in managing IBD patients with active disease.

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Nutrition status in pre-surgical Crohn's disease, active Crohn's disease, Crohn's disease in remission and ulcerative colitis in remission: a cross-sectional study

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Background: Malnutrition (undernutrition) in inflammatory bowel disease (IBD) is associated with increased morbidity, post-operative complications and reduced quality of life. Alterations in nutrition status in active versus remission IBD remain poorly characterised. Additionally, nutrition status has not been quantified in pre-surgical Crohn's disease (CD) patients requiring gastrointestinal resection. This study aimed to quantify body composition, muscle strength, micronutrients and lipid profile and to compare between the following IBD groups: pre-surgical CD; active CD; CD in remission; and ulcerative colitis (UC) in remission.

Methods: A cross-sectional study recruited IBD patients from a London teaching hospital. Body mass index (BMI) was measured. Di-

rect anthropometry was undertaken to determine mid-upper arm circumference (MUAC), tricep skinfold (TSF), mid-arm muscle circumference (MAMC) and waist circumference (WC). Bioelectrical impedance analysis (BIA) determined fat mass (FM) and fat-free mass (FFM). To establish muscle strength, dynamometers measured hand-grip strength (HGS). Blood tests determined plasma micronutrients and lipids. Comparisons between groups were made using one-way ANOVA for continuous data with significance at $p < 0.05$.

Results: Eighty-four IBD patients were recruited: 23 pre-surgical CD; 21 active CD; 27 CD in remission; and 13 UC in remission. Pre-surgical CD had significantly depleted body composition compared to CD in remission based on: BMI (22.11 ± 3.69 vs. $26.00 \pm 5.90 \text{ kg/m}^2$, $p = 0.035$); MUAC (26.8 ± 3.9 vs. $30.8 \pm 3.9 \text{ cm}$, $p = 0.010$); and MAMC (20.8 ± 3.3 vs. $24.1 \pm 3.0 \text{ cm}$, $p = 0.015$). In males only, pre-surgical CD had significantly depleted FFM compared to CD in remission (56.77 ± 13.41 vs. $68.69 \pm 7.46 \text{ kg}$, $p = 0.014$). Muscle strength did not differ across female IBD groups, but male HGS was lower in pre-surgical CD compared to CD in remission (29.55 ± 9.15 vs. $40.13 \pm 7.29 \text{ kg}$, $p = 0.002$) and UC in remission ($44.41 \pm 9.70 \text{ kg}$, $p = 0.006$). No significant differences in body composition or muscle strength existed between active and IBD groups in remission but CD in remission had significantly lower vitamin D compared to active CD (46.58 ± 20.15 vs. $70.53 \pm 28.17 \text{ nmol/L}$, $p = 0.035$). Pre-surgical CD had significantly lower mean zinc levels ($10.05 \pm 2.86 \mu\text{mol/L}$) compared to CD in remission ($12.34 \pm 2.45 \mu\text{mol/L}$, $p = 0.037$) and UC in remission ($12.84 \pm 2.05 \mu\text{mol/L}$, $p = 0.039$).

Conclusions: Across IBD phenotypes and disease activity groups, nutrition status is most depleted in pre-surgical CD patients. This study may help healthcare services prioritise dietetic provision to IBD patients, specifically for pre-surgical CD patients.

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Association between clinical outcome and post induction CT-P13 trough levels at week 14, in patients with inflammatory bowel disease. Preliminary results in an observational multicentric study

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Background: CT-P13 became the first Infliximab (IFX) biosimilar approved for the treatment of Inflammatory Bowel Disease (IBD) in 2013. Measurement of IFX trough levels has been suggested as a new approach to tailor the therapy. Few studies have evaluated in clinical practice the relationship between primary failure after induction therapy (10–30%) and trough levels of CT-P13. Our aim is to evaluate the usefulness of systematically testing trough levels of CT-P13 at week 14.

Methods: We conducted a multicentric observational study including all adult patients with IBD treated with CT-P13, excluding patients on CT-P13 to prevent post-surgical recurrence. Induction dose was

5mg/kg at week 0, 2 and 6. Trough levels were measured in week 14 using enzyme-linked immunosorbent assay (ELISA) (Promonitor-IFX; Progenika Biopharma®). In Crohn's Disease (CD) a decrease ≥ 3 points in Harvey-Bradshaw index (HBI) was considered partial response (PR) and a HBI lower than 5 was considered clinical remission (CR). In Ulcerative Colitis (UC) a decrease ≥ 3 points in Partial Mayo Index (MI) was considered PR and CR was a MI lower than 3.

Results: We included 80 patients with a median age of 47.55 ± 13.6 (62.7% males). CD patients (49) had a basal HBI of 7.88 ± 4.01 . UC patients (31) had a basal MI of 6.55 ± 2.11 . Patients had previous treatment with anti-TNF drugs in 38.5%, and 83.1% with immunomodulators (IMM). We associated IMM to CT-P13 in 59% of our patients.

Median trough levels at week 14 were 4.36 (CD 4.04 and UC 4.85). No differences were found between patients with concomitant IMM (4.40) or without it (4.31); naïve (3.97) and no naïve anti-TNF patients (5.07).

Postinduction trough levels in patients with NR were 2.897, PR 4.57 and CR 4.87. Patients with primary failure presented lower CT-P13 trough levels compared with patients in CR, although no statistical significance was found ($p = 0.539$).

Considering less than $3 \mu\text{g/ml}$ as infratherapeutic, only 39.7% of patients reached therapeutic levels (36.3% CD, 44.8% UC). NR had 33.3% of patients (CD = UC), PR 48% of patients (41.6% CD, 43.85% UC) and CR 36.3% (36.3% CD and 40% UC).

Conclusions: The median CT-P13 trough level in week 14 was $4.36 \mu\text{g/ml}$. No statistically significant differences were found between CD/UC, naïve/not naïve to anti-TNF therapy.

Association of immunomodulators did not increase CT-P13 postinduction levels.

Up to 60% of patients had infratherapeutic ($< 3 \mu\text{g}$) CT-P13 postinduction levels.

There were no statistically significant differences between therapeutic or infratherapeutic levels and clinical response at week 14.

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IBD cancer and serious infections in Europe (I-CARE): a European prospective observational study

The I-CARE Study Group

Background: Prospective studies specifically assessing the effectiveness and safety profile of current therapeutic strategies based on a wider use of biologics in inflammatory bowel disease (IBD) are lacking. The overall objectives of I-CARE are to assess: 1) the long-term safety profile (malignancy, infections) of immunomodulators (IMM), biologics (anti-TNF and vedolizumab) alone or in combination with an IMM 2) the potential for disease modification of biologics 3) the benefit-risk ratio of current therapeutic strategies 4) health economics of IBD care.

Methods: I-CARE is a prospective observational cohort study that will enroll more than 10,000 adult patients with IBD followed for 3 years in 15 European countries. Each investigator will enroll 22 patients divided into 5 groups: Group 1 (5 patients who have never received biologics or IMM); Group 2 (5 patients receiving IMM alone); Group 3 (5 patients treated with anti-TNF therapy alone); Group 4 (5 patients treated with anti-TNF therapy in combination with IMM); Group 5 (one patient treated with vedolizumab monotherapy and one patient in combination with IMM). At inclusion, investigators collect patients' and disease characteristics, history of cancer,

previous medications, and vaccination status. Clinical disease activity, surgical procedures, all hospitalization reports, IBD-related medications, serious infections, dysplasia/cancers are reported monthly by the patient and yearly confirmed by the investigator who also reports endoscopy and radiology findings.

Results: As of 4 Nov 2016, a total of 2,089 IBD patients have been included: 406 in group 1 (19.4%), 431 in group 2 (20.6%), 641 in group 3 (30.7%), 454 in group 4 (21.7%), and 157 in group 5 (7.5%). Among 1095 anti-TNF patients, 507 had Remicade, 136 infliximab biosimilars (Inflixtra or Remsima), 415 adalimumab and 37 golimumab. Mean age is 37.8 years (SD=12.3), 51.9% are female, and disease duration is 9.6 years (SD=7.8). We included 1,238 Crohn disease (59.3%/nileal=402 ncolonic=182 nileocolonic=472 others=182), 812 ulcerative colitis (38.9%/nProctitis=72 nLeft sided colitis=276 nExtensive UC=348 others =116), and 39 indeterminate colitis (1.9%) patients. 507 patients had a previous surgery (28.1%) and 46 a personal history of cancer (2.5%). The rate of follow-up at 1 month is 91% (n=1920).

Conclusions: The I-CARE project will provide unique information about the safety profile and the impact of biologics on patient- and disease-related outcomes in a real-life setting in a very large cohort of IBD patients followed for 3 years. This database will also offer a unique opportunity to investigate the pharmaco-epidemiology of current strategies in IBD. Recruitment is ongoing across Europe.

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Assessment of study group – patients with inflammatory bowel disease, treated with monoclonal anti-TNF alpha: a multicenter, prospective cohort observational study, Satimos – preliminary report in pediatric population

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Background: The incidence of the inflammatory bowel disease (IBD) is increasing in the pediatric population. Anti-TNF treatment is used more often. Because of this, a multicenter, prospective cohort observational study was started to prospectively evaluate the safety of anti-TNF alpha in adults and pediatric patients with IBD. Data collection began in January 2014. This preliminary report is based on the analysis of data collected until September 2016. From the database the information about pediatric population was analyzed in this report. The aim of the study is characteristic of pediatric population qualified to anti-TNF therapy in Poland.

Methods: Authors analyzed the data of 667 patients - 307 women (45.9%) and 360 men (54.1%).

Among the respondents, there were 270 patients aged below 18 years old (40.4%) and 397 adults (59.6%). The analysis omitted 74 patients for whom complete data were lacking.

Results: The pediatric group consisted of 214 patients suffering from Crohn's disease (CD) and 56 with ulcerative colitis (UC). The time between the first symptoms and diagnosis depends on the type of disease, UC was diagnosed after mean 8.1 months, CD after mean 11.8 months. Among children with UC, 60.4% of patients had extensive colitis (E3), 32.1% had left side colitis and 7.5% had proctitis. For pediatric patients with CD localisation of the disease was: upper gastrointestinal tract 27.1%, ileum terminale 38.3%, colon 40.2%, small intestine 22.0%, perianal changes were seen in 23.4% children. The most often, regards to CD 75.4% of children were qualified to biologic therapy because of luminal active disease and 24.6% of children with severe perianal changes. Among children with CU, 73.1% of patients were qualified to the therapy because chronic refractory course of disease, 26.9% because exacerbation of disease. Mean disease activity at the beginning was PCDAI 40.4, PUCAI 53.7.

80.3% of patients with CD and 87.8% with UC were qualified to treatment with Infliximab, 19.7% of children with CD and 12.1% with UC were qualified to treatment with Adalimumab. The response to treatment in the CD by decrease in PCDAI score was observed in 70.8% of children. In turn, the UC response to treatment was defined as a decrease in the PUCAI scale and was recorded in the case of 78.8% of children.

Among children with UC adverse events was observed in 58.9% of cases, with CD in 46.7%.

The most common adverse events which were reported could be classified as gastrointestinal disorders (24.3%) and mild infections (19.2%).

Conclusions: This preliminary report shows important data about pediatric population with IBD. Data also shows how large number of patients require biological treatment.

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Baseline characteristics of ulcerative colitis patients in the vedolizumab PASS study: a cohort study assessing the safety and effectiveness of vedolizumab compared to other biologic agents (01)

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Background: The aim of this study is to quantify and compare the safety and effectiveness of vedolizumab (VDZ) to other biologic agents (OBAs) in IBD. The study is currently recruiting 5,000 IBD patients across 23 countries in North America and Europe, and will follow patients for up to 7 years. This interim analysis presents the baseline data of ulcerative colitis (UC) patients.

Methods: The study is a multi-centre prospective observational cohort study recruiting patients with IBD, aged 18+, initiating or switching to a new biologic agent, and no prior VDZ exposure. Those initiating VDZ enter the VDZ exposure cohort, while those initiating OBAs enter the OBAs exposure cohort, with each cohort enrolling 2,500 patients.

Results: 249 UC patients had enrolled as of 30 September 2016, 135 initiated or switched to VDZ and 114 initiated or switched to an OBA. The VDZ and OBA cohorts were similar with regards to age (range 18–86 years, mean 44 years), gender (46% female), and BMI (range 13–40, mean 26). There was no baseline difference between groups for UC disease location, stool frequency, presence of rectal bleeding, physician rating of disease activity, partial Mayo score, proportion having had a surgical or non-surgical hospital admission in the previous 12 months or previous IBD medications. There was also no difference at baseline in concomitant use of corticosteroids or immunomodulators.

Patients initiating VDZ vs. initiating OBA had UC for longer (9.8 years vs. 7.6 years, $p=0.029$), were more likely to have had previous biologic therapy (74% vs. 19%, $p<0.001$), and less likely to have had extra-intestinal manifestations (15% vs. 27%, $p=0.016$).

Patient-reported quality of life was assessed using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ). Patients initiating VDZ gave a more positive (i.e. less severe) response at baseline for all questions on physical wellbeing (systemic and bowel), social and emotional functioning as compared to OBA cohort. The overall SIBDQ score suggests that, at baseline, patients who initiated VDZ reported a better quality of life than those starting OBAs (median 4.3 vs. 3.5, $p=0.020$).

Conclusions: UC patients starting VDZ are more likely, at baseline, to have longer duration of disease, previously used a biologic agent, and are less likely to have extra intestinal manifestations than patients initiating/switching OBAs. The data presented are preliminary as they represent the initial 10% of UC subject enrolment. It will be important to observe if these findings persist and if others emerge with continued and full study enrolment.

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Real world use of adalimumab: effects on corticosteroid treatment and hospital resource utilisation in UK patients with moderate/severe ulcerative colitis

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Background: Anti-TNF therapies are used to treat moderate/severe UC. Until 2015 adalimumab (ADA) was only available for treatment of UC in the UK through individual funding requests (IFRs). Data on the effect of ADA on IBD-related hospitalisation in these patients are scarce.

Methods: An observational retrospective chart review study was conducted across 6 UK hospitals to evaluate UC-related resource utilisation and outcomes in the 12-month periods pre- and post-ADA initiation. All eligible consenting patients aged ≥ 18 years treated with ADA for UC in the clinical setting prior to UK National Institute for Health and Care Excellence (NICE) approval (February 2015) were included.

Results: 42 patients were included (mean age: 40.6 [SD: 15.5] years; 22 females [52%]; median UC duration: 7.6 [IQR: 2.5–10.3] years). A significantly higher proportion of patients were corticosteroid-free (oral, rectal and intravenous) post-ADA initiation (29%) than pre-ADA (12%, McNemar test $p=0.008$; see table). Pre-ADA UC-related

Resource type per patient	UC-related hospital resource utilisation	
	Pre-ADA (n=42)	Post-ADA (n=41) ^a
Steroid-free, n (%)	5 (12%)	12 (29%)
Outpatient visits, mean (SD)	6.1 (2.4)	5.6 (4.5) ^b
A&E visits, n (%)		
0	41 (98%)	35 (88%) ^b
1	1 (2%)	2 (5%)
2	0 (0%)	3 (8%)
Unplanned admissions, n (%)		
0	33 (79%)	37 (90%)
1	7 (17%)	4 (10%)
2	2 (5%)	0 (0%)

^a1 patient lost to follow-up; ^bexcludes 1 patient with unknown visit type
 Where % do not total 100%, this is due to rounding

hospital resource use included a mean of 6.1 (range: 2–12) outpatient visits/patient, and a total of 1 A&E visit and 11 unplanned admissions (see table). Post-ADA initiation UC-related hospital resource use included a mean of 5.6 (range: 0–24) outpatient visits/patient, and a total of 8 A&E visits and 4 unplanned admissions (all 4 preceded by an A&E visit). The mean length of stay (LOS) per unplanned admission pre-ADA was 5.0 (SD: 4.3) days (n=9) and post-ADA was 2.5 (SD: 1.0) days (n=4; unpaired t-test p=0.28). This retrospective real world study relied on the severity scoring recorded in the medical records, which was limited at the time points of interest; in the subgroup of patients with paired disease severity scores pre- and post-ADA, disease severity improved in 8/11 (73%), 11/19 (58%) and 8/13 (62%) patients at 3-months, 6-months and 12-months post-ADA, respectively.

Conclusions: These data support a beneficial effect of ADA in reducing the levels of steroid use in this patient cohort, an important treatment goal in UC. Patients receiving ADA through IFRs could be considered as having exhausted all available therapies. Therefore, it is encouraging to note disease severity improvements in over half of patients with available data despite the need for ongoing hospital resource use in the 12 months post-ADA initiation. Evaluation of the resource use and patient outcomes in patients treated with ADA according to NICE recommendations in comparison with the IFI cohort will be of interest.

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Managing IBD patients on adalimumab based on trough levels and antibodies

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Background: Adalimumab (ADA) is a subcutaneous agent which blocks TNF α and has proven its efficacy in inducing and maintaining remission in IBD patients. Measuring ADA trough levels and identifying development of antibodies against ADA (AAA) may predict loss of response and alter medical management, however the optimal time of measurement and the most appropriate clinical decisions are yet to be defined. The aim of this study was to associate the time of measurement of ADA/AAA levels with results and to assess management based on these findings, particularly in association with AAA levels.

Methods: All IBD patients who had at least one measurement of ADA/AAA levels (ELISA) during their follow up in UCLH since January 2014 were included in the study. Patients' demographics, previous treatment, laboratory, endoscopic and imaging findings were recorded. Patients were divided in four categories using a previously described optimal cutoff of ADA levels at 4.9mcg/mL; those with satisfactory levels and presence or absence of AAA respectively and those with low levels and either positive or negative AAA. AAA titer was recorded both as complete count and in a centile.

Results: 71 IBD patients (63 Crohn's) were included. 40 (56%) had ADA/AAA measured due to clinically active disease, 29 (41%) as a routine check and 2 due to drug related side-effects. 42 (59%) were on a concomitant immunomodulator at the time of measurement. Median duration on ADA treatment was 2 years and 44% had weekly injections.

69 (97%) had detectable ADA levels. AAA were positive in 12 (17%) patients with a median titer of 42AU/mL. 70% had levels >4.9 and no AAA, 10% had low levels and no AAA, 10% had low levels and positive AAA and five patients had optimal ADA but positive AAA.

As expected, ADA titer was significantly higher when AAA were negative (10.5mcg/mL vs 5.6mcg/mL, p=0.019). AAA positivity was associated with clinical relapse at measurement (n=9/12, 25%) as opposed to routine check of levels and no symptoms (7%, p=0.01). Interestingly, AAA presence was not associated with concomitant IM. Among patients with detectable antibodies, AAA titer in the 1st centile (0–5) was associated with preservation of optimal ADA levels >4.9 (p=0.013), while detectable ADA levels were maintained up to the 4th centile (0–75) of AAA (p=0.017). Of the 4 patients with optimal levels and positive AAA who had repeat measurement, two had undetectable antibodies with no specific intervention in the meantime.

Conclusions: Measurement of ADA/AAA on patients who experience loss of clinical response is more likely to identify patients with positive antibodies as opposed to routine check. Low AAA titer is associated with preserved ADA levels and should not necessarily prompt change in medical treatment.

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Combination treatment with vedolizumab and anti-TNF- α in inflammatory bowel disease: safety data

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Background: During the last 15 years we have gained extensive clinical experience about anti tumour necrosis factor-alpha (anti TNF- α) in the treatment of ulcerative colitis (UC) and Crohn's disease (CD). Infliximab (IFX) and adalimumab (ADA) are most commonly used. Many patients have no, weak or diminishing effect of these drugs and some experience unacceptable side effects. In these patients, the anti-integrin vedolizumab (VDZ) is a novel treatment option, and combination therapy with anti TNF- α in a transition period until maximum VDZ effect is expected might represent a favourable clinical strategy and may reduce the need for prednisolone. Since VDZ is bowel-specific and not a systemic immunosuppressant, the combination with anti TNF- α may have an acceptable safety profile. The aim of this study was to examine the safety of the combination of VDZ and anti TNF- α in clinical practice.

Methods: IBD patients starting combination therapy with VDZ and anti TNF- α between November 2015 and June 2016 were followed prospectively. At baseline (start of combination therapy), diagnosis, extent and behaviour of disease, previous drug -and surgical treatment were recorded. During the observation period, adverse events, changes in medication and surgical interventions were recorded. By the end of 2016, all patients have been followed for at least six months.

Results: Fifteen patients with mean 3.9 years (range 0–16) of biological treatment, started combination treatment (10 UC and five CD). Eleven were given combination therapy with IFX and VDZ, two ADA and VDZ and two golimumab and VDZ. Ten patients received additional treatment with immunomodulator or prednisolone at inclusion.

As of today (30.11.16), the mean follow-up is 9 (5–12) months. Seven patients still receive combination biological therapy, seven have stopped anti TNF- α . The mean time on combination treatment of the latter group was 4.4 (1.4 to 8.4) months. One UC patient underwent a colectomy. This patient had onset of severe pustulosis during treatment with VDZ, IFX and methotrexate. One patient had a flare of monoarthritis after stopping IFX. Three patients received short-term,

systemic prednisolone during follow-up and two were steroid dependent throughout follow-up. Three patients were given antibiotics; two for upper respiratory infections and one for pouchitis.

Conclusions: The novel combination therapy with VDZ and anti TNF- α seems to have a frequency of adverse events comparable to therapy with anti TNF- α and conventional immunomodulators. Thus, these first experiences in clinical practice suggest that combination of VDZ and anti TNF- α is acceptable with regards to safety in IBD patients.

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Evaluation of treatment persistence of vedolizumab among Finnish inflammatory bowel disease patients in real-life clinical practice (FINVEDO)

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Background: Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody (mAb) directed towards the integrin $\alpha 4\beta 7$. Clinical trials in inflammatory bowel diseases (IBD) represent highly selected patient population and there is still limited data available of vedolizumab in real-world patient population. Therefore, we aimed to assess real-world treatment outcomes of vedolizumab in Finnish patients with IBD.

Methods: This was a nationwide, retrospective, non-interventional, multi-centre chart review study. All the adult (≥ 18 years of age) patients with a diagnosis of UC or CD and at least one vedolizumab infusion since the availability of the product in Finland in 2014 from 27 centres were included in the study. The exclusion criteria were the initiation of vedolizumab within < 6 months of the data collection, participation in a clinical trial during the follow-up period or planned cessation of vedolizumab treatment within follow-up period. Data were collected retrospectively from medical charts in a standardized case report form. The key data collection points were at baseline, week 14 and month 6 of vedolizumab treatment. The primary objective was to determine treatment persistence 6 months post initiation.

Results: A total of 232 patients (CD 105, UC 127) were included. Based on Physician's Global Assessment, 101 (96.1%) CD patients had either moderately or severely active disease (Harvey-Bradshaw index mean \pm SD, 12.7 \pm 8.5; moderate disease), and 112 (92.5%) UC patients had either mildly or moderately active disease (Partial Mayo score 5.2 \pm 1.7; moderate disease) at baseline. Majority of the patients were treatment refractory to previous anti-TNF- α treatment: 97.1% of CD patients and of 94.5% of UC patients were anti-TNF- α experienced. The majority (CD 43.8%, UC, 62.2%) were using concomitant steroids at baseline (Table 1).

Of all CD patients, 77 (73.3%) and of UC patients 84 (66.1%) were persistent on vedolizumab therapy 6 months post treatment initiation. The most common reason for discontinuation was primary lack of response (CD 63.0%; UC 75.0%), followed by secondary loss

Table 1. Baseline characteristics

	Crohn's disease (n=105)	Ulcerative colitis (n=127)
Age (years)	Mean (SD) 39.8 (13.6)	Mean (SD) 38.2 (14.2)
Gender:	n (%)	n (%)
Male	46 (43.8)	72 (56.7)
Female	59 (56.2)	55 (43.3)
Smoking	n (%)	n (%)
Yes	10 (9.5)	5 (3.9)
No	79 (75.2)	90 (70.9)
Unknown	16 (15.2)	32 (25.2)
Disease activity	Mean (SD)	Mean (SD)
Partial Mayo score	N/A	5.2 (1.7)
Harvey-Bradshaw Index score	12.7 (8.5)	N/A
Number of previous anti-TNF therapies	n (%)	n (%)
0	3 (2.9)	7 (5.5)
1	35 (33.3)	95 (74.8)
2	65 (61.0)	21 (16.5)
≥ 3	3 (2.9)	4 (3.1)
Concomitant treatments	n (%)	n (%)
Steroids	46 (43.8)	79 (62.2)
Mesalazine	28 (26.7)	78 (61.4)
Azathioprine	21 (20.0)	38 (29.9)
Methotrexate	23 (21.9)	11 (8.7)
6-merkaptopurine	6 (5.7)	18 (14.2)
Sulfasalazine	6 (5.7)	6 (4.7)
Cyclosporine	0 (0.0)	3 (2.4)

of response (CD 7.4%; UC 5.0%), adverse events (CD 14.8%; UC 17.5%), and other reasons (CD 18.5%; UC 12.5%).

Conclusions: Vedolizumab provides effective and well-tolerated treatment option in a real-world clinical setting even among treatment refractory IBD patients.

P16

Adrenal suppression in inflammatory bowel disease patients treated with glucocorticoids: a systematic review

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Background: Glucocorticoids are a mainstay of inflammatory bowel disease (IBD) treatment, with oral tapering courses frequently used to induce remission or control flares. Impairment of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in adrenal suppression (AS), is an established side effect of exogenous glucocorticoids. Currently however there is no standard guidance or recommendations to suggest routine screening of IBD patients for this potentially fatal complication following steroid use. We aimed to systematically review the published evidence for risk of AS in both adult and paediatric IBD patients treated with glucocorticoids.

Methods: An electronic literature search using PubMed, Ovid Medline and Embase was performed up to November 2016 using MeSH terms relating to IBD and adrenal function/insufficiency/suppression. A hand search of references of relevant papers was also performed. Papers presenting original data including biochemical evidence of adrenal function during or after glucocorticoid therapy for IBD, were included. Evidence was assessed using GRADE recommendations.

Results: 198 papers were initially retrieved and reviewed. Ten met the inclusion criteria (6 randomised controlled trials, 4 case series). 4

of the randomised trials (one paediatric) compared oral budesonide with prednisolone or placebo and measured AS as a secondary outcome. Results varied, with one study showing no increase in AS after budesonide, two suggesting AS in up to 62% of patients after budesonide, and one study showing AS in 89% of patients treated with prednisolone. 2 retrospective case series (one paediatric) specifically investigated adrenal function following oral prednisolone: one measured morning cortisol and found 20% to be low; the other demonstrated AS in 60%. Both papers measured the time taken for the HPA axis to return to normal (5.6 weeks and 7.2 months respectively). The remaining 2 randomised studies and 2 case series measured adrenal function after different steroid enemas and found some degree of AS after prednisolone and betamethasone preparations. Most papers had high risk of confounding/bias and heterogeneity.

Conclusions: AS in patients with IBD during or after therapy with either oral or rectal glucocorticoids has been shown to occur in up to 89% of patients. However good quality, adequately powered studies are lacking and methods of measuring adrenal function varied considerably. Stimulation testing with adrenocorticotropic hormone analogues is most sensitive but is a more complex procedure than a morning cortisol assay. Clinical presentation of AS was not explored in the selected studies but case reports and experience from other patient groups suggest that it can be non-specific, mimic IBD symptoms or even cause mortality.

P517

Features of cytomegalovirus infection in inflammatory bowel disease

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Background: To determine the relationship between frequency of cytomegalovirus infection (CMVI) and duration, severity and kind of treatment in IBD patients; to evaluate the rate of refractory disease in CMVI patients

Methods: During past 6 years 1652 inflammatory bowel disease (IBD) patients (ulcerative colitis – 1323, Crohn's disease – 329) were examined in Moscow region. CMVI was detected by PCR in blood and colon mucosa

Results: The percentage of CMVI in IBD patients increased from 0.6% in 2010 to 4.7% in 2015. In total CMVI was detected in 4.3% of IBD patients. Frequency of CMV among infected patients was different and depended on: a) the duration of IBD (Table 1), b) severity of IBD (Table 2), c) kind of treatment (Table 3).

Table 1

Duration of IBD	≤ 1 year	2–3 years	≥ 5 years
Frequency of CMV	10%	19%	35%

Table 2

Severity of IBD	Mild	Moderate	Severe
Frequency of CMV	0%	37%	63%

Table 3. Frequency of CMV, depending on the treatment

Kind of treatment	CMV (%), N=72
5-ASA	5.6
GCS	58.3
Azathioprine	6.9
GCS + Azathioprine	29.2
Infliximab/Infliximab + Azathioprine	0%

The most of CMV cases were detected in patients treated with GCS (prednisone) and with combination of GCS+AZA. Refractory IBD was found in 51% of CMV infected patients (37 pts). They were treated within gancyclovir during 2 weeks. As a result in 28 patients (75.6%) the sensitivity to base therapy was recovered. We called this phenomenon "pseudo refractory" due to CMVI, which can be overcome with antiviral treatment.

Conclusions: In total CMVI occurs in 4.3% of IBD patients; most of CMVI occurs in IBD with duration ≥5 years and in moderate to severe patients. The most CMVI was found in IBD patients treated with GCS as mono- or combo therapy and frequency of refractory IBD was highest in the same groups. CMVI can simulate "pseudo refractory" IBD which can be overcome with antiviral treatment. We mandatory recommend to detect CMVI in IBD patients before GCS or immunosuppressants

P518

Remission induction in corticosteroid naïve children and adolescents with ulcerative colitis by adsorptive leucocytapheresis as monotherapy or in combination with low dose prednisolone after failure of first-line medications

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Background: In patients with active ulcerative colitis (UC), myeloid lineage leucocytes are known to be elevated with activation behaviour including the CD14+CD16+ monocyte phenotype, which is a major source of tumour necrosis factor- α (Belge, et al. J Immunol 2002). Therefore, selective depletion of myeloid leucocytes by adsorptive granulocyte/monocyte apheresis (GMA) with an Adacolumn should promote remission, or enhance drug efficacy. Potentially, GMA should be a relevant option in paediatrics and adolescents settings where drug therapy may have limitations.

Methods: Between 2010 and 2015, 30 consecutive ulcerative colitis (UC) patients, age 11–19 years, body weight 33–55.5kg were given mesalazine (n=23) or sulphasalazine (n=7) as first-line medication. Twenty patients relapsed or did not respond and received GMA with the Adacolumn, at 2 sessions in the first week, then weekly, up to 11 sessions. Patients who achieved ≥5 decrease in the clinical activity index (CAI) continued with GMA while non-responders received GMA in combination with prednisolone (PSL, 0.5 to 1.0mg/kg body-weight). At entry and week 12, patients were clinically and endoscopically evaluated with each patient serving as her or his own control.

Results: At entry, all 30 patients were corticosteroid naïve and none had deep colonic UC lesions or extensive loss of the mucosal tissue at the affected sites (GMA non-responder features). Ten patients achieved stable remission with the first-line medications and did not receive GMA. Six patients did not respond well to the first 5 GMA sessions and received PSL together with GMA, while 12 patients responded well to GMA with stable remission and 2 withdrew to receive high dose PSL (up to 2mg/kg). At entry, the average CAI was 14.2±0.4, range 11–17, and the average endoscopic index was 9.2±0.4, range 7–11. The corresponding values at week 12 were 2.1±0.2 range 1–4 (p<0.001) and 2.4±0.2, range 1–4 (p<0.001). PSL was tapered to 0mg within 3 months. Therefore, at week 12, all 30 patients were in clinical remission, majority with mucosal healing.

Conclusions: In this investigation, GMA in young corticosteroid naïve patients with active UC refractory to the first-line medications was associated with clinical remission and mucosal healing, while in non-responders to GMA monotherapy, addition of a low dose PSL enhanced the efficacy of GMA and tapering of PSL was not associated with UC relapse. Therefore, the majority of young steroid naïve UC patients who fail to respond to first-line medications should respond well to GMA and be spared from pharmacological intervention. Additionally, GMA has a good safety profile, which is a very favoured feature in growing patients.

P519

Anti-tumour necrosis-alpha therapy during pregnancy in patients with inflammatory bowel disease: safety in women and children

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Background: Inflammatory bowel disease (IBD) is often diagnosed in women of childbearing age, which may influence therapeutic decisions in those patients. Despite several studies have suggested the safety of tumour necrosis alpha antagonists (anti-TNF α) during pregnancy, there are still concerns regarding their long-term effect, and the optimal timing for their discontinuation is not yet fully established. The aim of this study was to evaluate IBD and pregnancy-related outcomes in patients who were treated with anti-TNF α drugs, as well as their children's safety.

Methods: We conducted a retrospective review of women with IBD who received anti-TNF α therapy during pregnancy between 2004 and 2016. Clinical characteristics, disease and drugs history, pregnancy and neonatal complications and data regarding children's growth, development and medical history were collected.

Results: We analysed 22 pregnancies in 17 women: 15 with Crohn's disease (CD), 2 with ulcerative colitis (UC), mean age of 30 \pm 5 years, range 19–38 years. During gestation, 13 patients used infliximab and 9 used adalimumab; 41% of them (n=9) had concomitant treatment with azathioprine/6-mercaptopurine. Ninety-one percent of women (20/22) had inactive disease before pregnancy. Last anti-TNF α administration was performed between the 20th and the 35th week of pregnancy (median of 28 weeks gestation). The relapse rate during pregnancy and puerperal period was 14% (n=3): an UC patient and a CD patient had a flare in the 3rd and in the 1st trimester, respectively, both medically treated; a woman with CD, who had moderately active disease at conception, relapsed in the 2nd and required surgery in the 3rd trimester. Of the 22 cases, 21 were full pregnancies (one of which a twin pregnancy) and 1 is still in course. Apart from a case of twin-twin transfusion syndrome (successfully treated with good outcome) and a low-birth weight infant (in the patient who relapsed and underwent surgery), there were no other complications, including stillbirth, preterm birth or congenital anomalies. All children (n=22, from 21 full pregnancies; mean age of 62 \pm 40 months, range 1–134 months) had normal growth and the rate and severity of infections was not different from those observed in the pediatric non-IBD population.

Conclusions: In our study, the vast majority of women had inactive disease at conception and biological therapy was effective in maintaining their clinical remission. Moreover, anti-TNF α treatment was not associated with an increased risk of pregnancy/neonatal events, infectious complications or childhood development disorders. Our

data reinforces that controlling the disease, either before and during gestation, may be more important to pregnancy and IBD outcomes than the administered therapy.

P520

Perspective and self-efficacy of adolescents with inflammatory bowel disease post transition to adult care

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Background: IBD is a chronic disease and approximately a quarter of patients are diagnosed before 20 years of age. A well-structured transition pathway can increase their self-efficacy and independence. Patients transitioning to Beaumont IBD services attend a structured transition clinic in pediatric hospital and at Beaumont hospital.

The objective of this cross-sectional study was to assess adolescents' perspective and self-efficacy with IBD post transition to Adult care.

Methods: Adolescents who transitioned through the structured pathway were eligible for the study. Data on patient's age, gender, IBD type, disease history and treatment were retrieved from the medical records. A questionnaire (including VAS and Likert scale) on patient's perspective and self-efficacy containing items on knowledge of disease, diagnostic tests, medications, and transition process was rated by the adolescents over the phone. Collected data was analysed with SPSS software.

Results: Of 23 eligible adolescents 19 (82.6%) participated in the study. Patient demographics: Mean age (years): 17.52 \pm 0.90, Male: 8 (42.1%), Female: 11 (57.9%), Crohn's Disease (CD): 11 (57.9%), Ulcerative colitis (UC): 8 (42.1%). The domains on the self-efficacy questionnaire showed good internal consistency (Cronbach's α : 0.72). The median for the domains of independence, knowledge of disease, diagnostic tests, treatment and medication use were >70% of max score. Domains of comfort with adult IBD service, independence with OPD visits and transition process had median of >90% of max score. There was no statistically significant difference in mean scores for general independence and general comfort between male vs female; and between CD vs UC on unpaired t-test (p>0.10). 7 (36.8%) stated that their disease will improve, 2 (10.5%) stated stay the same and 10 (52.6%) don't know how their disease will evolve.

Conclusions: Adolescents who recently transitioned to the adult IBD services rated high levels of independence, knowledge of IBD, diagnostic tests, treatment, self-efficacy in medication use and independent OPD visits. Also there is no correlation between gender, type of disease and patients' independence and comfort scores. However more than half of the participants showed uncertainty about their future with IBD.

P521

A prospective cohort study to assess the relevance of Vedolizumab drug level monitoring in IBD patients

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Background: Vedolizumab drug monitoring strategies in IBD patients have not been investigated systematically so far. Our aim was

to evaluate the correlation between vedolizumab trough levels (VTL) and the treatment response in patients with IBD.

Methods: 51 adult patients with therapy-refractory chronic active ulcerative colitis (UC) (n=23), Crohn's disease (CD) (n=27) or indeterminate colitis (IC) (n=1) on or starting a therapy with vedolizumab were enrolled in this prospective single center study. Disease activity indices (Harvey-Bradshaw-Index, partial Mayo score), total blood count, albumine, ferritin, C-reactive protein (CRP), and anthropometric parameters were assessed. Over a time period of 6 months 155 vedolizumab serum trough levels were assessed directly before the next scheduled application using liquid chromatography mass spectrometry (LC-MS/MS).

Results: Vedolizumab treatment was found to be clinically effective in most of the enrolled patients as documented by a significant drop of the mean Harvey Bradshaw Index from 10 to 5.5 points ($p < 0.0005$) in CD patients (n=27) and a significant decrease of the partial Mayo score from 4.4 to 2.1 points ($p < 0.0005$) in UC patients (n=23). CRP level tended to decrease and hemoglobin levels to increase under vedolizumab therapy. We did not find a significant effect of the concomitant medication (prednisolone, azathioprine, and methotrexate) on VTL. We detected significantly higher VTL in patients with application of vedolizumab every 4 weeks than those receiving vedolizumab every 8 weeks (30.2 versus 17.2 $\mu\text{g/ml}$, $p = 0.005$). CD patients with a serum CRP level lower than 5 mg/l exhibited significantly higher VTL than those with elevated CRP levels (34.9 versus 21.7 $\mu\text{g/ml}$, $p = 0.00153$). UC patients with hemoglobin levels higher 12 g/dl at the time of VTL measurement had significantly higher VTL compared to patients with lower hemoglobin levels (35.4 versus 15.6 $\mu\text{g/ml}$, $p < 0.0005$). Statistical analyses (receiver operating characteristics) indicate a significant association between VTL and treatment efficacy measured by CRP level in CD and hemoglobin level in UC.

Conclusions: Our data suggest a significant correlation between VTL and clinical response in IBD patients treated with vedolizumab, where patients with high VTL have a higher chance to reach the treatment goal than those with low VTL.

P522

A multicenter study to validate Magnetic Resonance Enterography against histological assessments of stenotic disease in patients with Crohn's disease

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Background: Assessment of stenosis is important in the management of Crohn's Disease (CD). Magnetic Resonance Enterography (MRE) is a useful diagnostic tool for detecting bowel strictures, and parameters such as gadolinium contrast "delayed gain of enhancement" (DGE) and "magnetization transfer ratio" (MTR) have been associated with fibrosis in resected specimens. [1] [2] In an attempt to develop a CD MRE imaging protocol for clinical trial use, the pur-

pose of this study was to identify MRE techniques that show association with a predefined histological score of fibrosis, independent of inflammation, in CD. The primary objective was to verify concordance between DGE and a histopathology fibrosis score as a reference standard. MTR was evaluated as secondary and apparent diffusion coefficient (ADC) as exploratory objective.

Methods: Informed consent was obtained from 51 stenotic CD patients eligible for resection surgery across 6 European centers in a prospective trial evaluating MRE for the detection of fibrosis in CD. Imaging was performed a median of two weeks ($>90\%$ <8 weeks) prior to surgery with no treatment changes in between. Local pathologists and radiologists annotated the location of 56 histological samples on the MRE scans, which was identified in the most stenosed region of corresponding resected specimens. An experienced pathologist centrally read the 56 samples using the Chiorean score [2]. A single radiologist measured DGE, MTR, T2, ADC, and MaRIA index [1,3]. Correlation of histology and MRE metrics was performed using Pearson's R.

Results: No association of fibrosis or inflammation with either DGE or MTR was found. ADC was associated with fibrosis ($R = -0.36$, $p = 0.011$). MaRIA score was correlated with inflammation (0.31, 0.031). Monitoring of image data quality by central reader resulted in $>95\%$ evaluable scans.

Conclusions: In this prospective, multi-center study, DGE and MTR were not found to be in concordance with histological measure of fibrosis, in contrast to previously published findings. This may have been due to a spatial mismatch between histological tissue sample and imaging measurement region of interest, inconsistencies in the interval between imaging and surgery, the effects of histological preparation, or lack of granularity in histological scoring. However MaRIA scores were in good agreement with inflammation scoring, so it is possible that MRE metrics assist in the assessment of CD stenosis. Further development of histological scores and MRE metrics will inform upon MRE protocol development in CD.

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P523

Association between pharmacokinetics of adalimumab and disease outcome in Japanese patients with biologics naïve Crohn's disease: a subanalysis of DIAMOND trial

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Background: Recently, we reported the result of a randomized clinical trial to compare the clinical efficacy of adalimumab (ADA) monotherapy with the combination of ADA with azathioprine (AZA) in induction of remission for Japanese patients with Crohn's Disease (CD) naïve to tumor necrosis factor (TNF) antagonists (DIAMOND trial). However, whether ADA trough levels and anti-ADA antibodies (AAA) were relevant to disease outcome remains unclear. The aim of this study is to evaluate the impact of ADA trough levels and AAA at 26 weeks on clinical activity at 52 weeks and to examine the effect of AZA on ADA trough level in CD patients enrolled in DIAMOND trial.

Methods: In the preceding DIAMOND trial, 176 patients with active CD naïve to TNF antagonists were randomly assigned to either have ADA monotherapy or the combination therapy. The clinical efficacy was evaluated at Week 26 and 52. Clinical remission was defined as a CDAI score of less than 150 points. Serum samples from the patients in both groups at Week 26 were collected and trough levels of ADA and AAA were measured by using ELISA system. Also, blood samples were collected from patients in the combination group at Week 12, and processed to measurement of 6-TGN in red blood cells (RBCs). A multiple regression model was performed to identify factors independently related to trough levels of ADA and AAA at Week 26. Covariates included in the model were age, sex, body weight, the duration of the disease, disease location, previous surgery, presence of internal fistula, presence of anal fistula, smoking status and medication at entry.

Results: One hundred and fifty-one serum samples were analyzed from 176 patients enrolled in the study. Patients with clinical remission at 52 weeks had significantly higher trough level of ADA (7.7 µg/ml) at 26 weeks than those with active disease (5.4 µg/ml; $p < 0.001$). Development of AAA at 26 weeks was significantly and positively associated with disease activity at 52 weeks ($p = 0.021$). A multivariate logistic regression model revealed that sex and low body weight were factors independently associated with high ADA trough level, and that male sex was associated with occurrence of AAA. There was a trend towards a higher 6TG level at 12 weeks in CD patients negative for AAA at 26 weeks (322 pmol/8 × 10⁸ RBCs) than in those positive for it (137 pmol/8 × 10⁸ RBCs), despite no significant difference of mean dose of AZA between AAA negative and positive group.

Conclusions: Higher trough levels of ADA and absence of AAA at 26 weeks obviously affected clinical activity at 52 Weeks in CD patients

treated with ADA monotherapy or the combination therapy. A high 6TG concentration might be required for suppression of AAA.

P524

Long-term outcomes after restorative proctocolectomy and ileal pouch-anal anastomosis in children compared to adults

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Background: Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the surgical treatment of choice for therapy refractory ulcerative colitis and familial adenomatous polyposis (FAP). There are only a few studies addressing the outcome of IPAA in children compared to adults. This complicates decision making in children with therapeutic refractory UC or FAP. Therefore, we aimed to compare adverse events and pouch function between pediatric and adult patients who underwent IPAA.

Methods: In this cohort study, all consecutive children (<18 years) and adults with a diagnosis of inflammatory bowel disease or FAP that underwent IPAA were included (2000–2015). The IPAA's were performed in a Dutch tertiary referral center by the same team of colorectal surgeons in all subjects in this time period (IPAA's 30–35/year). Demographic and surgical characteristics, and adverse events were obtained by chart review. Pouch function was assessed by phone interview using the Pouch Function Score (PFS, scale 0–30). Differences in adverse events between pediatric and adult patients were analyzed using multivariate regression analysis, corrected for the moment of enrollment during the study period.

Results: In total, 445 patients underwent IPAA: 41 pediatric (median age 15 years) and 404 adult patients (median age 39 years). Median follow-up was 24 months (IQR 8–68). In pediatric patients, overweight, previous abdominal surgeries, open procedures (i.e. colectomy) and defunctioning ileostomy were less prevalent compared to adult patients ($p < 0.05$). All other characteristics, including type of diagnosis and duration of follow-up, were similar ($p > 0.05$).

The occurrence of anastomotic leakage, surgical related fistulas, chronic pouchitis and Crohn's of the pouch (in IBD patients) was not associated with pediatric age, neither was pouch failure on the long-term (table). Pediatric age at IPAA was an independent risk factor for developing anastomotic strictures (OR: 4.2 [95% CI: 1.1–15.8]; $p = 0.032$). These strictures were successfully treated through a single dilatation in all pediatric and 73% of adult patients. Current pouch function was similar between pediatric and adult patients (median PFS 5.0 vs. 6.0, $p = 0.164$).

Table 1

	Pediatric (n=46)	Adult (n=426)	OR (95% CI)
Anastomotic leakage	14%	16%	0.88 (0.35–2.22)
Pouch stricture	10%	3%	4.22 (1.13–15.77)*
Fistulas related to the pouch	2%	6%	0.63 (0.08–5.21)
Fistulas related to the pouch	5%	8%	0.58 (0.13–2.56)
Crohn's of the pouch [^]	15%	6%	3.07 (0.87–10.82)
Pouch failure	10%	6%	3.01 (0.89–10.14)

*Significantly associated with adverse outcome in multivariable regression analysis. [^]In IBD patients only (n=339).

Conclusions: Long-term pouch failure rates and pouch function were similar between pediatric and adult patients. There is no need for a

more cautious attitude in the application of IPAA in pediatric patients based on concerns of poor outcome on the long term.

References:

[1] K. Diederer, (2016), Table 1

P525

Effectiveness and safety of vedolizumab in IBD patients: a multicentre experience of “real world data” from the UK

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Background: Vedolizumab (VDZ) is an $\alpha 4\beta 7$ anti-integrin licensed to treat ulcerative colitis (UC) and Crohn's disease (CD). Its gut selectivity may suggest a favourable risk-benefit profile, including a low rate of immunosuppression-related complications. We aimed to assess clinical outcomes and safety of VDZ in IBD patients treated in several hospitals across northern England.

Methods: We retrospectively collected data from electronic records of patients treated with VDZ at 8 UK centres since 2014. Demographic, clinical, and adverse effects data were recorded. We evaluated clinical response at 12 and 52 weeks using the Physician Global Assessment (PGA), Harvey-Bradshaw Index (HBI) or Mayo score. We collected C reactive protein (CRP) and faecal calprotectin (FC) at baseline and follow-up. Fisher exact test and student's t-test were used to determine statistical significance.

Results: Of 183 patients (mean 41 years, F/M ratio 1.4:1) 120 (65.6%) had CD, 61 (33.3%) UC, and 2 (1.1%) IBD-U. 18 patients were active smokers. 57 (31%) received immunomodulators. 68 (37%) received steroid bridging therapy. 27 (15%) patients were anti-TNF naïve. PGA remission was observed in 33 (31%) CD, 26 (44.8%) UC and 2 (100%) IBD-U patients at 12 weeks and in 6/48 (12.5%) CD and 16/36 (44.4%) UC patients at 52 weeks. In addition a partial response was observed in 51 (48%) CD and 25 (43.1%) UC patients at 12 weeks and in 8/48 (16.6%) CD and 10/36 (27.7%) UC patients at 52 weeks.

At 52 weeks, VDZ was more effective in maintaining remission in UC than CD ($p < 0.05$). In CD patients, mean CRP, FC and HBI improved (25.4 vs 15, 862 vs 427, 9.3 vs 6.5; $p < 0.05$ respectively) at 12 weeks, with a further improvement of HBI at 52 weeks (4.45; $p < 0.05$). In UC, mean FC and Mayo score decreased (762 vs 353, 6 vs 3.5; $p < 0.05$) at 12 weeks, whereas CRP did not improve (13.8 vs 11.5; ns). Non-smoking status was associated with better response ($p < 0.05$), regardless of concomitant medications and prior anti-TNF exposure. Forty-three patients (23.5%) discontinued vedolizumab (average exposure 4.5 months).

Reported side effects occurred in 21 cases (11%): 3 urticarial rashes, 6 pneumonias, 3 nasopharyngitis, 2 skin infections, 2 sepsis, 1 viral meningitis, 1 EBV infection, 1 urinary tract infection, and 2 abnormal liver function tests. 1 unrelated death occurred in this cohort. Overall incidence of infection was 12 per 100 person-years of VDZ exposure.

Conclusions: VDZ is a safe and effective therapy even in this cohort of refractory, predominantly anti-TNF exposed patients. Induction data are similar for CD and UC, but VDZ seems to be more successful in maintaining remission for UC compared to CD. The incidence of infectious complications was comparable to that seen with anti-TNF therapies (average 14 per 100 person-years).

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A prospective 52-week mucosal healing and deep remission assessment of small bowel and colonic Crohn's disease as detected by colon capsule endoscopy

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Background: There are no data on long-term mucosal healing (MH) and deep remission (DR) in children with Crohn's disease (CD). Previously, we reported prospectively assessed MH and DR rates on the entire GI tract by performing two CCE over 24 weeks in children with CD, in comparison with biomarkers, magnetic resonance enterography (MRE) and SB contrast ultrasonography (SICUS). This extension evaluates MH and DR in the same cohort of patients at 52-week follow-up. The long-term efficacy of a “treat-to-target” strategy was also evaluated at the end of the study.

Methods: Children with known CD were prospectively recruited and underwent imaging studies followed by CCE, at 0, 24 and 52 weeks. The Lewis score (LS) and Simple endoscopic score for Crohn's disease (SES-CD) were calculated for SB and colon, respectively. C-reactive protein (CRP) and fecal calprotectin (FC) were also evaluated for their association with clinical activity, imaging and CCE findings. Clinical remission was defined as PCDAI < 10. SB and colonic MH were defined as LS < 135 and SES-CD ≤ 1 , respectively; moderate-to-severe inflammation was defined as LS > 790 or SES-CD > 7. Biomarker remission (BR) was defined as a combination of clinical remission (PCDAI < 10) and normal biomarkers. Deep remission (DR) was defined as a combination of BR and MH. Therapy was calibrated according to CCE results at baseline and week 24.

Results: Of 48 patients (pts) recruited, 46 completed the 52-week evaluation (2 developed an ileo-cecal valve stricture). At baseline, 22 were clinically active and 26 were in remission. After a “treat to target strategy”, at week 24, only 8 were in clinical activity, while 40 were in remission. CCE identified DR in 26/40 (54%) of the remission group; while in 8 with mild clinical activity (100%) showed a partial MH (according to baseline evaluation). At 52 weeks, CCE showed DR in 28 (58%); with the detection of new lesions in 4 and a complete MH in 6 (with previous partial MH at 24 weeks).

MRE and SICUS had good concordance in evaluating DR (24/28, 86%), but did not identify mucosal lesions in 4 as well as mucosal improvements after therapy ($p < 0.05$). FC and CRP were not able to accurately evaluate DR at 24 and 52 weeks (BR in 65% and 69%, respectively). The DR and MH rates increased over the time (23% to 58%) by using CCE and a treat to target strategy.

Conclusions: This study evaluates long-term MH and DR rate in children with CD and indicates that CCE is effective for monitoring long as well as short term DR and MH of the entire GI tract and in directing therapy for pediatric patients with CD. Additional studies are needed to explore these issues further.

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Infliximab biosimilar switching program overseen by specialist pharmacist saves money, realises investment and optimises therapy

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Background: The parity of efficacy and safety of the biosimilar infliximab (IFX) has been demonstrated with data on switching still emerging. Specialist gastroenterology pharmacists are ideally placed to manage medicines optimisation and therapeutic drug monitoring (TDM) [1], overseeing the switch, realising considerable cost savings and income through negotiations with commissioners.

Methods: A payment per switched patient was negotiated with commissioners for reinvestment into the inflammatory bowel disease (IBD) service. Information was sent to each patient offering counseling with the pharmacist. Over 8 weeks all patients were switched from Remicade[®] to Remsima[®], IFX trough levels and antibodies, C-reactive protein (CRP), Harvey Bradshaw (HB) or simple clinical colitis activity score (SCCAI) and faecal calprotectin (FCLP) were recorded prior to the infusion of the first dose of biosimilar. 6 month later HB or SCCAI, CRP and FCLP were remeasured and compared. The pharmacist reviewed all results and managed any therapy changes, if necessary with multidisciplinary team (MDT) review. Savings were recorded.

Results: A payment of £1250/patient was negotiated to fund the switch. 71 (60 CD, 11 UC) patients were switched realising an income of £88,750 used to fund a specialist IBD nurse.

No patient requested an additional appointment due to the pharmacist conducting counselling during infusion clinics prior to the switch. 17 patients stopped IFX, 7 due to antibodies and 2 due to loss of response (LOR) and need for surgery, 8 patients were changed to alternatives by MDT review.

Table 1. Financial impact

	Number of patients (N=71)	Yearly cost vs Remicade [®]	Yearly cost vs Remsima [®]
Patients changed to Remsima [®]	54	-£223,970	£0
Patients treatment stopped	9	-£80,490	-£43,160
Patients changed to adalimumab	4	-£1,980	+£14,620
Patients changed to golimumab	3	-£4,855	+£7,590
Patients changed to vedolizumab	1	+£2,760	+£6,910
Patients with dose reduced	6	-£15,230	-£8,165
Patients with dose increased	8	+£20,310	+£10,887
Charges for IFX and FCLP/savings			
OPA tests	71/28	+£4290	+£4290
Total costs		-£299,170	-£7,030

Table 2. Patients clinical parameter pre and post switch

	Crohn's disease (N=60)	Ulcerative colitis (N=11)
No. (%) of pts with IBD score changes of ≤ 1	28 (52%)	6 (60%)
No. (%) of pts with IBD score reduction ≥ 2	11 (20%)	1 (10%)
No. (%) of pts with IBD score raise ≥ 2	14 (26%)	3 (30%)
No. (%) of pts with IFX antibodies	5 (8%)	2 (18%)
No. (%) of pts IFX levels below ≤ 1.9	15 (25%)	2 (18%)
No. (%) of pts IFX levels ≥ 8.1	5 (8%)	4 (36%)
No. (%) of pts with CRP change of ≤ 5 pre switch	43 (71%)	9 (81%)
No. (%) of pts with CRP ≤ 5 post switch	44 (73%)	9 (81%)
FCLP submitted pre/post / pre&post	38 (63%/12 (20%)/	6 (55%)/2 (18%)/
	8 (14%)	1 (9%)

54 patients continued on IFX infusions without experiencing LOR in the following 6 months. Savings on drugs was £224,000 and overall £300,000.

TDM results were analysed by the pharmacist who initiated 14 dose adjustments preventing 28 clinic appointments.

CRP and IBD scores were reviewed at each infusion. A minority of patients submitted FCLP pre and post preventing meaningful analysis.

Conclusions: Switching to biosimilar IFX is safe.

Active management of treatment around the switch by the Specialist IBD pharmacist saves money, realises investment into the service, optimises therapy in a timely manner and reduces outpatient appointments.

IBD pharmacists are familiar with TDM, management of IBD patients and able to negotiate with commissioners directly.

References:

- [1] A St. Clair Jones, M Smith, (2015), Embedding pharmaceutical care into the multidisciplinary team, *Ecco 2015 Abstract P306*, <https://www.ecco-ibd.eu/index.php/publications/congress-abstract-s/abstracts-2015/item/p306-embedding-pharmaceutical-care-into-the-multidisciplinary-team.html>, 2016-01-01

P528

Long-term outcome of ulcerative colitis patients responders to cyclosporine in the biological era

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Background: Corticosteroids remain the treatment of choice for patients with moderate and severe UC. Cyclosporine (CsA) and inflix-

imab (IFX) are effective rescue agents for patients refractory to IV steroids, with similar short-term outcomes between the two. Traditionally, there has been reluctance to use CsA due to an increased risk of long-term colectomy (50% at 5 years); however, this situation may have changed since the advent of infliximab. Our hypothesis is that nowadays salvage therapy with biologics can improve long-term colectomy rates in patients with UC who are treated with CsA, and thus, that CsA may still be considered an effective treatment option for these patients

Aim: To assess the long-term outcome and colectomy rate of patients with moderate-to-severe UC who initially respond to CsA

Methods: This is a multicenter retrospective cohort study including patients with moderate-to-severe corticorefractory UC and early response to CsA. Exclusion criteria were: colectomy requirement, rescue therapy with a biologic agent within the first 3 months after CsA treatment, and contraindication for the use of IFX. We defined two cohorts: 1) the first cohort (C1) included patients with UC who were treated before the advent of biologics, between the years 1995 and 2000; and 2) the second cohort (C2) comprised patients with UC treated between 2005 and 2010, after IFX became available.

Results: A total of 192 patients were included (56 in C1 and 136 in C2). Median age was 38 years, 99 (51.6%) patients were male, 149 (77.6%) had extensive colitis, 104 (54.2%) were non-smokers, mean disease duration was 47 months and 38 (19.8%) had been treated previously with thiopurines. Mean CsA duration was 107 days and after CsA withdrawal, 173 (90.1%) patients received maintenance treatment with thiopurines. During follow-up, 89 (46.4%) patients received steroids and 61 (31.8%) required an admission. In C2, 38 (27.9%) patients were treated with IFX within the 5 years. The global colectomy rate were 16.14% at 5 years. Colectomy rates in C1 were 10.7%, 17.6%, 25% and 26.8% at 12, 24, 36 and 60 months respectively. Colectomy rate was lower in C2 (5.1%, 9.6%, 11% and 11.8% at 12, 24, 36 and 60 months respectively), ($p=0.01$). Predictors of colectomy in the multivariate analysis were previous treatment with thiopurines (OR 2.9 (95% CI: 1.2–6.7)) and patients of the first cohort (C1) OR 2.7 (95% CI: 1.3–6).

Conclusions: The long-term outcome of UC patients treated with CsA has been improved in the biological era. CsA may be considered in UC patients who are refractory to intravenous steroids and naive to thiopurines

P529

Impact of stress in inflammatory bowel disease. Effect of a group psychological intervention program

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Background: Stress, anxiety and depression have been identified as important factors on the development and course of inflammatory bowel disease (IBD). The aim of this study is to evaluate the efficacy of a psychological intervention programme on the course and quality-of-life of patients with IBD

Methods: IBD Patients were initially evaluated using the following stress questionnaires: Perceived Stress Scale (PSS) and perceived disease stress (EAE); the hospital anxiety and depression scale (HAD) and the quality-of-life questionnaire (IBDQ). Activity of the IBD was

measured using the CDAI scale for Crohn's disease and the Mayo score for ulcerative colitis. Patients were randomized to receive or not an intervention cognitive and behavioural therapy program consisting of 8 sessions (90 minutes each). After intervention patients and controls were re-evaluated using the same scales.

Results: A total of 114 patients with IBD (78 Crohn's disease and 36 ulcerative colitis) were included. All the patients had at least one flare during the last 18 months. A total of 58 patients were assigned to the intervention group and 56 to the control group. Mean age 43.41 (SD 11.842) years. Patients included in the intervention and control group did not show differences in CDAI or Mayo score, stress scales, HAD or IBDQ at the baseline evaluation. After intervention, results in the tests were evaluated comparing the intervention versus the control group. There was a significant improvement of PSS ($p=0.001$), EAE ($p=0.0001$), anxiety ($p=0.006$), depression ($p=0.008$) and quality-of-life IBDQ ($p=0.01$), especially in its social and emotional dimension ($p=0.002$) in the intervention group. In the control group only marginal improvement in EAE ($p=0.04$), anxiety ($p=0.01$) and depression ($p=0.03$) were found, whereas no improvement was found in IBDQ and PSS. Patients from both groups showed a reduction in the CDAI scale of Crohn's disease. No changes in Mayo score were found in ulcerative colitis patients.

Conclusions: A psychological intervention program achieves improvement in stress, anxiety and depression scales as well as in quality-of-life in patients with IBD. This improvement was not found in the same way in the control group.

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Azathioprine in the maintenance of steroid-free remission in inflammatory bowel disease patients: efficacy and safety in five years of follow-up

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Background: Purine analogue azathioprine (AZA) is widely used for induction and maintenance of remission in steroid dependent patients with inflammatory bowel disease (IBD). The treatment must be withdrawn in 5–30% of patients due to the occurrence of adverse events. We investigated its efficacy and safety in maintaining steroid-free remission in steroid dependent IBD patients five year after the institution of treatment.

Methods: Data from consecutive IBD outpatients referred in our Institution, between 1985–2014, were reviewed and all patients treated with AZA were included in this retrospective study. AZA was administered at the recommended dose of 2–2.5 mg/kg.

Results: Out of 2684 consecutive IBD outpatients visited in the index period, AZA was prescribed to 398 patients, 216 (54.3%) were affected by Crohn's disease (CD) and 182 (45.7%) by ulcerative colitis (UC). One hundred and thirty-eight patients with a follow-up <60 months were excluded from the study. Two hundred and sixty patients were evaluated, 145 (55.8%) with CD and 115 (44.2%) with UC. One hundred and forty-six (56.2%) were male and 114 (43.8%) female (average age of 34.85±14.92 SD years, range 14–74 years). Five year after the institution of treatment, 135 (51.9%) patients still were in steroid-free remission (86 CD vs 49 UC, 59.3% and 42.6%, respectively, $p=0.0087$), 71 (27.3%) had a relapse requiring retreatment with steroids (29 CD vs 42 UC, 20% and 36.5%, respectively,

$p=0.0033$), 54 (20.8%) discontinued the treatment due to side effects (30 CD vs 24 UC, 20.7% and 20.9%, respectively). Loss of response from 1st to 5rd year of follow-up was low, about 18%.

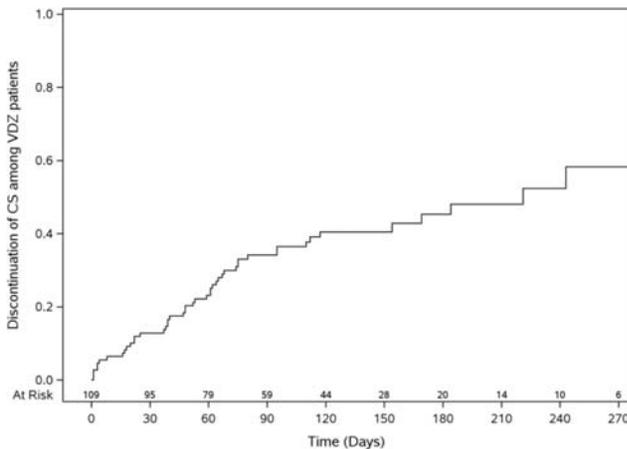
Conclusions: Five year after the onset of treatment 52% of patients did not require further steroid courses. After the first year loss of response was low in four subsequent years. In the present series the maintenance of steroid-free remission was significantly higher in CD than in UC patients. The occurrence of side effects leading to the withdrawal of AZA treatment has been low.

P531 Discontinuation of corticosteroids among Crohn's disease patients treated with vedolizumab in the United States

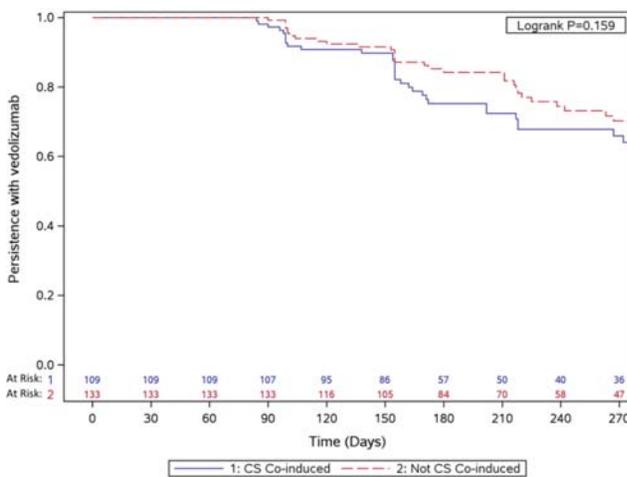
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Background: Corticosteroids (CS) are effective in the short-term induction of patients with moderate to severe Crohn's disease (CD) but not for maintenance of remission, due to the associated risks.



Patients were censored at discontinuation of VDZ or the end of follow-up.



Patients were censored at the end of follow-up.

Figure 1. a. Discontinuation of corticosteroids among patients with Crohn's disease treated with VDZ. b. Persistence with VDZ among patients co-induced with and without corticosteroids.

Vedolizumab (VDZ), a humanized monoclonal anti- $\alpha 4\beta 7$ integrin antibody, is approved for the treatment of adults with moderately-to-severely active CD. This study assessed VDZ treatment persistence and CS discontinuation among CD patients co-induced with CS.

Methods: Adult (≥ 18 years) CD patients initiating VDZ between 1 May 2014 and 30 September 2016 were identified in the US Optum Research Database. Patients with ≥ 12 months history (baseline) before their first VDZ claim (index date) and who completed induction (defined as ≥ 3 infusions in ≥ 98 days post-index) were included. CS-related measures included: dependence ($\geq 80\%$ CS use during the 6 months immediately prior to index date), co-induction with CS (CS fill for ≥ 28 days during the induction phase), CS discontinuation (treatment gap ≥ 60 days between CS fills) while on VDZ therapy. VDZ persistence was defined as no treatment gap ≥ 90 days between consecutive infusions. CS discontinuation and VDZ persistence were measured using the Kaplan-Meier method.

Results: A total of 242 VDZ patients were included with a mean (SD) age of 43.8 (14.6) years; 60% female, median follow-up period of 280.5 days. During baseline, 33%, 41% and 81% of patients were treated with aminosalicylates, immunomodulators, and CS, respectively; 71% of patients had received a biologic before initiating VDZ. Of CD VDZ patients, 45% (n=109) were co-induced with CS during the induction phase, of whom 17% (18/109) were CS-dependent. Overall, 43% (47/109) of CS co-induced patients discontinued their CS and among CS-dependent patients, 28% (5/18) discontinued their CS. CS discontinuation and VDZ persistence are shown in Figures 1a & 1b.

Conclusions: This real-world study, using a nationally representative US database, showed that over half of CD patients receiving VDZ were not co-induced with CS. Among VDZ patients co-induced with CS, 43% discontinued over the follow-up period. Despite the treatment-refractory patients included in this study, the CS discontinuation rate at 26 weeks among VDZ patients was higher than what was reported from the GEMINI clinical trials. VDZ persistence was similar between CS co-induced patients versus those without CS co-induction. Future studies should examine CS-related outcomes over a longer follow-up period.

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P532 Biosimilar infliximab in anti-TNF naive inflammatory bowel disease patients – one-year clinical follow-up

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Background: First biosimilar infliximab (IFX) has been approved in European Union for treatment of inflammatory bowel disease (IBD) since September 2013. The approval process included extrapolation of clinical data from other indications, namely rheumatoid arthritis and ankylosing spondylitis. Data from clinical practice are therefore

desirable to confirm efficacy and safety of biosimilar IFX in IBD population.

Despite growing data on early treatment results, the evidence on long-term efficiency and safety of maintenance treatment with biosimilar IFX in patients with IBD is only sparse.

Methods: Data from consecutive patients with CD and UC starting on biosimilar IFX between January 2015 and May 2016 at our center were analyzed. Patients were assessed as non-responders (NR), partial responders (PR), or complete responders (CR) based on clinical, endoscopic, and laboratory parameters. Besides clinical and endoscopic evaluation, C-reactive protein (CRP) levels, faecal calprotectin (FC), blood count, IFX trough levels (TL), and antibodies-to-infliximab (ATI) were measured. All adverse events were recorded. Final analysis was performed at week 54 (W54).

Results: One hundred forty IBD patients (CD, 107; UC, 33) were included into the analysis. In total, 94% of CD and 82% of UC patients responded to induction therapy (W14) with biosimilar IFX. At W54 the response rates were 87% in CD and 60% in UC and 47% and 36% of patients, respectively, were in remission.

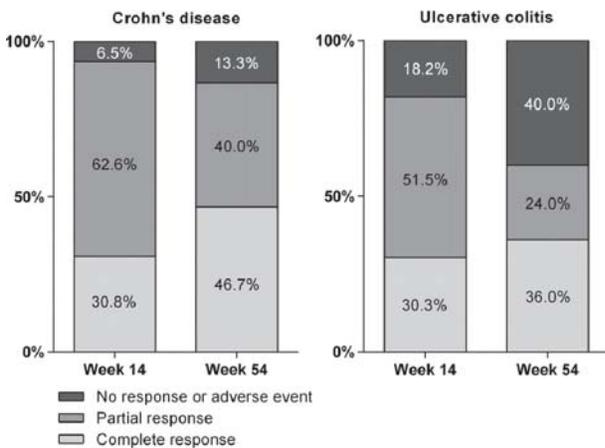


Figure 1. Response to therapy with biosimilar infliximab at weeks 14 and 54.

Fifty two percent of UC patients experienced mucosal healing at W14 and improvement of perianal disease occurred in 96% of CD patients at W54 including 59.1% with complete cessation of drainage. Steroid-sparing effect was markedly present in all patients. Therapy was continued in 83% of patients at the end of the follow-up (89% CD and 64% UC). Trough level of at least 8.9 µg/mL at W6 was best predictive of response at W54 in both CD and UC with a sensitivity of 70.0% and specificity of 74.1% which well corresponds with the results of previous studies on original IFX. Our findings thus suggest that the same association applies also to the biosimilar IFX. Pharmacokinetic properties, immunogenicity and frequency and character of adverse events were similar to those previously observed during treatment with the original IFX.

Conclusions: Biosimilar IFX after one year in naive patients with IBD patients seems to be effective and safe, gaining similar treatment results with no additional safety issues comparing to the originator.

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Anaemia and iron deficiency in gastroenterology: a Scandinavian prospective, observational study of iron isomalto side in clinical practice

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Background: Iron deficiency with or without anaemia is common in patients treated in Gastroenterology, especially in inflammatory bowel disease (IBD). IBD patients with iron deficiency usually need high doses of iron, and intravenous iron is an established therapy for these patients. The aim of this study was to investigate treatment routine, effectiveness and safety of iron isomalto side in clinical practice. The primary endpoint was to determine the probability of relapse of iron deficiency over time defined as re-treatment related to the dose given.

Methods: Participants were recruited from ten hospitals in Denmark, Norway and Sweden as part of a prospective, observational, multicenter study conducted from August 2013 to November 2015. Patients were treated with iron isomalto side according to the product label and clinical routine.

Results: Of patients included, 82/282 (29%) had Crohn's disease (CD) and 67/282 (24%) had ulcerative colitis (UC). The reference group of 133/282 (47%) non-IBD patients had iron deficiency with or without anaemia due to chronic blood loss, systemic inflammation, malabsorption or malignancy. The median age was 46 (17–93) years and 173/282 (61%) were female. Patients treated with a dose of iron isomalto side above 1000 mg had 65% lower odds (hazard ratio 0.351) of needing re-treatment compared to those given 1000 mg ($p < 0.05$). There was no significant difference between UC and CD patients (odds ratio 1.65; 95% CI 0.81, 3.35). The majority of the patients 170/278 (61%) received only one treatment of iron isomalto side during the study, median observation time 19 (1–27) months. In addition to administered dose, baseline haemoglobin (Hb) was an independent predictor of the probability for re-treatment. Administration of iron isomalto side led to a significant increase in Hb, ferritin and transferrin saturation for both IBD and non-IBD patients ($p < 0.05$). The mean administered dose of iron was 1100 mg, which was lower than the calculated total iron need of 1481 mg for the same patients if calculated from the simplified dosing table as recommended in the ECCO guidelines. After the first treatment 71/191 (37%) of patients were still anaemic. Adverse events were rare, with infusion reactions reported in 6/282 (2%) of patients, one patient being admitted to hospital for treatment. All patients had an uneventful recovery.

Conclusions: Iron isomalto side was effective with a good safety profile in both IBD and non-IBD patients with iron deficiency. A high dose, especially over 1000 mg, reduced the need for re-treatment. The administration of even higher doses would have been required for full iron correction, indicating that patients receive inadequate iron dosing in routine clinical practice.

P534 Illness perception in IBD patients: a prospective study

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Background: Inflammatory bowel diseases (IBD) are characterized by significant quality of life (QoL) impairment, as well as an altered illness perception. Evaluation and characterization of illness perception may play a role in optimizing the clinical management of IBD patients.

Methods: This was a single-center, observational, transversal study. Consecutive adult IBD patients were enrolled and stratified according to disease activity (active/remission). The validated Revised Illness Perception Questionnaire (IPQ-R), based on identity (defined as the presence or absence, since diagnosis, of the commonest symptoms associated with chronic disease, and their relationship with the disease), current view (patient's opinion about emotional dimensions), and causes (patient's opinion about 18 possible illness causes and indication of the three most relevant causes of actual health status) was administered to all patients. Comparison in IPQ-R parameters was done between active patients and those who were in remission.

Results: In the entire study population (n=201, CD=47%; UC=53%), the most reported symptoms were fatigue (86.9%), loss of strength (83.3%), pain (80%), weight loss (68.2%). Patients with active disease reported significantly more fatigue (p=0.005), sore eyes (p=0.046), sleep difficulties (p=0.001) as related to their disease, and reported more symptoms as related to their disease (p=0.023). Active IBD patients were significantly more convinced about the cyclical timeline of the disease (p=0.002), more negative thoughts on prognosis (p=0.001) and more negative emotions (p=0.000). Patients in remission were significantly more convinced about for treatment control (p=0.007) and had clearer understanding of illness (p=0.009) towards active patients.

Stress (84.1%), altered immunity (69.32%), familiar problems (49.4%), emotional status (40.9%) were considered as the main causes of IBD in the entire study population. Job overload was more frequently considered as a disease cause in active patients than in those in remission (p=0.002). Smoking, familial history, previous inadequate therapy (19.3%, 26.1%, 18.7%, respectively) were not considered as a relevant factor for illness.

Conclusions: Illness perception is impaired in IBD patients, especially in active disease. Adequate educational and psychological support may be helpful in the optimal management of IBD patients.

P535 Outcomes of endoscopic resections of large non-polypoid lesions inflammatory bowel disease: a single United Kingdom centre experience

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Background: Patients with colitis carry an increased risk for the de-

velopment of dysplasia. The SCENIC consensus statement recommends endoscopic resection (ER) of all visible dysplasia [1]. Due to technical challenges and limited ER experience in the West of large colitis associated non-polypoid (NP) lesions, such patients are often subjected to colectomy.

The King's Institute of Therapeutic Endoscopy (KITE) is a tertiary centre for assessment and ER of challenging colorectal polyps. Here we present the largest single centre case series of large colitis associated NP resections.

Methods: Patient demographics, clinical history, lesion characteristics, method of ER and surveillance were collected prospectively in patients undergoing ER of NP lesions 20mm within known distribution of colitis from January 2011 to November 2016. ER techniques included endoscopic mucosal resection, endoscopic submucosal dissection (ESD) and hybrid ESD. Surveillance of resection site with magnification chromendoscopy (mCE) was performed at 3 months (m) with pan colonic mCE at 1-year post ER and annually thereafter.

Results: Thirteen lesions satisfied the inclusion criteria in n=13. Patient demographics/clinical data are presented in Table 1.

Table 1. Baseline characteristics

Age at time of resection (mean, SD, range) (years)	57.31, 12.7, 30–81
Male (n) (%)	10 (77)
Female (n) (%)	3 (23)
Duration of disease (mean, SD, range) (years)	19.9, 14.2, 1–50
Colitis to splenic Flexure (n) (%)	3 (23)
Pan-colonic/ Extensive (n) (%)	10 (77)
5-aminosalicylic acid (n) (%)	11 (84)
Azathioprine (n) (%)	2 (15)
Biologics (n) (%)	1 (7)

Mean lesion size was 47.3±22.4 (20–90)mm. All lesions were NP with distinct margins and no ulceration. High frequency mini-probe ultrasound confirmed intramucosal lesions in n=5 where surface pattern was distorted by inflammation. En bloc resection was achieved in n=6. 69% lesions were deeply scarred of which 66% experienced prior instrumentation. ER of 1 lesion was abandoned due to intense fibrosis. Macroscopic evidence of complete ER was achieved in all remaining cases. Endoscopic diagnosis of pre-cancerous lesions of less than 1000µm submucosal invasion was confirmed histologically in 100% of ERs. Complete excision was confirmed in all en bloc resections. A single case of perforation and 1 with delayed minor bleeding were both managed endoscopically. Mortality/hospital admission within 30 days post ER was 0%. Median follow up was 28m (12–35) with no recurrence. Alternative site dysplasia was detected in n=2. All lesions were <20mm and underwent ER. Two patients were referred for colectomy due to a concomitant diagnosis of neuroendocrine tumour and the second with alternate site advanced dysplasia.

Conclusions: This case series demonstrates that ER of large colitis associated NP lesions is feasible using an array of methods, safe and has good long term outcomes in a western tertiary endoscopic centre.

References:

- [1] Laine L, Kaltenbach T, Barkun A et al. (2015), SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease, Gastrointestinal Endoscopy

P536 Combination therapy of bone marrow mesenchymal stromal cells and azathioprine not affect the clinical course luminal Crohn's disease

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Background: New treatments for Crohn's disease (CD) is a biologic therapy using mesenchymal stromal cells (MSCs) of the bone marrow. In some cases, together with the MSC, patients receiving concomitant immunosuppressive therapy. The aim of our work was to study the effect of the combined use of bone marrow MSCs and azathioprine (AZA) on the clinical course of CD.

Methods: 34 patients with BC luminal form divided into two groups. The first group of patients aged 19 to 58 years old (Me-29) (n=15) was treated with anti-inflammatory therapy with MSCs culture 2 million cells/kg+AZA 2 mg/kg. The second group of patients with CD (n=19) aged 23 to 60 years old (Me-31) received MSCs according to the recommended scheme (without AZA). Culture MSCs were injected three times a month at intervals of 1 week after 6 months from the date of the first administration of MSCs. The initial average index of activity of Crohn's disease (CDAI) in the first group amounted to 337.6±17.1 points, the second group – 332.7±11.0 points (p=0.3). Evaluation of efficacy was performed at 12, 24 and 36 months.

Results: After 12 months in the first group of patients relapse occurred in CD 1 (6.6%) patient, the second – in 2 (10.5%) (OR- 0.63; 95% CI 0.06–6.34, p=0.82). Middle CDAI in the first group of patients – 99.9±10.8 points, the second – 100.6±12.1 points (p=0.8). After 24 months in the first group of patients with relapsed CD occurred in 3 patients (20.0%), the second – in 4 (21.05%) (OR- 0.95; 95% CI 0.25–3.61, p=0.72). Middle CDAI in the first group of patients with CD was 133.2±28.3 points, the second – 120.8±15.5 points (p=0.2). Through 36 months in the first group of patients with CD relapse occurred in 5 (33.3%) patients with CD, the second – in 6 (31.6%) (OR-1.06; 95% CI 0.4–2.8, p=0.79). Middle CDAI in the first group of patients with CD was 139.9±23.4 points, the second – 141.7±20.8 points (p=0.9).

Conclusions: During three years of follow up in patients treated with MSCs and AZA, and in patients receiving only MSCs, there was no difference in the frequency of relapses and CD clinical activity.

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Is anti-TNF therapeutic drug monitoring of value in IBD patients in clinical remission?

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Background: Therapeutic drug monitoring (TDM) and the concept of treat-to-target are yielding better outcomes in patients with inflammatory bowel disease (IBD). Serum levels of anti-TNF therapy are associated with clinical response and mucosal healing. This study aims to evaluate the association between serum levels of anti-TNF therapy and faecal calprotectin, disease activity scores, endoscopic findings and biochemical markers in IBD patients.

Methods: Serum drug levels were measured in patients presenting between 2014-August 2016. Demographic information and clinical characteristics were retrieved retrospectively from medical records. Disease activity scores (CDAI, Mayo), endoscopic findings, biochemical data (CRP, platelet, albumin) and faecal calprotectin levels were obtained close to the time of serum levels of anti-TNF therapy. Pa-

tients with sub-therapeutic and therapeutic serum levels of anti-TNF therapy were compared using Fisher exact tests. Simple linear regression was performed to correlate CRP, platelet and albumin levels with anti-TNF levels.

Results: The 67 patients with available serum levels were included. Patients had a mean age of 34 years (SD =18.5) and 60% were female. The majority (79%) had Crohn's disease and 82% were on maintenance infliximab. 41 (61%) patients had sub-therapeutic drug levels.

All 17 (100%) of those with therapeutic levels on maintenance therapy were in clinical remission (CDAI score <150 or partial Mayo score of <2). All 7 (100%) of those in clinical relapse had sub-therapeutic levels but in contrast, most patients {29/52 (56%)} who were in clinical remission did not have therapeutic levels of anti-TNF agents (p=0.036).

14/15 (93%) of those with sub-therapeutic levels and 4/9 (44%) with therapeutic levels on maintenance therapy had elevated faecal calprotectin (FC >50 mg/kg) whilst 5/6 (83.3%) patients who had normal faecal calprotectin and 4/18 (22%) of patients who had elevated faecal calprotectin had therapeutic levels (p=0.015).

There was no difference with respect to endoscopic activity and anti TNF levels although there was a significant trend (p=0.051). Platelet levels correlated with anti TNF levels (simple linear regression; p=0.042) but there were no differences with respect to CRP and albumin levels.

Conclusions: In the presence of clinical remission and/or a normal faecal calprotectin assay, TDM is unlikely to alter management. "Therapeutic" trough levels for patients in clinical remission may differ from those with active disease. Further data is required to confirm these findings.

P538

Can enteral polymeric diet change the post-surgical outcome in Crohn's disease patients? A pilot study

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Background: Approximately 40% of patients affected by Crohn's Disease (CD) require surgical treatment in their lifetime. An adequate pre-operative management including improvement of nutritional status may decrease the complication rate. An enteral polymeric diet (EPD) enriched with transforming growth factor-beta2 has been shown to be useful in patients with CD, and able to induce remission in pediatric patients. No data is still available about patients with CD scheduled for surgery.

The aim of the study was to assess the efficacy of EPD as nutritional support to standard of care diet (SCD) in CD patients undergoing surgery.

Methods: We evaluated patients with ileal CD referred to our center and treated with laparoscopic ileo-cecal resection throughout 12 months; we excluded patients with colonic resection in order to have a more homogeneous sample. Medical treatment, Body Mass Index (BMI), serum albumin and hemoglobin were assessed in all patients the day before the surgical procedure.

We evaluated the operative and postoperative course (conversion to laparotomy, need for surgical re-treatment in the following three months, days of stay in hospital). We considered as a worse outcome the conversion, the surgical re-treatment, and a stay in hospital exceeding 7 days after surgery.

According to nutritional therapy, patients were divided into 2 groups: EPD (SCD with 50g EPD in 210ml of water four times a day) and SCD (without any supplementation).

Statistical analysis was performed by Student-t-test for continuous and Fisher exact test for categorical variables.

Results: Fifty-eight CD patients underwent surgery in the study period; we recruited 35 CD patients (16 M), treated with ileo-cecal resection. Mean age was 43.8 ± 14.7 years, mean stay in hospital 7.28 ± 3.34 days.

Four patients needed a conversion to laparotomy (2 for a massive abscess, 2 for mesentery retraction); 4 patients needed surgical re-treatment (1 the day after surgery, 1 two weeks later, 1 two months later, 1 three months later); eleven patients had a post-surgical stay in hospital of 8 or more days. Ten patients were treated with EPD and 25 with SCD.

No difference was observed in medical treatment, hemoglobin, serum albumin or BMI values between the two groups before surgery. Patients treated with EPD showed a better outcome in comparison with SCD ($p < 0.05$).

Table 1

	Good outcome	Bad outcome	p
SCD	10	8	0.035
EPD	15	2	

Conclusions: Our results showed that EPD, when administered before surgical ileo-cecal resection in CD patients, seems to prevent complications, improving the outcome during the postoperative course and considerably reducing costs.

P539

Does a change in therapeutic approach modify outcome in IBD patients? A comparison between two cohorts 2004–2007 and 2010–2013

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Background: With the introduction of biologics in the past 15 years, therapeutic approach to IBD has been modified, not only in terms of available medications but also in terms of therapeutic goals.

The aim of the present study was to assess if the newly introduced therapeutic and strategic changes have led to measurable outcome differences.

Methods: we retrospectively assessed in two cohorts of patients (cohort 1: 2004–2007, cohort 2: 2010–2013) followed since diagnosis for at least 3 years at the IBD-unit Messina, the therapeutic approach (i.e. use of immunomodulators (IMM) and biologics (BIO)) and outcomes (i.e. steroid-free remission at 1 to 3 years, surgeries, and hospitalizations). Time to IMM or BIO therapy was assessed by Kaplan-Meier analysis

Results: Sixty-nine patients were identified in cohort 1 (UC: 41 patients, CD: 28 patients) and 77 patients in cohort 2 (UC: 39, CD: 38). Mean age was for cohort 1: 35 ± 14 years, cohort 2: 37 ± 17 years: There was a significant increase of an earlier use of biologics in cohort 2 ($p < 0.001$) together with a slight, but significant, lesser use of IMM.

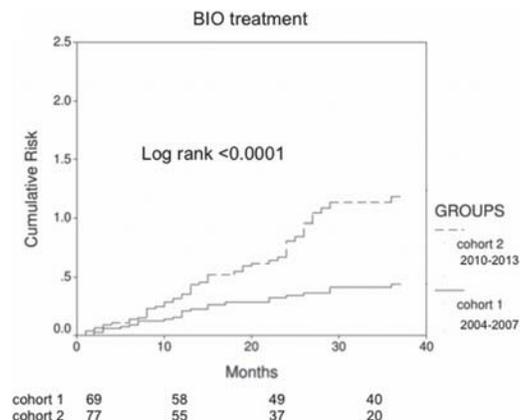


Figure 1. Time to BIO treatment in the two IBD cohorts.

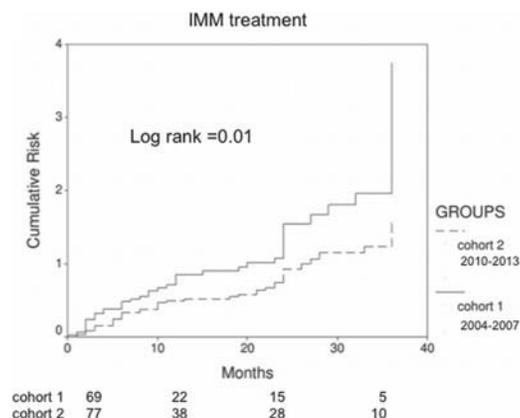


Figure 2. Time to IMM treatment in the two IBD cohorts.

A significant ($p < 0.009$) reduction of surgery in CD patients registered in cohort 2 compared with cohort 1 (60.7 vs 39.3%) with the main indication for stenosing behaviour; overall rates in surgery in UC reached 6% without differences between the two cohorts. Steroid-free remission was achieved in 71%, 69%, and 20%, respectively in year 1, 2, and 3 of follow-up in cohort 1 and in 73%, 47%, and 53% in cohort 2. There was a significant difference ($p < 0.02$) in the 3rd year in favour of cohort 2. An early use of BIO represented a significant predictor for steroid-free remission only at year 2 of follow-up ($p < 0.049$, OR 0.53, CI 95% 0.281–0.999), but not at year 1 or 3, whereas IMM was not associated with steroid-free remission in any year. Hospitalisation rates did not differ between the two cohorts (17% vs 25%)

Conclusions: despite a significant change in therapeutic approach, only modest outcome differences were observed. Most importantly, differences were noted for the surgical approach in CD and a lower steroid use in the third year after diagnosis in all IBD patients in the third year after diagnosis. Our result suggest that the anticipated use of biologics alone does not make an important difference but therapy needs still to be optimized.

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Efficacy of granulocyte and monocyte apheresis for antibiotic-refractory pouchitis after proctocolectomy for ulcerative colitis: an open-label, prospective, multicentre study

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Background: Granulocyte and monocyte apheresis (GMA) has shown therapeutic efficacy in patients with active ulcerative colitis (UC). We thought that in patients with pouchitis, GMA should produce immunoregulatory effects in the intestinal mucosa, and improve clinical symptoms. With this in mind, we undertook a prospective study to evaluate the efficacy of GMA for antibiotic refractory pouchitis after proctocolectomy for UC.

Methods: Thirteen patients with pouchitis disease activity index (PDAI) >7 unresponsive to 2 weeks of optimal antibiotic therapy were included. All patients received 10 GMA sessions with the Adacolumn at two sessions/week over five consecutive weeks. The primary endpoints were response, as a decrease of ≥ 3 points in the PDAI score and remission (PDAI <4). Secondary endpoints included reduction of white blood cells (WBC), C-reactive protein (CRP), faecal markers (calprotectin and lactoferrin), reduction of the PDAI endoscopic subscore, and GMA treatment safety.

Results: The median PDAI score was significantly decreased from 11 (range, 9–15) at entry to 9 (range, 6–13) assessed within one week after the last GMA session ($p=0.02$). Six patients (46%) responded to the treatment, but none of the patients achieved remission. The median endoscopic subscore (maximum: 6) was 5 (range, 4–6) at entry and 5 (range, 1–6) after the treatment ($p=0.10$). None of the laboratory markers (WBC, CRP, faecal calprotectin and lactoferrin) significantly changed during the treatment. Transient adverse events (AEs) were observed in two patients (15%), dyspnoea in one and headache in one. The AEs were not serious, and all patients including the 2 with AEs completed the 10 GMA sessions.

Conclusions: GMA has a good safety profile, but its efficacy appears to be limited in the management of chronic drug refractory pouchitis. However, a large controlled study is warranted to fully evaluate the efficacy of GMA in patients with pouchitis, at an earlier clinical stage.

P541

Intestinal failure: a rare but significant outcome of restorative proctocolectomy

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Background: Restorative proctocolectomy with ileal pouch-anal anastomosis (RPC-IPAA) removes the entire colon & rectum, while preserving the anal sphincter, maintaining intestinal continuity^{1–4}. RPC-IPAA is offered to patients with ulcerative colitis (UC) refractory to treatment or associated with dysplasia, and some patients with familial adenomatous polyposis (FAP). Complications are well described, but intestinal failure (IF) requiring parenteral support (PS)

is an uncommon complication of this surgery that carries with it significant morbidity & mortality. We report of the complication of IF as a complication of RPC-IPAA.

Methods: Adult patients with RPC-IPAA as an underlying cause of IF who were treated at our institution, were identified between 1/1/1998 & 1/1/2016. Information on complications, small intestinal length & pathophysiological causes of IF were recorded. Date & cause of death were also recorded. Comparison was made with other patients who had received PS for IF at the same unit during the same time period. Patients were excluded if RPC-IPAA was not a direct cause of IF, or if the cause of the IF was due to malignancy.

Results: Of 807 in the IF database, 35 were identified with a RPC-IPAA and met the inclusion criteria. There were 13 male patients in the pouch group with IF. The pouch was formed for UC in 26, FAP in 6, & other reasons in 3. The pathophysiological classification of IF was short bowel in 49% ($n=17$), mechanical obstruction in 29% ($n=10$), intestinal fistulae in 14% ($n=5$), intestinal dysmotility in 6% ($n=2$) & small bowel mucosal disease in 3% ($n=1$). Survival was 96% at 1 year and 75% at 5 years. This compared to 76% & 48% respectively in the non-pouch group ($p=0.02$).

IF was a potentially avoidable complication in three patients (9%) with a pouch.

Two developed IF due to short bowel after index pouch formation (residual small bowel length of 50–100cm). One patient underwent a pouch originally for ulcerative colitis but developed IF due to small bowel Crohn's disease with no prior small bowel imaging prior to pouch formation was documented.

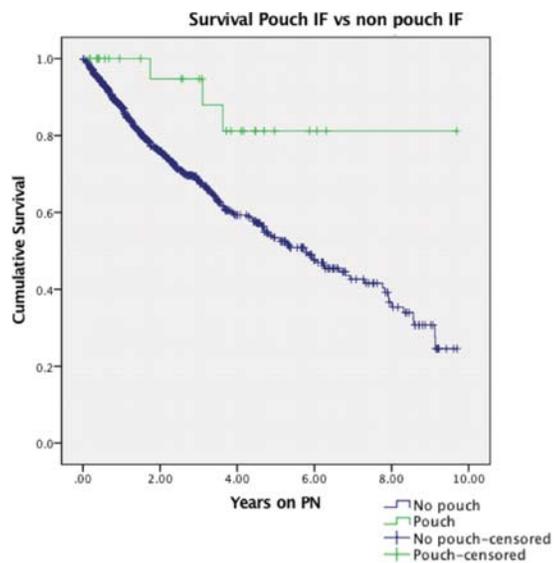


Figure 1. Survival pouches with IF vs non pouches with IF.

Conclusions: IF is a rare complication of RPC-IPAA surgery, but carries with it a high disease burden. Our data has shown that survival is better in RPC-IPAA patients compared to patients who have IF for other conditions. We recommend documenting the pre and post-operative bowel length, with appropriate pre-operative imaging of the small bowel as standard practice in RPC-IPAA surgery.

P542

Long-term outcomes after switching from originator infliximab to biosimilar in paediatric-onset inflammatory bowel disease patients: a single centre prospective observational study

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Background: The biosimilar of infliximab, CT-P13, has been approved worldwide for treatment in inflammatory bowel disease (IBD) patients. However, there is scarce data of its outcomes after switching from originator infliximab to CT-P13 among paediatric-onset IBD patients in real-life practice. We aimed to investigate the long-term efficacy, safety, pharmacokinetic profiles, and immunogenicity after switching from infliximab to CT-P13 for 1 year in paediatric-onset IBD patients.

Methods: This study was a prospective observational study of paediatric-onset IBD patients who had switched from infliximab to CT-P13 during September 2015 to December 2015 at the Department of Pediatrics, Samsung Medical Center. Clinical activity scores, laboratory test results, infliximab trough level (TL), and antibody to infliximab (ATI) levels were compared between the point of switch and 1 year after. Loss of response and adverse events were also investigated during the switch period.

Results: Thirty-eight paediatric-onset IBD patients [32 Crohn's disease (CD), 6 ulcerative colitis (UC) patients] were included in this study. The median age at infliximab start was 15.1 years (range: 7.6–19.9), and the median age at CT-P13 switch was 19.2 years (range: 8.7–22.5). The median duration from infliximab start to CT-P13 switch was 1.9 years (range: 0.6–7.8). Among the total subjects, 27 subjects had finished follow-up at 1 year, while 2 subjects were lost during follow-up, and 1 subject had discontinued CT-P13 after a prolonged period of clinical remission and complete mucosal healing on endoscopy. Eight subjects had not yet been followed up to 1 year. Among the 27 subjects who had finished follow-up at 1 year, 21 subjects were treated with concomitant azathioprine (77.8%). Com-

parison between switch point and 1 year follow-up revealed no significant differences in Harvey-Bradshaw Index (HBI) scores for CD patients, Simple Clinical Colitis Activity Index (SCCAI) scores for UC patients, white blood cell (WBC) counts, serum albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, infliximab TLs, and ATI levels between the two time points. Loss of response was observed in 3 patients (11.1%), who all responded well to dose intensification. No serious adverse events or infusion related adverse events occurred.

Conclusions: Switching from originator infliximab to the biosimilar infliximab, CT-P13, was feasible without serious adverse events for up to 1 year in a real-life cohort of paediatric-onset IBD patients.

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Structured transition enhances clinical outcome without an increase in healthcare cost in adolescent patients with IBD: the UK TRANSIT study

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Background: IBD presents in childhood/adolescence in up to 25% of patients. Evidence that a coordinated transition programme prior to transfer to adult care improves outcomes is lacking. The TRANSIT study compared the impact of transition vs non-transition on outcome and hospital resource utilisation in patients with IBD.

Methods: TRANSIT was an observational retrospective case note review and prospective patient questionnaire study of patient outcome conducted in 11 UK centres. Consenting patients with a confirmed diagnosis of IBD before age 16 with ≥ 12 months' care under adult services and aged ≥ 16 years at recruitment were included. Structured transition visits in this study were defined as involving clinical staff

Table 1. Comparison between CT-P13 switch point and 1 year follow-up (n=27)

	At switch	1 year follow-up	P
HBI score (n=23)	0 [IQR 0–1]	0 [IQR 0–1]	0.610
SCCAI score (n=4)	0 [IQR 0–1.5]	0 [IQR 0–1.5]	1.000
WBC count, / μ L	6,284 \pm 1,565	5,908 \pm 1,327	0.345
Albumin, g/dL	4.5 \pm 0.3	4.6 \pm 0.3	0.764
ESR, mm/hr	11 [IQR 7.5–20.5]	13 [IQR 8–18.5]	0.993
CRP, mg/dL	0.06 [IQR 0.03–0.2]	0.04 [0.03–0.11]	0.368
Infliximab TL, μ g/mL	5.34 [IQR 4.85–8.05]	6.38 [IQR 4.3–7.58]	0.500
ATI, μ g/mL	2.3 [IQR 1.65–3.1]	2.3 [IQR 1.7–3.0]	0.869

Abstract P543

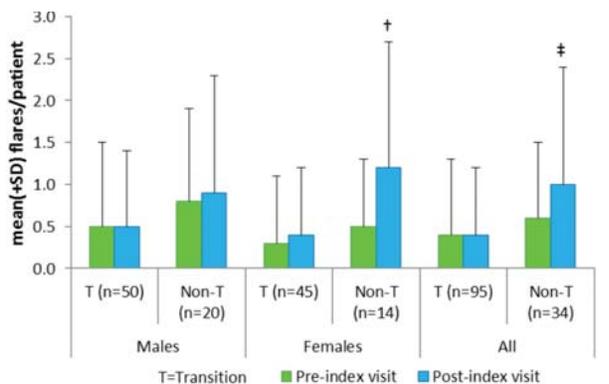
Table 12 month post-index visit hospital attendances and associated costs

	Transition (n=95)		Non-transition (n=34)	
	n (%) of patients with visit	Mean (SD) cost ^a /patient	n (%) of patients with visit	Mean (SD) cost ^a /patient
Hospital visits/admissions				
Non-elective				
A&E only	4 (4%)	£9.80 (58.98)	0 (0%)	-
A&E leading to admission	5 (5%)	£19.52 (99.99)	6 (18%) ^b	£60.59 (148.11)
non-elective inpatient	6 (6%)	£260.38 (1,460.68)	7 (21%)	£906.06 (2,204.15)
Elective				
Elective inpatient	6 (6%)	207.85 (1,091.64)	0 (0%)	-
Day case	26 (27%)	£410.53 (840.44)	9 (26%)	-
outpatient visits (physician)	87 (92%)	£581.40 (401.03)	25 (74%) ^b	£253.68 (536.09)
outpatient visits (non-physician)	21 (22%)	£53.09 (151.99)	8 (24%)	£316.24 (382.36)
				£37.09 (75.57)
Mean (SD) total 12 month cost per patient	£ 1,537.64 (2,274.14)		£ 1,573.65 (2,765.69)	

^abased on published reference costs (<https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015>), excluding hospital admissions with unknown length of stay; ^bP<0.05 comparing transition and non-transition patients

from both paediatric and adult services. Transition patients attended ≥ 2 and non-transition patients zero transition visits. The index date was defined as the first visit involving adult IBD services. Data on IBD disease flares (defined as any CD- or UC-related hospitalisations, or increases CD/UC therapy) and hospital resource utilisation for 12-months pre- and post-index visit were collected retrospectively from medical records.

Results: Patient demographic and clinical characteristics at recruitment were similar in transition (n=95; median age 19.6 years; 47% female; 78% CD; median 2.1 years post-index) and non-transition patients (n=34; median age 19.3 years; 41% female; 74% CD; median 2.3 years post-index; all $p>0.05$). Transition patients had significantly fewer flares/patient in the 12 months post-index (0.4 [SD: 0.8]) vs non-transition patients (1.0 [SD: 1.4], $p<0.05$), whereas mean flares/patient in the 12 months pre-index were similar (transition 0.4 [SD: 0.9] vs non-transition 0.6 [SD: 0.9], $p>0.05$). Non-elective admissions and associated costs were lower whereas elective inpatient and outpatient attendances and associated costs were higher in transition vs non-transition patients (see table). The mean total cost of hospital attendances/patient in the 12-month post index period in transition and non-transition patients were £1,537.64 and £1,573.65, respectively.



† $P<0.05$ comparing female transition and non-transition patients post-index
$P<0.05$ comparing transition and non-transition patients post-index

Figure 1. Mean flares/patient pre-index and post-index.

Conclusions: These data show structured transition enhances clinical outcome with no increase in hospital utilisation cost. This suggests that structured transition may be a better use of healthcare resource.

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Combination therapy of vedolizumab and a TNF antagonist in IBD patients with severe chronic active, therapy refractory disease course

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Background: Vedolizumab and TNF antagonists are biologicals with different modes of action. Vedolizumab a humanized monoclonal antibody that specifically binds to the $\alpha 4\beta 7$ integrin, blocks the interaction of the $\alpha 4\beta 7$ integrin with MAdCAM-1 and inhibits the migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue. TNF antagonists neutralize the proinflammatory cytokine TNF, but the mode of action still remains unclear. Induction of mucosal T-cell apoptosis and down-regulation

of proinflammatory cytokines are only some of the identified mechanisms. 50% of IBD patients have a chronic active course of disease. Some of them suffer from a severe, so far therapy refractory disease course. A combination therapy of different biologicals might be effective in these patients.

Methods: 7 patients with IBD (4 with Crohn's disease and 3 with ulcerative colitis) were treated with vedolizumab in combination with a TNF antagonist as an individual healing attempt through a case by case decision. Patients were seen as standard clinical care at baseline, week 2, 6, 14 and week 30. CDAI, CRP and calprotectin were assessed at all visits. Sonography and ileocolonoscopy or sigmoidoscopy (in ulcerative colitis patients) was performed at baseline, week 14 and week 30. SES-CDEIS and complete Mayo score was assessed also at baseline, week 14 and week 30.

Results: Mean CDAI at baseline: 410 (CD), Mayo score 11 (UC), CRP 39.76 mg/l (both UC and CD), fecal calprotectin 2100 mg/kg (UC), 883 (CD), SES-CDEIS 31 (CD). CRP at week 2: and 6: 35.74 mg/l and 21.21 mg/l (both UC and CD), calprotectin at week 2 and 6: 1956 mg/kg (UC), 798 (CD), 1287 mg/kg (UC), 580 (CD). Mean CDAI at week 2 and 6: 404 and 383 (CD). Mean CDAI at week 14: 262 (CD), Mayo score 8 (UC), CRP 15.71 mg/l (both UC and CD), fecal calprotectin 760 mg/kg (UC), 465 (CD), SES-CDEIS 22 (CD). Mean CDAI at week 30: 172 (CD), Mayo score 4 (UC), CRP 3.46 mg/l (both UC and CD), fecal calprotectin 377 mg/kg (UC), 215 (CD), SES-CDEIS 11 (CD). Even so none of the patients were in complete deep remission, a significantly improvement could be seen in disease symptoms like abdominal pain and stool frequency and a significant improvement in the mucosal inflammation could be assessed by endoscopy.

Conclusions: Combination therapy was well tolerated and effective. No severe infections or other severe adverse events could be seen so far. Further and larger clinical trials have to be performed in the future to investigate the efficacy and safety of anti-integrin antibodies and TNF antagonists as a combination therapy for a fast remission induction or as a maintenance combination therapy.

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Clinical outcomes following a switch from Remicade® to the biosimilar CT-P13 in inflammatory bowel disease patients in clinical remission: preliminary results

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Background: The biosimilar of infliximab, CT-P13, recently entered the European market. It has been approved for the same indications held by the infliximab reference product. Clinical data on switching from originator infliximab to CT-P13 in inflammatory bowel disease (IBD) are scarce. The aim of this study was to assess the efficacy, safety, bioavailability profile and factors associated with relapse after switching in IBD patients.

Methods: Remicade®-treated IBD patients for at least 6 months and in clinical remission for at least 3 months (Harvey-Bradshaw index of ≤ 4 points and partial Mayo score of < 2 points) who switched to CT-P13 were included in this retrospective observational study.

Epidemiological, clinical and analytical data, including C-reactive protein (CRP), infliximab trough level (TL) and antidrug antibodies (ADAs), were collected. The incidence of relapse, adverse effects and possible changes in bioavailability after switching were evaluated. A multivariate analysis was performed, using Cox proportional hazards regression to identify factors associated with the relapse.

Results: 36 patients were included, 58.3% women, mean age 41.3 years (SD \pm 15.7), 23 Crohn's disease (CD) and 13 ulcerative colitis (UC). The mean follow-up was 8.4 months (SD \pm 3.5). 13.9% of the patients lost efficacy during follow-up with a mean time to relapse of 2.4 months (SD \pm 1.9). In the multivariate analysis, the factors that were associated with a lower risk of relapse were: longer clinical remission time before switching (HR 0.54, 95% CI 0.29–0.98, $p=0.04$) and detectable infliximab levels at the time of switching (HR 0.03, 95% CI 0.001–0.89, $p=0.04$). The disease duration, time on treatment with infliximab reference product, previous intensification and Non-detectable ADAs, were not associated with the risk of relapse. No differences were found between infliximab levels at the time of switching, at week 8 and 16 after switching ($p=0.94$). During the follow-up, 8.3% of the patients had some adverse effect, motivating in one case the suspension of biosimilar for severe pneumonia.

Conclusions: Switching from Remicade® to CT-P13 in a real-life cohort of IBD patients in clinical remission did not have a significant impact on short-term clinical outcomes. The factors associated with relapse were similar to those expected during follow-up in patients continuing with infliximab reference product. However, until prospective and controlled data are available, this clinical practice should be evaluated with caution.

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Which are the optimal adalimumab trough levels associated with biological remission in patients with inflammatory bowel disease?

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Background: Anti-TNF trough levels have been associated with clinical outcomes in inflammatory bowel disease (IBD). Several therapeutic algorithms based on therapeutic drug monitoring have been proposed. Such algorithms require knowing the optimal drug trough level therapeutic window. However, there are few data about which levels of Adalimumab (ADA) are associated with remission. The aim of this study was to evaluate the relationship between ADA trough levels (ADA-TL) and faecal calprotectin (FC) and to determine the optimal ADA-TL associated with biological remission (BR).

Methods: Prospective observational study including IBD patients under ADA treatment in steady state. ADA-TL, anti-ADA antibodies and biological markers (FC and C-reactive protein [CRP]) were measured. BR was defined as FC <250 μ g/g along with CRP <5mg/L.

Results: 49 samples from 34 patients were included: 94% corresponded to Crohn's disease, 61% were female, 14% smokers, 25% under intensified treatment, 74% on concomitant immunosuppressive treatment and 45% were naive to anti-TNF.

There was a statistically significant inverse correlation between ADA-TL and biomarkers of inflammation (FC: $R=-0.54$, $p=0.0002$; CRP: $R=-0.32$, $p=0.02$).

The proportion of cases in BR was significantly higher in those with the highest ADA-TL (ADA-TL <9.5 mg/L: BR 7.1%; ADA-TL 9.5–11.8mg/L: BR 38.5%; ADA-TL >11.8 mg/L: BR 71.4%; $p=0.002$). The performance of ADA-TL to identify BR can be considered fair: the area under de curve was 0.79. The accuracy qualities of 2 cut-off points of AD-TL to predict BR, one that prioritizes the sensibility (9.5mg/L), and another that prioritizes the specificity (12mg/L), are shown in Table 1.

Table 1. Accuracy of AD-TL to predict biological remission (FC <250 μ g/g + CRP <5 mg/L)

ADA-TL cut-off	AUC	S	E	PPV	NPV
9.5 mg/L	0.79	88%	52%	54%	87%
12 mg/L	0.79	56%	92%	82%	77%

Conclusions: There is an inverse correlation between ADA trough levels and FC values. ADA trough levels below 9.5mg/L are associated with a low probability of biological remission.

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Is there an association between bariatric surgery and Crohn's disease?

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Background: Bariatric surgery is an established treatment for selected obese patients resulting in significant long-term weight reduction. The most commonly performed technique is the Roux-en-Y gastric bypass. This procedure can however lead to nutritional deficits and can cause adverse gastrointestinal symptoms like diarrhea, abdominal bloating or abdominal pain. Symptoms, which are also found in patients with Crohn's disease (CD).

The association of morbid obesity, bariatric surgery and Crohn's disease is not well understood. Up to date, only few cases have been described in the English literature.

Methods: The aim of this study was to determine the frequency of new onset Crohn's disease in patients after bariatric surgery. In a retrospective chart review all patients undergoing bariatric bypass surgery in a defined time period were evaluated. We report clinical and endoscopic findings of these patients, together with histopathological characterization of biopsies from the lower GI tract.

Results: From January 2009 to October 2016, 490 gastric bypass procedures were performed in our institution. During regular clinical follow-up, 21 patients (4.3%) underwent colonoscopy because of unexplained chronic diarrhoea (8/21 pts.), abdominal pain (11/21 pts.), abdominal bloating (5/21 pts.) or anemia (6/21 pts.). In 27.3% (6/21 pts. – age range 19–46, BMI from 32 to 40 m²/kg), endoscopy revealed small ulcerations in the terminal ileum suspicious of Crohn's disease. All patients had elevated calprotectin levels. Histology confirmed clinical findings: focal chronic active enteritis (terminal ileitis) with aphthous ulceration was seen in all biopsy specimens. In one patient, focally enhanced gastritis was also found. Subsequently all patients were diagnosed with Crohn's disease. 5/6 pts. received therapy and were eventually free of symptom.

Conclusions: Our study shows a potential association between bariatric surgery and development of postoperative Crohn's disease. These findings have also been described recently in several case reports. We speculate that the anatomic changes caused by bariatric

surgery trigger alteration of the intestinal microbiome in predisposed patients. This may result in chronic inflammation of the bowel mucosa causing changes seen in Crohn’s disease.

Our findings should increase the awareness of the clinicians regarding patients undergoing bariatric surgery and the possibility of developing Crohn’s disease with subsequent impact on clinical management, such as follow-up and surveillance strategies. Further studies in this field are mandatory.

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Hepatitis B virus reactivation in hepatitis B virus infected patients with inflammatory bowel disease receiving anti-tumor necrosis factor-alpha therapy

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Background: Reactivation of hepatitis B virus (HBV) is one of the most important side effects in IBD patients with HBV infection treated with anti-TNF-alpha agents. We investigated the rate of prophylaxis and the risk of HBV reactivation in HBV infected patients with IBD receiving anti-TNF-alpha therapy.

Methods: This was a retrospective multicenter study including 14 academic teaching hospitals in Korea. IBD patients with HBV infection (HBsAg-positive) who treated with anti-TNF-alpha agents were enrolled. Medical records of patients were reviewed and data were collected using web-based case report form.

Results: A total of 61 patients (18 UC, 43 CD) were included. 70% were male and mean age at diagnosis was 34.9±12.0 years. Indications for anti-TNF-alpha therapy were steroid-dependency, refractoriness to conventional therapies, or fistulizing disease. Among 43 patients who tested serum HBV-DNA levels, 35 (81%) were positive for HBV-DNA prior to anti-TNF-alpha therapy. Only half of the patients (51%) received prophylactic anti-viral agents. During the follow-up of median 24 months, 16.4% of patients experienced

HBV reactivation, of which 6 patients (60%) were taking concomitant azathioprine. Median duration of anti-TNF-alpha therapy before HBV reactivation was 9 months. HBV reactivation was managed by change or adding of anti-viral agents in 6 patients, discontinuing ant-TNF-alpha in 1 patient, and combination of both in 2 patients, achieving virological response in most patients (90%). HBV reactivation was more frequent in non-prophylaxis group than prophylaxis group (10% vs 24.1%, p=0.15). No other predictors for HBV reactivation were identified. There was no difference in the rates of IBD flare, IBD-related surgery or hospitalization between two groups.

Conclusions: HBV reactivation was not infrequent in HBsAg-positive IBD patients treated with anti-TNF-alpha agents. Prophylaxis for HBV reactivation and careful monitoring should be performed for such patients.

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Effect of maintenance Ustekinumab on corticosteroid-free clinical outcomes in patients with Crohn’s disease

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Background: The use of corticosteroids (CS) in the management of Crohn’s disease (CD) is limited by important toxicity. Ustekinumab (UST) has been shown to induce (UNITI 1&2) and maintain (IM-UNITI) clinical response and remission in CD. We evaluated the efficacy of UST on the achievement of CS-free remission and response in participants in IM-UNITI.

Methods: IM-UNITI was a Ph3, double-blind placebo (PBO)-controlled maintenance trial in moderate-severe CD pts who achieved clinical response to UST at wk 8 in one of two UST IV induction UNITI studies. Pts could enter the induction studies while receiving CS; the dose remained stable throughout the 8 wk induction trials. Pts on CS and in clinical response upon entry into IM-UNITI began mandatory CS tapering at wk 0 of maintenance. At wk 44,

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Table: Corticosteroid endpoints in IM-UNITI at Week 44		Ustekinumab		
All randomized patients	Placebo N=131 ^{a,b}	90 mg q12 N=129 ^b	90 mg q8w N=128 ^b	Combined N=257
Corticosteroid-Free Clinical Remission ^{c,d,*}	29.8%	42.6%	46.9%*	44.7%
in remission and off corticosteroids=30 days	29.8%	42.6%	46.9%	44.7%
in remission and off corticosteroids=90 days	29.0%	41.1%*	45.3%*	43.2%
Corticosteroid-Free Clinical Response ^{c,d,*}	36.6%	51.2%*	50.8%*	51.0%
Randomized patients receiving corticosteroids at baseline:	Placebo N=58	90 mg q12w N=57	90 mg q8w N=59	Combined N=116
Corticosteroid-Free Clinical Remission ^{c,d,*}	15.5%	29.8%	30.5%	30.2%*
Corticosteroid-Free Clinical Response ^{c,d,*}	19.0%	32.2%	35.1%	33.6%*

a The PBO group consisted of patients who were in response to a single dose of UST IV induction and were randomized to receive PBO at week 0 of maintenance.
 b Patients who achieved 100 point clinical response to UST at start of maintenance therapy
 c Patients who had a prohibited Crohn’s disease-related surgery, had a loss of response, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening Crohn’s disease prior to the designated analysis timepoint are considered not to be in clinical remission or clinical response, regardless of their CDAI score.
 d Patients who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission or clinical response.
 e Patients who had a missing value in corticosteroids use at designated analysis time point had their last value carried forward.
 *p < 0.05
 Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission

CS-free remission, CS-free response, and CS-free remission without the use of CS for at least 30 and 90 days were assessed in the primary randomized population regardless of baseline CS use. Similarly, CS-free remission and CS-free response were also assessed at wk 44 in pts who were receiving CS at enrollment baseline.

Results: A significantly greater proportion of pts in the UST 90mg q8w group (46.9%, $p=0.004$) and a nominally significant greater proportion of pts in the 90mg q12w group (42.6%, $p=0.035$) were in CS-free remission at wk 44 compared with the PBO group (29.8%) (Table). Likewise, a greater proportion of pts in the UST 90mg q12w group (51.2%, $p=0.024$) and 90mg q8w group (50.8%, $p=0.026$) were in CS-free response at wk 44 compared with pts the PBO group (36.6%). The proportions of pts in the PBO group that were in remission and off CS for 30 and 90 days (29.8% and 29%, respectively) were lower than in the 90mg q12w (42.6% and 41.1%, respectively) and 90mg q8w group (46.9% and 45.3%, respectively; $p<0.05$ for all comparisons vs PBO).

Among the subgroup of pts receiving CS at baseline (44.8%), a greater proportion of these pts in the combined UST group discontinued CS and achieved clinical remission or clinical response at wk 44 (30.2% and 33.6%, respectively) compared with the PBO group (15.5% and 19.0%, respectively; $p<0.05$ for both). A numerically higher proportion of pts in each of the two dosing groups (q12w and q8w) achieved CS-free remission and response at wk 44 compared with PBO.

Conclusions: UST achieved a higher rate of CS-free remission and response vs. PBO and this CS-sparing effect was observed over 44 wks of treatment. For pts on CS at study entry, UST showed evidence of benefit reducing the need for CS while still achieving clinical response/remission.

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Clinical features of demyelination following anti-TNF α therapy

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Background: Anti-TNF α therapy has been associated with demyelination since early trials in Multiple Sclerosis (MS) demonstrated disease exacerbation. Subsequent small case series have reported plausible clinical associations, although epidemiological studies have produced conflicting data. The specific clinical features of demyelination following anti-TNF therapy have not been described. This study uses a systematic independent assessment of causality to describe the clinical characteristics and outcomes of anti-TNF α associated demyelination.

Methods: Patients were recruited from 27 hospitals. Inclusion criteria included i) no history of neurological symptoms prior to anti-TNF α exposure, ii) MRI brain and/or spinal cord or electrophysiological tests consistent with PNS or CNS demyelination, iii) demyelination illness confirmed by neurologist and drug withdrawn. An

adjudication panel comprising at least 3 neurologists and a neuro-radiologist identified definite and probable cases from case report forms. Probable cases required a consistent history and signs and objective radiological \pm electrophysiological evidence of demyelination. Definite cases had a recurrence of demyelination on drug rechallenge.

Results: 52 cases were recruited, of whom 34 (23 female) were adjudicated as definite or probable cases. Adalimumab, Infliximab, Etanercept and Certolizumab were implicated in 16/34 (47%), 12/34 (35%), 5/34 (15%), and 1/34 (3%) of cases respectively. Average age at symptom onset was 40 (95% CI 36–44) yrs. The mean duration of anti-TNF α exposure was 29 (95% CI 20–39) months prior to onset of demyelination. 19 (56%) cases presented with brain \pm spinal lesions, 9 (26%) spine only demyelination, and 5 (15%) peripheral demyelination. 1 patient (3%) presented with both central and peripheral demyelination. On drug withdrawal patients were followed for a mean of 40 (95% CI 32–48) months. 11 (32%) of patients developed a relapsing demyelinating syndrome or MS and only 6 (18%) had complete resolution of their symptoms with a mean time to resolution of 381 days (95% CI 80–682).

Conclusions: This case series reports the clinical features of demyelinating events associated with anti-TNF α therapy. Consistent with known risk factors for MS, young females appear to be over represented. Approximately one third of patients appear to develop a relapsing illness/MS and complete neurological recovery is uncommon. We aim to build this cohort further to explore clinically useful genetic markers that identify at-risk patients.

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Smooth Seton[®] for perianal fistulas: a knot-less solution

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Background: Perianal fistulas are a common incapacitating problem. Many patients are treated by seton drainage to prevent recurrent abscess formation. For centuries, a vessel loop or suture has been used for seton drainage. The knot (or suture) that is necessary to tie both ends together, is well known for causing complaints interfering with daily quality of life. To inventory complaints associated with knotted setons, a web-based questionnaire was performed by the Dutch Crohn and Ulcerative Colitis Association (CCUVN). Twenty-four out of 46 patients (52%) reported to have daily complaints of pain, irritation, itchiness or discharge caused by the knot. MediShield B.V. designed a knotless seton, the Smooth Seton, in order to decrease these complaints. With this study we aim to determine the advantages of a Smooth Seton for patients with perianal fistulas.

Methods: A prospective cohort study was performed in a consecutive series of fistula patients. All patients ≥ 18 years, with perianal fistulas and a seton *in situ*, or patients presenting with a new perianal fistula, and no defunctioning stoma, were eligible. Existing setons were replaced at the outpatient clinic whereas new setons were placed at the operating theatre in day care setting. The primary outcome was seton failure (loosening of the connection). Secondary outcomes were complications, and quality of life measured by the PDAI ("Perianal Disease Activity Index"). For the patient group with seton replacement, preoperative PDAI was compared to postoperative PDAI. Results were analysed using the paired t-test.

Results: Twenty patients (40% male, mean age 42 (SD 12.81)), were

included between August and November 2016. Seventeen patients had perianal fistulas due to Crohn's disease and 3 had fistulas of cryptoglandular origin. In one patient, the outpatient replacement failed, and the Smooth Seton was placed subsequently in theatre. The median number of Smooth Setons placed per patient was 2 (range 1–3). Follow-up was performed in 17 patients with a median of 23 days (range 11–71). Loosening of the connection occurred in one of the patients. Mean PDAI in patients with a knotted seton was 11.36 versus 8.69 after Smooth Seton placement ($p=0.006$). Looking at each of the 5 subscales of the PDAI, only pain significantly decreased ($p=0.003$). Ten out of 16 patients (63%) reported less cleaning problems with the Smooth Seton when compared to the regular knotted seton. No postoperative complications occurred during the study period.

Conclusions: The Smooth Seton is a feasible novel technique for patients with new and recurrent perianal fistulas with promising short term results. Replacement of the conventional knotted seton by the Smooth seton significantly decreases complaints measured by the PDAI.

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An online educational portal improves concerns of inflammatory bowel disease patients regarding pregnancy and medication

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Background: The impact of a mother's chronic disease on fetal development makes dealing with inflammatory bowel disease (IBD) during pregnancy complicated. Almost 50% of women with IBD have poor reproductive knowledge; this has been associated with unsubstantiated concerns toward pregnancy, and towards IBD medications. With the help of Pixel Designs Company, we developed an educational web portal and evaluated the portal for effectiveness at improving pregnancy and medication concerns in IBD patients.

Methods: IBD patients aged 18–45 years were invited to participate in a study to evaluate the effectiveness of an educational web portal covering the topics of heritability, fertility, surgery, pregnancy outcomes, delivery, postpartum, and breastfeeding in the context of IBD

and IBD medications. Patients completed pre- and post-study questionnaires about seven IBD-specific pregnancy concerns, and identified Likert scores for nine medication concerns from the Beliefs About Medicines Questionnaire (BMQ). McNemar's non-parametric test was used to determine if the proportion of patients who had each pregnancy concern decreased post-intervention. For medication concerns, Wilcoxon signed-rank test was used to compare median differences between Likert scores. P values of 0.05 were used for analysis with SPSS version 23.

Results: Seventy-eight of 111 patients (70.3%) completed pre and post-study questionnaires. Demographics for the 78 are as follows: median age 29.3 (IQR 25.6–32.9) years; 54 (69.2%) Crohn's disease; 21 (26.9%) ulcerative colitis; 63 (80.3%) females, 5 (7.9%) currently pregnant and 19 (30.2%) previously pregnant. Medication history: 10 (12.8%) sulfasalazine, 67 (85.9%) mesalamine/5-ASAs, 17 (21.8%) budesonide, 63 (80.8%) steroids, 12 (15.4%) methotrexate, 55 (70.5%) azathioprine/mercaptopurine, 42 (53.8%) biologics, and 38 (48.7%) antibiotics. The intervention significantly decreased the proportion of patients who reported reproductive concerns regarding: fertility, added stress of raising a child affecting IBD, birth defects from IBD, pregnancy causing a flare-up, and inability to breastfeed due to IBD or medications. The BMQ Likert scores significantly decreased post intervention for concerns about having to take IBD medication, becoming too dependent on IBD medication, and the long-term effects of IBD medication.

Conclusions: Our educational web portal reduces the proportion of patients who report certain concerns about pregnancy in IBD, in addition to concerns regarding their IBD medications.

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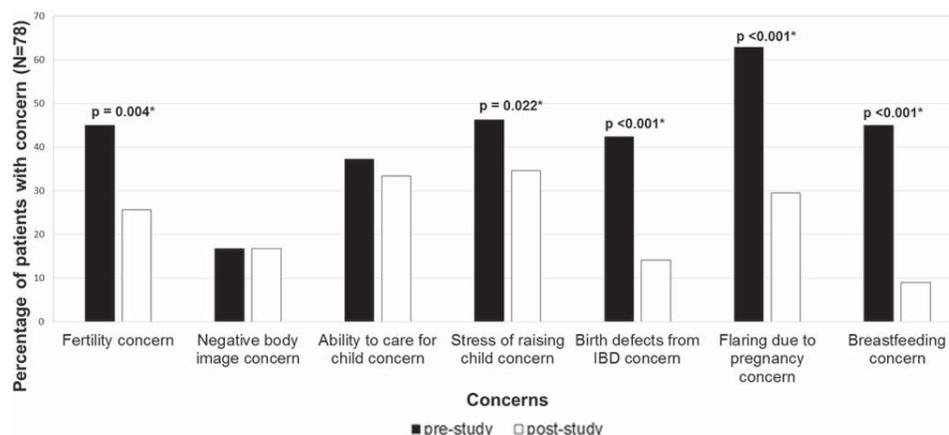
Long-term outcomes of seton drainage for perianal fistulizing Crohn's disease

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Background: Treatment of perianal fistulizing Crohn's disease (PFCD) is challenging. Placement of a draining seton as the first step is considered gold standard therapy. The aim of this study was to determine the long-term efficacy of draining setons in PFCD.

Methods: Charts of patients with PFCD treated with a draining seton over a five-year period ending November 2015 were reviewed. Patients were primarily treated with silastic seton without planned future seton removal or fistula repair. Short-term (<6 months from



Abstract P552 – Figure 1. IBD specific reproductive concerns improve after accessing online educational portal.

the time of initial seton placement), intermediate-term (<12 months from the time of initial seton placement), and long-term (>12 months from the time of initial seton placement) outcomes were analyzed.

Results: The study cohort included 41 patients. Indication for placement of draining seton alone rather than definitive surgical fistula repair was presence of anal ulceration, stenosis and/or proctitis (n=30; 73%), complex fistulae not amenable to surgical repair (n=8; 26%) or patient preference (n=3; 7%). Concomitant medical therapy using biologics, immunomodulators, and/or steroids was used in 28 (68%), 14 (34%) and 13 (32%) patients, respectively. Median length of follow-up after seton placement was 35 months (range, 8–69). Over the short-term, 16/41 (39%) patients required additional seton placement for new or persistent fistula after median follow-up time of 2.2 months (range, 0.2–5.5 months). Over the intermediate-term, 6/37 (16%) more patients required additional seton placement for new or persistent fistula after a median follow-up time of 7.7 months (range, 7–11.4 months). Over the long-term, 7/35 (20%) more patients required additional seton placement for new or persistent fistula after a median follow-up time of 16.8 months (range, 14.5–29.5 months). Overall, 29 (71%) patients required additional seton placement for new or persistent fistula after a median time of 7 months (range, 0.2–29.5 months) after initial seton placement (Figure 1). The majority of patients requiring additional seton placement also had concomitant medical therapy with a biologic agent (19/29; 66%). Patients who had a family history of CD had a significantly lower incidence of additional seton placement (50%) compared to patients who did not have a family history of CD (90%) (p=0.04). All other clinical factors including concomitant medical therapy were not associated with additional seton placement.

Conclusions: Almost 75% of patients with planned long-term seton drainage for PFCD required additional setons. These data suggest that draining setons in PFCD, even in combination with biologic agents, may not have as promising results as previously believed. Progression of PFCD remains high despite biologic therapy and seton drainage.

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Impact of real world home based remote monitoring on quality of care and quality of life in inflammatory bowel disease patients: one year results of pragmatic randomized trial

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Background: Patients with IBD are ideal candidates for home-based remote monitoring care that is centered on enhanced symptom tracking and improved communication with care teams. The objective of this pragmatic randomized controlled trial is to determine the impact of the HealthPROMISE app in improving outcomes quality of care [QOC] and quality of life [QOL] as compared to a patient education app.

Methods: Participants were randomized to either interventional (HealthPROMISE) or control (education app). All patients completed intake questionnaires assessing health literacy, disease severity, general health status, and demographic information. Patients in the HealthPROMISE arm were able to update their information and receive disease summary, QOC metrics and a graph trending QOL (SIBDQ) scores over time (<https://clinicaltrials.gov/ct2/show/NCT02322307>).

Results: 320 patients were enrolled in the study at Mount Sinai Medical Center (MSMC) (see Table 1). Baseline assessment showed that fatigue and tension (anxiety) were the two most important drivers of poor quality of life. Patients with College Education reported less symptom burden (29.2 vs 36.8, range 10- 70; p<0.01) and better

Table 1. Baseline characteristics of patients in the control and intervention arm

	Control (%)	Intervention (%)
Number (N)	158 (49.4%)	162 (50.6%)
Age	40.9±13.8	39.5±12.8
Male	82 (51.9%)	81 (50.0%)
Female	76 (48.1%)	81 (50.0%)
Quality of Life (QOL)	31.9±11.9	30.2±11.3
Inflammatory Markers Normal (Patient Reported)	46 (29.1%)	49 (30.2%)
Mucosal Biopsy Normal (Patient Reported)	26 (16.5%)	34 (21.0%)
Quality of Care (Overall percentage of Metrics Met)	50%	50%

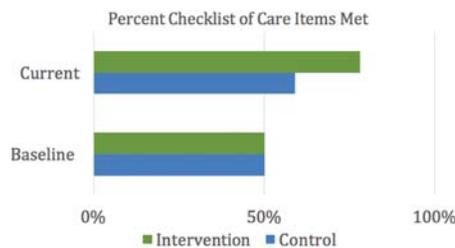
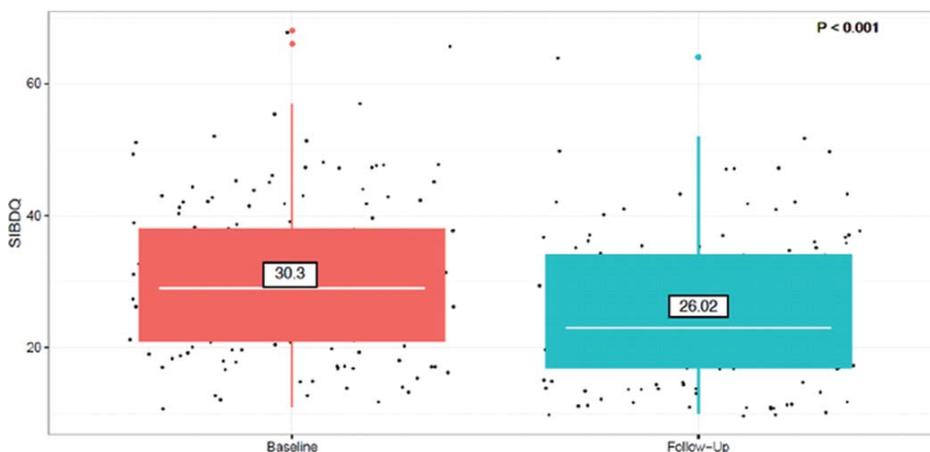


Figure 1. Improvement in percentage of patients meeting eligible quality of care metrics in control (9%) versus Intervention (28%), p<0.01.



Abstract P554 – Figure 2. Interim analysis showing improvement in symptom burden among intervention cohort (p<0.001).

QOL (0.8 vs 0.7; $p < 0.01$), an effect that remained significant in multivariable models.

In a median follow up of 495 days (± 135), the proportion of patients meeting all eligible QOC significantly increased in intervention group versus control group (increase of 38% versus 9%, $p < 0.01$) (Fig. 1). Overall QOL started to improve among HealthPROMISE patients within 5 months and has consistently been above the control arm through a median interval of 495 days (Fig. 2).

Conclusions: This is one of the first randomized controlled trials of app-based home monitoring in IBD patients. Fatigue and tension are the top two drivers of poor QOL among IBD patients. We found a significant improvement in QOC and QOL in intervention group. With a move towards value based care, digital medicine technology can play an effective role in tracking and managing patient population in IBD centers. Remote monitoring coordinators can help support proactive care without disrupting physicians' workflow.

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Systematic review of interventions for chronic abdominal pain management in inflammatory bowel disease

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Background: Chronic abdominal pain is frequently reported by adults with inflammatory bowel disease (IBD), even when disease is in remission. Pain is an under-recognised and under-treated symptom. This paper will systematically review evidence on interventions for chronic abdominal pain management in patients with IBD.

Methods: Databases (MEDLINE, EMBASE, PsycInfo, CINAHL, Scopus and Cochrane Library) were searched (February 2016). Two researchers independently screened the retrieved references and extracted data.

Results: Fourteen papers were included: 12 intervention studies and two cross-sectional surveys. A range of pharmacological, non-pharmacological and dietary supplement interventions were tested. Reduction of abdominal pain was reported for: psychologist-lead stress management ($p < 0.05$) and self-directed stress management ($p < 0.05$), interventions with guided relaxation for both groups; relaxation in groups or individually (pain less intensive $p < 0.002$, less frequent $p < 0.04$, greater pain relief $p < 0.001$ and less pain distress $p < 0.001$). Cognitive behavioural therapy focusing on disease-related concerns also showed pain reduction. Provocative dietary supplements resulted in more pain from alcohol with high sugar content compared to ethanol ($p < 0.05$); there was no difference in pain induced by processed and unprocessed cereals. Current and past cannabis users reported less pain with cannabis use. These results need to be treated with caution, as data were derived from predominantly small uncontrolled studies of moderate to low quality.

Conclusions: Few interventions have been tested for IBD abdominal pain. The limited evidence suggests that relaxation and changing cognitions are promising approaches, possibly with some individualised dietary changes. There is a need to develop and test interventions for abdominal pain management in IBD.

P556

Female Crohn's disease patients and ulcerative colitis patients on biologic therapy are most disabled

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Background: There is limited disability data in the biologic era using Patient Reported Outcomes. The aims of this study were to describe the disability status and identify determinants of disability in a well characterized cohort of IBD patients using the Inflammatory Bowel Disease Disability Index (IBD-DI).

Methods: From June 2015 to September 2016, the IBD-DI was administered to adult IBD patients. Natural history data were available for each patient from time of diagnosis to time of completing the questionnaires. Clinical remission status at time of answering the questionnaire was also recorded.

Results: 250 patients with IBD completed the IBD-DI. The median duration from diagnosis to completion of questionnaire was 45 months. The median age at diagnosis was 30 years.

The median IBD-DI was 31.3 (IQR 17.9–41.1). The median IBD-DI score for CD was 32.14 (IQR 19.2–45.1) in CD and 28.71 (IQR 17.4–44.5) in UC. CD females were more disabled than males (IBD-DI score 36.6 vs 27.1, $p = 0.001$). There was no significant gender bias in the UC group (female IBD-DI score 32.6 vs male 30.6, $p = \text{NS}$).

Patients with active disease at the time of answering the questionnaires had a higher IBD-DI score compared with patients in remission (42.4 vs 29.0, $p < 0.001$). Disease phenotype or disease location did not influence the IBD-DI score in CD or UC. Female CD patients in remission were also more disabled compared with male CD patients (33.9 vs 23.9, $p = 0.002$). There was no difference in disability scores by gender in the UC group adjusted for clinical activity. UC patients on biologic therapy were more disabled than those who were not, despite being in clinical remission (IBD-DI score 36.7 vs 25.9, $p = 0.03$). CD patients who had undergone intestinal resection demonstrated a trend towards reduced disability compared to those who had not (IBD-DI score 30.5 vs 35.3, $p = 0.059$). CD patients with perianal disease were not more disabled than those without, (IBD-DI score 34.0 vs 32.0, $p = 0.3$).

52 patients were severely disabled (IBD-DI score > 50). 62% had CD, 71% were female, and 46% were in clinical remission at the time of answering the questionnaires. Of the CD patients, 70% had an inflammatory phenotype, 15% had perianal disease, and only 31% had prior intestinal resection. Only 10% of the UC patients with severe disability had undergone colectomy for refractory disease.

Factors associated with high disability scores on multivariate analysis were female gender ($p = 0.01$) and active disease ($p = 0.001$) in CD, and need for biologic therapy ($p = 0.027$) and active disease ($p = 0.005$) in UC.

Conclusions: Female CD patients are more disabled than males. The need for biologic therapy in UC is associated with higher disability. Severe disability is present in the absence of clinical activity.

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Utility of "trough levels" adalimumab determination in patients with inflammatory bowel disease. Estimation of individual pharmacokinetic parameters through population pharmacokinetic model

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Background: Adalimumab (ADM) is effective in inducing and maintaining remission in patients with Inflammatory Bowel Disease (IBD). However, 10% are primary non-responders and even 15% patients/year lose the response in the follow-up, mainly in relation with immunogenicity and their effect on the trough levels of infliximab (TLI). The importance of the plasma clearance of the drug has been pointed out in the individualization of treatment.

Aim: Analyzing trough levels of Adalimumab in a cohort of patients with IBD. Estimating individual pharmacokinetic (PK) parameters through population pharmacokinetic model and bayesian adjustment.

Methods: Prospective, descriptive study of 30 patients with IBD and with ADM therapy (2014–15). Two cohorts were included: A) monitoring during induction phase (week 4); B) monitoring during maintenance phase (in clinic remission at least 12 weeks). Blood samples for TLI analyses were obtained prior to ADM administration. Samples were analyzed by ELISA (Promonitor). Individual PK parameters were estimated using NONMEN VI program and different dosing regimens were simulated.

Results: 30 patients (25 CD/ 5 UC);16M/14W; average age 42 years (12–70). 18 patients with Azathioprine. Group A: 12 patients (31 samples); TLI (median) 12.0 µg/ml (RIQ 11.99 µg/ml); > 12.2 µg/ml, 80%. Only one patient with undetectable TLI and antibody anti-ADM (+). Group B: 19 patients (31 samples); TLI (mean): 8.5

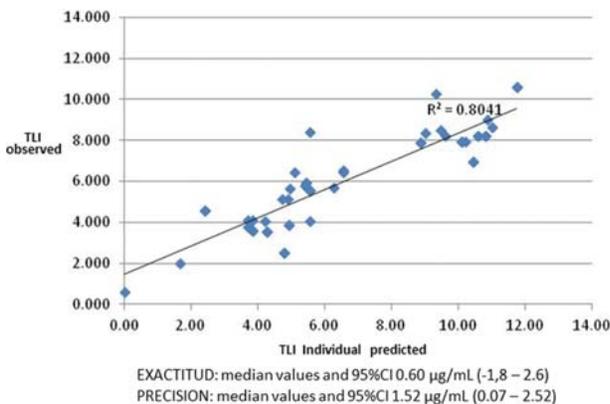


Figure 1. External validation of the population pharmacokinetic model of adalimumab.

µg/ml (95% CI: 7.15–9.86). Levels distribution: <4 µg/ml, 16%; 4–8 µg/ml, 29%; 8–12 µg/ml, 19%; >12.2 µg/ml); 36% (high level detected).

The overall pharmacokinetic parameters of Adalimumab are expressed in Table 1. The external validation of the pharmacokinetic model (IMAGE01) has an accuracy of 0.60 mcg/ml (95% CI: -1.8–2.6) and an accuracy of 1.52 mcg/ml (0.07–2.52). IMAGE02 shows a case of individual predictive model with Bayesian adjustment.

Table 1. Pharmacokinetics parameters of adalimumab

Pharmacokinetics parameters (N=30)	Mean (95% CI)
Plasma clearance (L/day)	0.26 (0.21–0.31)
Biological half life (t _{1/2}) (day)	26.8 (21.4–32.2)
Central distribution volumen (L)	8.81 (7.2–10.4)
AUC (mg·d/L)	113.3 (100.7–125.8)

Conclusions: Determining TL-ADM along with the estimation of individual PK parameters allows to optimize the treatment in patients with IBD.

References:

[1] Br J Clin Pharmacol, (2014), 79:2;286–97

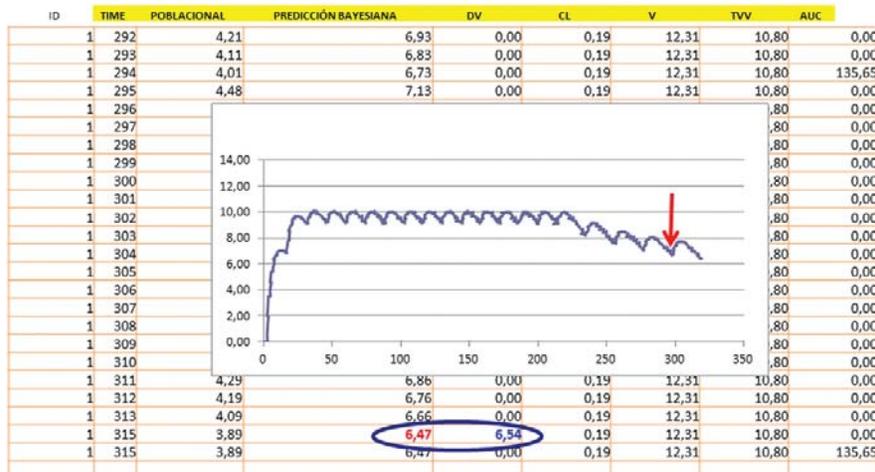
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The SF-36® Health Survey distinguishes disease burden on functioning and well-being between patients with active vs inactive ulcerative colitis

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Background: Active ulcerative colitis (UC) is characterised by symptoms of fatigue, abdominal pain and increased stool frequency, which directly affect how patients feel and function, but even inactive disease may adversely affect patients’ functioning. The objective of this



Abstract P557 – Figure 2. Individual predictive model with Bayesian adjustment.

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Table 1. Mean differences from benchmark samples in SF-36 T-scores for samples of UC patients with active or inactive disease

Disease status	Statistic	Physical Functioning (CID = 3)	Role Physical (CID = 2)	Bodily Pain (CID = 3)	General Health (CID = 3)	Vitality (CID = 3)	Social Functioning (CID = 3)	Role Emotional (CID = 4)	Mental Health (CID = 3)
Active (14 studies)	Mean difference from benchmark	-3.6 [†]	-6.4 [†]	-5.5 [†]	-8.6 [†]	-4.9 [†]	-6.6 [†]	-4.5 [†]	-4.0 [†]
	% studies where deficit > CID	50%	93%	79%	93%	71%	86%	64%	71%
Inactive (15 studies)	Mean difference from benchmark	0.3	-1.1	-0.2	-3.5 [†]	-1.6	0.0	-1.1	0.0
	% studies where deficit > CID	7%	33%	7%	53%	40%	13%	13%	7%

[†]Absolute value exceeds CID

CID, clinically important difference; SF-36, SF-36 Health Survey; UC, ulcerative colitis

analysis was to characterise the impact of active or inactive UC on patient functioning by synthesising data from prior published studies that compared scores from the SF-36[®] Health Survey (SF-36), a generic measure of eight domains of functioning and well-being, between UC patients and general population or healthy benchmark samples.

Methods: This systematic literature review used search terms entered into electronic medical databases (eg, PubMed, EMBASE) including “ulcerative colitis”, “inflammatory bowel disease” and “SF-36”. We selected articles reporting SF-36 domain scores from both UC and benchmark samples. We extracted SF-36 scores, converted them into norm-based standardised T-scores (mean=50, SD=10), and summarised across studies. We assessed burden of disease by comparing differences in mean scores between UC and benchmark samples to clinically important difference (CID) thresholds established for each domain.

Results: We reviewed 27 articles that met criteria, and assessed burden in 14 studies of patients with active UC, and 15 studies of patients with inactive UC (either in clinical remission or post-surgery). Results are presented in Table 1. Across studies, patients with active UC exhibited clinically meaningful differences in all SF-36 domains: mean differences with benchmark samples across studies exceeded CID thresholds for all eight SF-36 domains. Findings across studies of patients with inactive UC showed little or no evidence of disease burden, with mean differences less than CID thresholds for seven of the eight SF-36 domains (all but General Health).

Conclusions: Patients with active UC experience a clinically meaningful burden of disease across all domains of physical and mental functioning and well-being that are captured by the SF-36. Patients with inactive UC are comparable to healthy controls and the general population on these outcomes. These findings support the benefit of effective treatments of UC to reduce the broad and substantial burden on patients' feeling and functioning, or even eliminate this burden, resulting in normalised functioning and well-being. Inclusion of the SF-36 in future studies of UC induction and maintenance will enable assessment of treatment impact on disease burden.

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Treatment goals in IBD: a perspective from patients and their partners

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Background: As Inflammatory Bowel Disease (IBD) is a chronic disease, many treatment decisions have to be made during its course. For physicians, an important treatment aim is mucosal healing (normal colonoscopy) as it improves long-term outcomes. Little research has focused on what patients see as treatment goals, whether this dif-

fers between patients and partners, and whether their views can be adjusted by patient education, to bring patient and physician goals closer together and improve shared decision making.

Methods: During an IBD patient information day in our hospital (190 patients and partners), a survey was distributed asking patients and their partners their preferred treatment goals after 6 weeks and 6 months. Treatment goals were divided between short-term goals (such as being symptom-free) and long-term goals (such as preventing surgery). A validated mobile health index (mHI) for Crohn's Disease (CD) and ulcerative colitis (UC) was used to assess disease activity. These two questionnaires consist solely of 4 Patient Reported Outcomes (PROs) for remote monitoring of patients with IBD (van Deen et al). After receiving the initial survey, an IBD specialist gave a presentation about treatment goals and why physicians aim for mucosal healing. After this, patients and partners were asked to fill in the same survey.

Results: 91 patients (of which 67% had CD and 33% UC) and 34 partners responded to the initial survey and 114 people (81 patients, 33 partners) to the after-talk survey. Age, gender and education did not affect the individual treatment goals. Most respondents chose “symptom-free” as goal. Patients with higher disease activity chose more short-term goals than long-term goals (p=0.03) at 6 weeks. Compared to patients, partners chose more short-term goals (p=0.03) at 6 weeks. Only 4.2% of all respondents chose a normal colonoscopy as goal at 6 months. After the presentation, the number of people who chose a normal colonoscopy at 6 months as treatment goal increased significantly (18.3%, p=0.001), of which 80% were patients and 20% partners.

Conclusions: Patients' 6-week treatment goals focused on being symptom-free and a high QOL, especially those patients with high disease activity. Partners chose more short-term goals than patients at 6 weeks. Six month-goals are more balanced between long- and short-term goals in both groups. The discrepancy between the physician's treatment goal, “a normal colonoscopy”, and goals of patients and partners, can be improved by providing patients tailored information regarding treatment goals. This proves that better information and/or improved communication techniques help patients understand that a normal colonoscopy as treatment goal may lead to achieving other treatment goals.

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Trough levels at induction: impact on long term response when re-initiating infliximab

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Background: Infliximab (IFX) is indicated for the treatment of inflammatory bowel disease (IBD) (ulcerative colitis (UC) or Crohn disease (CD)). Nevertheless, a significant proportion of patients will experience a loss of response (LOR) to IFX over time which may require despite optimization a switch to another anti-TNF or to swap out to another biotherapy. We have recently reported that week 2 and 6 IFX trough levels (TLs) can be predictive of treatment failure and long term response. Only one study has shown that week 14 TLs can be predictive of long term response on re-initiation of IFX therapy. Our objective is to evaluate early on at induction IFX TLs and antibodies to IFX (ATI) in patients previously exposed to anti-TNF.

Methods: 269 IBD patients (194 CD – 75 UC) have been treated with IFX on follow-up. 2331 samples were prospectively collected but measured retrospectively by ELISA in parallel with clinical data. 91 samples (TL measured <1µg/ml) were analyzed for IFX ATI using drug-sensitive bridging ELISA

Results: At follow-up, patients were subdivided into three groups: long-term responders, patients who had LOR but responded to optimization or patients who had LOR but did not respond to optimization and were switched to another biotherapy. Each group was subdivided according to naïve or previous treatment with anti-TNF (IFX or Adalimumab) status. During induction, in the LOR switched group, median IFX TL was significantly lower in previously exposed patients than in naïve patients (0.92µg/ml vs 6.6µg/ml, p=0.044) (Figure 1A). Inversely, there was no statistical difference between median TL in the LOR optimized group between naïve and previously exposed patients (9.38µg/ml vs 11.82µg/ml, p=0.52) as well as in naïve and previously exposed Long-term responders (9.57µg/ml vs 11.91µg/ml, p=0.92). Overall, among the previously exposed patients, the LOR switched group had a lower median IFX TL (0.92µg/ml) compared to the Long-term responders (9.57µg/ml, p=0.015) and LOR optimized group (11,82µg/ml, p=0.005) (Figure 2). The percentage of ATI occurrence was statistically lower in the Long-term responders (5.7%) than in the LOR optimized (37.5%), p=0.002 and LOR switched groups (40%) (p=0.002). Interestingly, among the LOR switched group, the percentage of ATI occurrence was similar in patients whether naïve or previously exposed to anti-TNF (38.8% vs 42.9%, p=0.86) (Figure 1B). The same observation was found in the LOR optimized group (25% vs 45%, p=0.45).

Conclusions: In LOR switched group, patients previously exposed to anti-TNF seem to have lower IFX TLs at induction than naïve patients. This may not be related to immunogenicity as the presence of ATI was similar in patients whether naïve or previously exposed to anti-TNF.

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Can we predict adherence to treatment in IBD patients?

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Background: Adherence is generally associated with improved treatment outcome in patients with IBD and is estimated to be between 30–60%. Capturing non adherence in daily practice remains a challenge. Risk factors for non-adherence are still contradictory. The study aimed to identify risk factors for non-adherence in IBD patients

Methods: All participants filled questionnaires including: demographic, clinical, socioeconomic data and accessibility to GI services. Psychological features were assessed using: Sense of Coherence, Hospital Anxiety and Depression Scale, IBD self-efficacy scale and Brief Illness Perception questionnaires. Adherence to treatment was evaluated using the Morisky (8 questions) score.

Results: This study included 224 patients; 64.3% females, median age 37 years (IQR 27–44). Of them 70% had Crohn's disease (CD), 25% Ulcerative colitis (UC) and 5% undetermined colitis. A third of UC and 20% of CD patients had an extensive disease. Seventy percent had at least 1 hospitalization, 33% underwent at least one operation and 50% received biological treatment. Backward multivariate regression analysis demonstrated that high adherence was associated with biological treatment (OR 0.33; 95% CI 0.135–0.784, p=0.012) and depression (OR 0.1; 95% CI 0.26–0.415, p=0.001). Low adherence was associated with anxiety (OR 3.43; 95% CI 1.47–7.98, p=0.004) and past smoking (OR 6.95; 95% CI 1.59–30.42, p=0.010). Marital status and number of medications taken by the patient were not associated with adherence. Type of disease, time from symptoms, age, gender, employment, use of 5-ASA, hospitalization and severity of disease score were associated with adherence in the univariate analysis but not in the multivariate analysis.

Conclusions: Psychological factors (depression or anxiety) as well as disease related factors (biological treatment and smoking status) can strongly influence adherence status in IBD patients.

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Real-life infliximab trough levels among inflammatory bowel disease patients on maintenance therapy: should we redefine therapeutic range based on inflammatory load?

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Background: Infliximab (IFX) trough levels (ITLs) have emerged as a promising tool for the management of inflammatory bowel disease (IBD) patients. However, optimal therapeutic range in clinical practice is still under debate and might vary depending on factors such as the inflammatory burden.

Methods: Observational study where IBD patients on maintenance IFX therapy were prospectively included from June 2015 to June 2016. Clinical and biological data including C-reactive protein (CRP) levels from the same infusion day were collected. ITLs were measured just before the infusion and were considered as infratherapeutic if they were <3 µg/mL. The aims were to describe real-life ITLs and to identify factors associated with infratherapeutic ITLs.

Results: A total of 235 infusions were analyzed among 77 patients (76% Crohn's disease). Median (IQR) disease and IFX duration was

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Table 1. Risk factors for infratherapeutic ITLs. Univariate and multivariate analysis.

Risk factors	ITLs (ug/ml)	P value ^{1,3}	OR (95%CI)	P value ⁴
	Median (IQR)	(univariate)		(multivariate)
IFX dose frequencies ¹			2.52 (0.89-7.11)	0.80
Escalated (every 6 weeks)	3.8 (1.3-4.8)	0.029 ¹		
Standard (every 8 weeks)	1.8 (0.4-4)			
Reduced (every 10-12 weeks)	1.2 (0.1-2.9)			
Clinical and/or biological activity ²			2.93 (1.47-5.87)	0.002
Yes	1.1 (0.1-2.9)	0.002 ²		
No	2.7 (0.8-4.5)			
Smoking habit			2.55 (1.14-5.69)	0.027
Yes	1.1 (0.1-2.6)	0.005 ²		
No	2.3 (0.5-4.3)			

¹ Kruskal-Wallis test; ² Biological activity defined by C-reactive protein ≥ 5 mg/dl;
³ U Mann-Whitney test; ⁴ Logistic regression.

10 years (5–18) and 23 months (7–61), respectively; 44% of patients had previous abdominal surgery; 88% received concomitant immunosuppressant therapy; and 35% presented also perianal disease. Median (IQR) ITLs and CRP levels were 0 ug/mL (0–1) and 3.1 mg/mL (1.5–6.1), respectively. Despite 61% of the patients were in clinical and biological remission, a total of 66% had infratherapeutic ITLs. Of note, loss of response occurred only in 28% of the cases. In the univariate analysis, being on a standard or reduced dose the presence of clinical and/or biological activity, and active smoking were associated with infratherapeutic ITLs. In the multivariate analysis, the presence of clinical and/or biological activity and active smoking remained as independent risk factors (Table 1). When analyzing only patients in clinical and biological remission and excluding those with an escalated dose, the proportion of patients with infratherapeutic ITLs was still high (56%) and smoking habit remained as a risk factor for these infratherapeutic ITLs.

Conclusions: In our cohort, more than half of the IBD patients on maintenance IFX therapy present infratherapeutic ITLs as conventionally defined, even among those in clinical and biological remission. Clinical and/or biological activity and active smoking were independent risk factors for ITLs < 3 . This highlights the strong impact of the inflammatory burden on ITLs and the need of re-defining the therapeutic range of ITLs, probably towards a more personalized method based on patient's characteristics such as inflammatory load.

P563

Psychotherapy experience and demand for it and their association in inflammatory bowel disease – results from an internet-based survey

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Background: Quality of life is often negatively affected in patients with inflammatory bowel diseases (IBD) (Crohn's Disease, CD; ulcerative colitis, UC) associated with depression and anxiety. The clinical need as well as the efficacy of psychotherapeutic interventions in IBD patients is a matter of constant debate. However, the perspective of IBD patients has largely been ignored in this debate.

Methods: Psychometric tests namely the Short-Form IBD Questionnaire (SIBDQ) for quality-of-life assessment, the ADAP test measuring demand for psychological therapy and the Fear-of-Progression

Questionnaire Short Form (FoP-Q-SF) as well as disease related questions, e.g. experience with psychotherapy were web-based positioned and advertised by the DCCV (“Deutsche Crohn und Colitis Vereinigung”), the biggest IBD patient organization in Germany. Data were analyzed by a stepwise forward regression model using SPSS Version 19. Statistical significance was set at < 0.05 .

Results: A total of n=631 patients responded. Data from n=578 (356 CD, 219 UC, 3 unclear) were complete and used for the analysis. 90% of the respondents show an at least slightly diminished quality of life (SIBDQ < 60) and 60% had significant fear of disease progression (FoP-Q-SF > 36). 55% had a demand for psychotherapy (ADAPT > 60). More than half of all IBD patients (n=296) had previous experiences with psychotherapy, while the remaining had not (n=282). This distribution clearly determined the factor “demand for psychotherapy” (chi-square = 23.7, $p < 0.001$). Regression model analysis revealed that psychotherapy demand was dependent on previous experience ($p < 0.001$), fear of progression ($p < 0.001$), quality of life ($p = 0.001$), smoking ($p = 0.003$) and previous surgery ($p = 0.005$) with the total model explaining 29.7% of the variance. The total explained variance of this model was higher in UC alone (37.6%) than in CD alone (25.4%). Other models showed similarly high explanation using fear of progression (49.7%) or quality-of-life (48.5%) as dependent variable.

Conclusions: A high number of patients showed a diminished quality of life as well as a high demand for psychotherapy. Demand for psychotherapy as additional therapy in IBD depends on previous experience with psychotherapy, fear for disease progression but also other disease characteristics. To improve the quality of life of IBD patients, physicians should be aware of the enormous need of IBD patients for additional therapeutic interventions as shown in our cohort. Psychometric tests, as used in our study, could help to identify patients with a need for psychotherapy in the daily routine, to deliver the best possible combined treatment options for IBD patients.

P564

Low-dose azathioprine improves long-term efficacy of infliximab maintenance treatment in Japanese patients with Crohn's disease

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Background: Several studies have reported on the efficacy of combination therapy with infliximab and immunomodulators (IM) in pa-

tients with Crohn's disease (CD). Here, we investigated the efficacy of IM in long-term treatment with infliximab in Japanese patients with CD.

Methods: Retrospective data were collected from luminal CD patients treated with 5 mg/kg of infliximab for ≥ 14 weeks between January 2003 and December 2015 at two institutions. The efficacy of infliximab maintenance treatment was evaluated by the rate of sustained clinical benefit, which was estimated using the Kaplan–Meier method. Sustained clinical benefit was defined as the lack of treatment failure. Treatment failure was defined as the discontinuation of infliximab, dose escalation, or surgery for CD. Combination therapy with infliximab and IM was defined as the initiation of IM within 6 weeks from the first administration of infliximab and continuation until 14 weeks. Combination therapy was divided into IM naïve and IM exposed group. IM naïve and IM exposed group were defined as receiving IM treatment for less and more than 3 months prior to infliximab administration, respectively. Sustained clinical benefits of infliximab according to the type of IM treatment were investigated using the log-rank test.

Results: A total of 341 patients were included in this study. Of these, 243 patients received combination therapy. Of the 243 patients, 211 and 32 patients were administered azathioprine (AZA) and 6-mercaptopurine (6-MP), respectively. Of these, 83 and 126 patients were treated with 25 and 50 mg of AZA once a day, respectively. In addition, 23 patients were treated with 30 mg of 6-MP once a day. There were 190 patients in the IM naïve group and 53 patients in the IM exposed group. The 5 and 10-year cumulative sustained clinical benefit rates in all patients were 49% and 39%, respectively. Sustained clinical benefit rates were significantly higher in patients receiving a combination of infliximab and AZA than in those receiving infliximab monotherapy. Whereas, there was no significant difference in sustained clinical benefit rates between patients receiving a combination of infliximab and 6-MP and infliximab monotherapy. Patients receiving a combination of infliximab and AZA in IM naïve, but not IM exposed group achieved a significantly higher clinical benefit than those receiving infliximab monotherapy. Sustained clinical benefit in patients receiving a combination of infliximab and either 25 or 50 mg of AZA was significantly higher than that in patients treated with infliximab monotherapy.

Conclusions: Our data suggested that the combination of infliximab and low dose AZA (25 or 50 mg) as early as possible resulted in the better clinical outcome in Japanese patients with CD.

P565

Assessments of clinical efficacy and mucosal healing in ulcerative colitis patients undergoing granulomonocytapheresis at different treatment frequencies

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Background: Patients with active ulcerative colitis (UC) are known to have elevated myeloid lineage leucocytes including the CD14+CD16+ monocyte phenotype known to release tumour necrosis factor- α . Accordingly granulomonocytapheresis (GMA) with an Adacolumn has been applied to deplete inflammatory cytokine releasing leucocytes as a remission induction therapy. In general, patients who respond well continue responding and favour GMA over pharmacologics. However, published data indicate that patients with extensive deep ulcers and loss of the mucosal tissue at the affected sites may not respond well to GMA, while steroid naïve patients

respond well. We have focused on GMA frequency and long term efficacy as supported by endoscopic findings.

Methods: In a retrospective setting, and with interest on long term mucosal healing, we assessed the efficacy of the Adacolumn GMA in patients with active UC treated at different GMA frequencies in the past 10 years. In our data base, we found 99 corticosteroid naïve patients who had received GMA at one session per week (n=18, group 1), at 2 to 4 sessions per week (n=31, group 2) or daily (intensive) GMA (n=50, group 3). Each patient could have received up to 11 GMA sessions. Initial efficacy evaluations were undertaken within 10 days following the last GMA session. Clinical activity index (CAI) ≤ 4 meant remission, while Mayo 0 or 1 meant mucosal healing. The included patients had been followed for ≥ 12 months on maintenance mesalamine.

Results: The average baseline CAI in groups 1 to 3 were 7.9, 7.8, and 8.4, respectively; the number of GMA sessions were 9.1, 9.7 and 10.1 sessions, respectively; the GMA treatment periods were 55.1, 26.5 and 15.5 days, respectively. The mean CAI after the conclusion of GMA treatment courses were 2.5 ± 2.7 , 3.4 ± 3.1 and 3.5 ± 2.7 , respectively. The rates of mucosal healing were 76.9%, 60.0% and 61.8%, respectively. At 12 months, 40.0% in group 1, 57.1% in group 2 and 61.9% in group 3 had maintained mucosal healing. No GMA related serious adverse event was observed.

Conclusions: This efficacy evaluation undertaken in steroid naïve patients with active UC showed that for an equal number of GMA sessions, the clinical efficacy was not significantly affected by the frequency of GMA sessions, but the time to remission and the rate of mucosal healing at 12 months were significantly better for intensive GMA. However, the efficacy outcomes in our 99 patients are higher than reported for GMA in patients with severe UC refractory to the current pharmacologicals, reflecting the fact that GMA is more effective in steroid naïve patients who have mild or moderately active UC, but not so effective in patients with severe UC in whom drug therapy has failed.

P566

Frequency and type of drug-related side effects necessitating drug cessation in the Swiss inflammatory bowel disease cohort

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Background: Systematic analyses of drug-related side effects necessitating drug cessation in large cohorts of patients with inflammatory bowel disease (IBD) are lacking. We aimed to assess the frequency and type of drug-related side effects requiring drug cessation in patients included into the Swiss IBD Cohort (SIBDCS).

Methods: Data were retrieved from the datacenter of the SIBDCS,

into which IBD patients from all over Switzerland were enrolled starting in 2006. Eighty percent of patients were included in hospitals whereas 20% of IBD patients were recruited in private practice. The side effects to the following drug categories were analyzed: aminosalicylates, steroids, thiopurines, methotrexate, TNF-antagonists, and cyclosporine/tacrolimus.

Results: Of the total of 3,192 patients analyzed, 1,792 patients (56.1%), 1,322 patients (41.4%), and 78 patients (2.5%) had Crohn's disease (CD), ulcerative colitis (UC), and unclassified IBD (IBDU), respectively. Of these 3,192 patients, 2,129 (66.7%) presented with one or several drug-related side effects necessitating drug cessation. The remaining 1,009 patients (31.6%) did not experience this type of side effects. Median disease duration was not different between the group with and without IBD-drug-related side effects necessitating drug cessation (12 years, IQR 6–20 vs. 12 years, IQR 7–19, $p=0.675$). When all IBD-drug-related side-effects necessitating treatment cessation were examined, the frequencies attributed to various medications were as follows: 4.5% to steroids, 7.9% to 5-ASA, 13.5% to cyclosporine, 14.4% to adalimumab, 15.0% to certolizumab pegol, 19.8% to methotrexate, 20.6% to infliximab, 25.1% to azathioprine, and 30.1% to 6-mercaptopurine. A significant positive correlation between the number of concomitantly administered IBD drugs and the occurrence of side effects requiring drug cessation ($p<0.01$) was observed. Using logistic regression modeling, we identified UC diagnosis (OR 0.735, $p=0.017$), presence of extra-intestinal manifestations (OR 2.262, $p<0.001$), IBD-related surgery (OR 1.419, $p=0.006$), and the increasing number of concomitant IBD drugs (OR 2.007 [$p<0.001$] for 2 concomitant IBD drugs; OR 3.225 [$p<0.001$] for ≥ 3 concomitant IBD drugs) as factors that are associated with the occurrence of IBD drug-related adverse events that necessitated drug cessation.

Conclusions: Physicians treating patients should keep in mind that the number of concomitantly administered IBD drugs is one of the important risk factors for drug-related adverse events necessitating drug cessation.

P567

Cross-sectional study of the low serum concentrations of testosterone in IBD and the influence on disease activity

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Background: Sex differences in the incidence and progression of inflammatory bowel diseases (IBD) have been reported in observational studies. The effect of testosterone on the pathogenesis of IBD is unknown.

Methods: The aim was to assess the serum concentration of testosterone in IBD male patients, to describe the prevalence of low serum concentration of testosterone and to investigate the effect of testosterone on disease activity. The cohort consisted of 113 consecutive IBD male patients (66 CD and 47 UC) examined at a tertiary IBD centre. Clinical and demographic characteristics of every patient were recorded, i.e. age, duration of the disease, clinical behaviour, location of disease according to Montreal classification, IBD related surgeries, concomitant medications. We measured the morning serum concentration of testosterone, luteinising hormone, cortisol, ACTH, CRP, vitamin D in each patient. Disease activity was

assessed by Harvey-Bradshaw Index (HBI) in CD patients and by partial Mayo score in UC patients. The prevalence of low serum concentration of testosterone below the cut-offs 6nmol/l and 10nmol/l was assessed and risk factors analysed by univariate analysis.

Results: The median serum concentration of testosterone both in CD and UC male patients was 11nmol/l. The low serum concentration of testosterone with cut-offs ≤ 6.0 nmol/l and ≤ 10.0 nmol/l was noted in 4/113 (3.5%) IBD male patients (3 CD and 1UC) and in 38/113 (33.6%) (22CD and 16UC), respectively. We found significant negative correlation between age and testosterone in all patients ($r^2=0.067$, $p=0.006$) and between CRP and testosterone in CD males ($r^2=0.073$, $p=0.028$). No similar correlation was seen in UC patients. We did not observe any significant correlation between clinical activity although there was a trend towards significance in correlation of partial Mayo score and level serum concentration of testosterone in UC males ($r^2=0.076$, $p=0.061$). Patients who undergone appendectomy had significantly lower serum concentrations of testosterone in comparison to those who did not with median of 11.3 vs 8.4nmol/l ($p=0.005$).

Conclusions: The prevalence of low serum concentration of testosterone was observed in 3,5% (cut-off ≤ 6.0 nmol/l) and 33,6% (cut-off ≤ 10.0 nmol/l) of IBD male patients. Serum concentration of testosterone correlated with age in all IBD patients and CRP in CD patients.

P568

Does infliximab therapy increase incidence of tuberculosis in patients with inflammatory bowel disease in an endemic area: a nationwide study from China

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Background: An increasing number of patients with inflammatory bowel diseases (IBD) are being treated with infliximab in China and are at increased risk of activating tuberculosis infection. Real-world epidemiological data on tuberculosis infection in patients with IBD receiving infliximab are scarce in China, where tuberculosis is endemic. The aim of our study is to investigate the risk of tuberculosis in a large cohort of IBD patients treated with infliximab in China.

Methods: An observational study on all tuberculosis cases identified in IBD patients receiving infliximab was performed in 23 tertiary referral hospitals between 2009 and 2016 in China. Results of tuberculosis screening tests, which included interferon-gamma releasing assay (IGRA), tuberculin skin test (TST), chest X-ray, and computed tomography of the chest, prophylaxis against tuberculosis prior to infliximab therapy, and events of active tuberculosis infection after infliximab therapy were recorded and analyzed.

Results: 1233 IBD patients receiving infliximab were recruited with a median follow up of 13 months (interquartile range [IQR] 6–24). 98% of the patients underwent screening tests prior to infliximab therapy. Screening results suggested the proportion of Chinese IBD patients with latent tuberculosis infection (LTBI) prior to infliximab therapy is 7.22% (89/1233). Twelve cases of active tuberculosis infection occurred after infliximab therapy. The incidence of active tuberculosis infection in Chinese IBD patients receiving infliximab therapy is 746 per 100,000 person-years, which is 9 times higher than that of the general Chinese population (75 per 100,000 person-years). Among IBD patients with LTBI, the incidence of subsequent active tuberculosis after infliximab therapy is 8 times higher than pa-

tients without LTBI (5.62% [5/89] versus 0.61% [7/1144], $p < 0.01$). 97% of 89 LTBI patients and 30% of 1144 patients without LTBI received prophylaxis against tuberculosis. After prophylaxis, the incidence of tuberculosis infection didn't decrease in IBD patients without LTBI (0.57% [2/348] versus 0.62% [5/797], $p = 0.638$).

Conclusions: Infliximab therapy increased the incidence of tuberculosis in Chinese IBD patients. Routine prophylaxis may not reduce the risk of active tuberculosis infection in Chinese IBD patients without LTBI. Tuberculosis screening should be strongly recommended in Chinese IBD patients before initiating infliximab therapy.

P569

Sequential rescue treatments in steroid refractory ulcerative colitis: two-year follow-up

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Background: A medical intervention with sequential rescue treatments among patients with steroid refractory ulcerative colitis showed encouraging results, with lower adverse events (AE) risk than previously reported. Despite the potential risk, many patients like to have additional rescue therapies to avoid colectomy. Our recent study showed that a second or even third line rescue therapy in steroid-refractory UC patients might reduce the colectomy rate at one year. Still, it is unknown whether sequential therapies will only postpone colectomy and what percentage of patients will remain in a long-term remission.

Aim: To evaluate two-year outcome of the cohort of patients with refractory UC treated either with single or sequential rescue therapies.

Methods: The outcome after two years follow up of the cohort of 108 patients with steroid-refractory moderate to severe ulcerative colitis treated with a single or sequential rescue treatments with Infliximab (5mg/kg intravenously at week 0, 2, 6 and then every 8 weeks), Cyclosporine (iv CsA 2mg/kg/daily and then oral CsA 5mg/kg/daily) or Tacrolimus (0.05mg/kg divided in 2 doses, aiming for serum trough levels of 7–12 ng/mL) was retrospectively evaluated. The primary endpoint was two-year colectomy rate; the secondary endpoint was corticosteroid free remission rate.

Results: Out of 108 patients in the primary cohort, 103 patients (95%) were followed at least 2 years; 74/76 patients treated with single, 23/26 patients with double and all 6 patients on triple rescue treatment. Five patients were lost to follow up (FUP). Two-year colectomy rate was non-significantly increased to 25% (26/103) compared to 18% (19/108) after first year ($p = 0.121$, OR 1.69; 95% CI 0.87–3.30). During the 2nd year of FUP no new colectomy was observed among the group of patients with triple rescue treatments (3/6 after 1st year), while among the patients on the double rescue

treatments only 1 new colectomy was identified. Steroid free remission rate slightly decreased from 39% (42/108) after first year to 30% (31/103) [$p = 0.118$ OR 1.59 CI 0.89–2.86]. The AE rate in the 2nd year of follow up was 13.6% (14/103). Additionally, 14.5% (15/103) of patients were withdrawn from the last rescue agent during 2nd year of FUP.

Conclusions: Considering our results, it seems that second and third line rescue therapies in steroid refractory UC have prolonged beneficial effects in avoiding colectomy even two years after the induction. Still, further follow up and adverse effects analysis will be necessary for the estimation of future role of sequential rescue therapies in UC patients.

P570

Current status of the effectiveness of infliximab in patients with ulcerative colitis

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Background: Increasing numbers of patients are receiving biologics to treat ulcerative colitis (UC).

We prospectively studied treatment outcomes including measurement of serum infliximab (IFX) concentrations and the titers of antibodies to IFX (ATI).

Methods: The study group comprised 21 patients with UC who received induction therapy with IFX.

Disease activity was evaluated according to the Seo index (severe, ≥ 220 ; moderate, 150–219; and mild, 121–149). Treatment response defined remission ≤ 120 ; response < 150 or ≥ 70 lower than the value at the start of IFX. The remission and response patients were considered to have improved.

Endoscopic findings were evaluated using the Mayo endoscopic score (MES). MES of 0 was defined as mucosal healing.

Loss of response (LOR) was defined as the occurrence of flare-ups of symptoms after the induction of remission.

The following variables were studied: (1) improvement rates 14 and 54 weeks after starting IFX, (2) serum IFX concentrations and ATI rates at these times, (3) the mucosal healing rate at 54 weeks, (4) the rate of LOR and serum IFX concentrations at the time, (5) the rate of continuing treatment with IFX, and (6) the rate of surgery.

The rate of LOR, IFX continuation rate and surgery rate were calculated by the Kaplan-Meier method.

This study was approved by the ethics committee of our hospital (B13–156).

Results: (1) The Seo index at the start of IFX therapy was 207 ± 45 . The improvement rate was 62% at 14 weeks and 47% at 54 weeks. (2) The serum IFX concentration was 2.9 ± 2.3 $\mu\text{g/mL}$ in patients with improvement and 3.0 ± 2.2 $\mu\text{g/mL}$ in patients without improvement at 14 weeks (NS) and was 7.0 ± 4.4 $\mu\text{g/mL}$ in patients with improvement and 1.0 ± 0.4 $\mu\text{g/mL}$ in patients without improvement at 54 weeks ($p < 0.05$). The ATI rate was 5% and was found in a patient with improvement at 14 weeks.

(3) The MES of 0 at 54 weeks was 36%. The serum IFX concentration was 8.9 ± 2.7 $\mu\text{g/mL}$ in patients with an MES of 0 as compared with 1.3 ± 0.8 $\mu\text{g/mL}$ in patients with an MES of 2 or 3 ($p < 0.001$).

(4) The rate of LOR was 32% at 30 weeks and 46% at 54 weeks. The serum IFX concentration was 1.8 ± 1.9 $\mu\text{g/mL}$ at the onset of LOR. The final serum IFX concentration in patients who remained

in remission was 5.5 ± 4.5 $\mu\text{g/mL}$. These values differed significantly ($p < 0.05$).

(5) The IFX continuation rate was 86% at 14 weeks and 59% at 54 weeks.

(6) The surgery rate was 5% at 14 weeks and 15% at 54 weeks.

Conclusions: It was difficult to evaluate response to treatment at 14 weeks solely on the basis of the serum infliximab concentration and ATI.

Mucosal healing and LOR were related to the serum IFX concentration.

These variables can be indices at the time of treatment reassessment. Measurement of these variables is useful that therapy is performed efficiently.

P571

Can Crohn's colitis be cured by surgery?

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Background: Large bowel localization of Crohn's disease occurs in more than 60% of all patients. In approximately 50% of those patients small bowel localization coexists, while in the other half, colon is the only localization. Rectum is involved in about 40% of patients. At least 30% of patients with colonic Crohn' disease will require surgery during their lifetime. For patients with extensive colonic disease the first-choice surgical therapy consist in rectum sparing colectomy and ileorectal anastomosis.

In this study we evaluated the long-term outcome of patients with ileo-rectal anastomosis relatively to the disease localization prior to surgery.

Methods: We retrospectively went through clinical records of patients followed at our referral IBD center who underwent colectomy and ileo-rectal anastomosis for Crohn's colitis to evaluate if there were differences in relapse rate among patients with or without involvement of ileum and/or rectum.

Results: Between 1996 and 2016 86 patients underwent colectomy and ileo-rectal anastomosis for Crohn's colitis. We excluded from the study patients with perianal active disease, patients with subsequent diagnosis of ulcerative colitis and patients with less than five years follow-up.

Fifteen patients had no ileum or rectum involvement prior to surgery (group A); 19 had colon and rectum involvement (group B), 23 had colon and ileum involvement, but no rectal localization (group C); and 8 patients had both localization in ileum and rectum, as well as of the colon (group D). No one patient with ileum and rectum sparing colitis (group A) had disease relapse. 15 out 19 patients (79%) of group B had disease relapse after a median time of 2.1 years (0.5–7), mostly in the rectum (73%). 91% (21/23) of patients in group C experienced disease relapse (47% ileum, 19% rectum, 9% both sides) after an average of 3.2 years (0.5–9). 7 out of 8 patients of group D had a disease relapse (42% ileum, 42% rectum, 14% both) after a median time of 2.2 years (0.5–5). For groups B and C at least two thirds of patients required immunosuppressive therapy (thiopurines or anti-TNF α) to treat disease relapse, while in group D every patient with disease relapse needed anti-TNF α therapy. 3 patients of Group B (15%) and 2 patients of group D (25%) underwent permanent ileostomy.

Conclusions: Our data show that patients with Crohn's colitis with

rectum and ileum sparing who underwent colectomy with ileo-rectal anastomosis may represent a subgroup of patients in which Crohn's disease can be cured by surgery. Obviously this preliminary data should be confirmed by further studies.

P572

Medical therapies for stricturing Crohn's disease: efficacy and cross-sectional imaging predictors of therapeutic failure

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Background: Medical therapy efficacy remains controversial in stricturing Crohn's disease.

In the present study, we aimed to assess the long-term impact of medical therapies in stricturing CD and to identify both the clinical and radiological factors associated with long-term therapeutic failure in patients receiving medical treatments for stricturing CD. In addition, we aimed to assess the factors associated with short-term clinical response in stricturing CD.

Methods: In this retrospective study, therapeutic failure was defined as symptomatic stricture leading to surgical or endoscopic therapeutics, hospitalization, treatment discontinuation or additional therapy. The short-term clinical response was defined as clinical improvement based on obstructive pain intensity, associated signs such as nausea and vomiting or dietary restrictions assessed by two IBD physicians between week 12 and week 24. The 55 cross-sectional imaging examinations (33MRI, 22CT-scan) before starting medical therapy were analyzed independently by two radiologists.

Results: Overall, 84 patients were included in the study. Their characteristics at the time of inclusion are given in Table 1.

Among them, therapeutic failure rate within 60 months was 66.6%. In multivariate analysis, Crohn's disease diagnosis after 40 years-old (HR = 3.9 95% CI [1.37–11.2], $p=0.011$), small stricture luminal diameter (HR = 1.34 95% CI [1.01–1.80], $p=0.046$), increased stricture wall thickness (HR = 1.23 95% CI [1.04–1.46], $p=0.013$), and fistula with abscess (HR = 5.63 95% CI [1.64–19.35] $p=0.006$) were associated with therapeutic failure while anti-TNF combotherapy (HR = 0.17 95% CI [0.40–0.71], $p=0.015$) prevented it. Considering 108 therapeutic sequences, the short-term clinical response rate was 65.7%. In multivariate analysis, male gender (OR = 0.15 95% CI [0.03–0.64], $p=0.011$), fistula with abscess (OR = 0.09 95% CI [0.01–0.77], $p=0.028$) and comb sign (OR = 0.23 95% CI [0.005–0.97], $p=0.047$) were associated with short-term clinical failure.

Conclusions: Anti-TNF combotherapy seemed to be the best long-term therapeutic option in stricturing CD. Some morphological characteristics of the stenosis independent from the inflammation/fibrosis dichotomy as well as some factors reflecting inflammation and/or fibrosis retrieved from cross-sectional imaging are predictive of therapeutic failure in stricturing CD. Cross-sectional imaging especially MRI should be performed before starting medical therapy in CD

Table 1. Baseline characteristics and factors associated with therapeutic failure (univariate analysis) in a cohort of 84 patients receiving medical therapy for stricturing Crohn's disease

Crohn's disease patients	
n=84	
Age, mean (\pm SD), years	39 (\pm 15)
Disease duration at inclusion, mean (\pm SD), years	11.1 \pm 10.0
Male gender, n (%)	34 (40.5)
Tobaccouse, n (%)	
Active smokers	30 (35.7)
Previous intestinal resection, n (%)	33 (39.3)
Early Crohn	24 (28.6)
Familial history of IBD	9 (10.7)
Montreal Classification	
Age at diagnosis	
A1, n (%)	17 (20.5)
A2, n (%)	50 (60.2)
A3, n (%)	16 (19.3)
Disease location	
L1, n (%)	33 (39.3)
L2, n (%)	10 (11.9)
L3, n (%)	41 (48.8)
L4, n (%)	5 (5.9)
Behaviour	
B1, n (%)	0 (0)
B2, n (%)	55 (65.5)
B3, n (%)	29 (34.5)
Perianal lesions, n (%)	21 (25)
Concomitant therapy at inclusion	
Steroids, n (%)	43 (51.2)
Immuno suppressive therapy, n (%)	36 (42.9)
Anti-TNF, n (%)	41 (48.8)
Anti-TNF combotherapy, n (%)	22 (26.2)
Other therapies, n (%)	12 (13.2)
CDAI, mean (\pm SD)	213 \pm 84
CRP, mean (\pm SD)	43.4 \pm 62.7
Faecal Calprotectin, (μ g/g) median (\pm SD)	1046.9 \pm 700.2
Obstructive symptoms, n (%)	65 (77.4)
Occlusion, n (%)	14 (16.7)
Subocclusive episodes, n (%)	34 (40.4)
Obstructive symptoms duration at inclusion, months, median [IQR]	12.2 [0.7-50.6]
CDOS global (\pm SD)	2.6 (1.9)

with stenosis as it is very helpful to guide therapeutic decision-making.

P573

Impact of the duration of combination therapy on clinical and pharmacological efficacy of infliximab in inflammatory bowel diseases

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Background: Aims of the present study were to compare clinical outcomes and IFX pharmacokinetics between patients treated with IFX in monotherapy vs those in combination therapy with IS (azathioprine, methotrexate) for at least three months, and to isolate the most effective duration of this combination in terms of clinical and pharmacological outcomes.

Methods: All IBD patients treated with IFX from January 2012 to January 2016 were retrospectively included. Activity disease and TLI were measured before each IFX infusion, using clinical validated

scores (Crohn's disease: Harvey-bradshaw index; ulcerative colitis: Mayo clinic), and immunoassay (Theradiag®), respectively. A prior monotherapy with IS was not an exclusion criterion. Patients under combotherapy less than 14 weeks were excluded. An unfavorable pharmacokinetic was defined as a TLI < 1 μ g/mL during the follow-up period, regardless the presence or absence of antibodies anti-Infliximab. Kaplan Meier method and univariate Cox proportional hazard regression were performed to assess clinical relapse free survival and unfavorable IFX pharmacokinetics free survival.

Results: Of the 139 patients included (median age: 34 yrs, sex ratio M/F: 1/3; median follow-up: 40 months), 60 (43%) were under combination therapy during a median time of 11 months. There was no difference in terms of clinical characteristics at baseline between the two groups (mono- vs combotherapy with IFX). The median clinical relapse free survival was higher in the combination therapy group (>80 months) compared to the group of monotherapy (30 months; HR=2.73 CI 95% 1.62-4.6, p=0.001). However, none optimal duration of combination therapy was identified by univariate Cox regression (p>0.05 for 3, 6, 9, 12 and 18 months, as cut-off). There was no difference between naïve patients and those previously treated with IS in terms of clinical relapse free survival and unfavorable IFX pharmacokinetics free survival. By an independent analysis, the proportion of trimesters with TLI < 1 μ g/mL was lower under combination therapy (3.8%) compared to monotherapy (11.8%; (p<0.001).

Conclusions: This retrospective study confirmed that combination therapy with IFX and IS improves clinical free survival compared to monotherapy, in unselected IBD patients. However, there was no demonstrated benefit for the maintenance of this combination over three months, despite it seems that unfavourable IFX pharmacokinetic occurs when IS are withdrawn early. Prior treatment with IS appears not to impact on these outcomes.

P574

Limitations and difficulties in using anti-TNF-alpha agents in inflammatory bowel disease. A survey of the Italian Group for Inflammatory Bowel Disease (IG-IBD)

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Background: It is known that Italian physicians managing IBD use anti-TNFalpha agents in a less extensive way in comparison with European specialists. The aim of the study was to investigate the reasons and situations limiting the use of these medications.

Methods: A questionnaire was submitted to physicians attending the National Congress and the Residential Courses of IG-IBD.

Results: 280 physicians (156 men) completed the questionnaire. Mean age \pm SD was 44.4 \pm 10.7 years; 95 (33.9%) were working in Academic hospitals. Behavior about anti-TNF use (49, 17.5% did not answer this question) is: 176 (62.9%) use anti-TNF every time is needed; 29 (10.4%) have limited budget and are not able to treat all the patients needing the drug, 5 (1.8%) can not to use the drug,

2 (0.7%) do not use anti-TNFalpha. The most important limitations in using anti-TNFalpha (55 did not answer this question, 19.6%) are: fear of side effects (88, 31.4%), costs (86, 30.7%), administrative and/or bureaucratic limitations (18, 6.4%), lacking of dedicated staff (14, 5.0%), lacking of solid scientific data (5, 1.8%), inefficacy (4, 1.4%), fear of poor compliance (3, 1.1%), other (7, 2.5%). The most feared side effect (48 did not answer this question, 17.1%) is: opportunistic infection (106, 37.9%), neoplasm (59, 21.1%), allergic reactions (29, 10.4%), TB reactivation (17, 6.1%), onset of autoimmune disease (17, 6.1%), other (4, 1.4%). On a 5-point Likert scale, the less satisfying features of anti-TNFalpha were: costs (2.2±1.1), easy prescription (2.7±1.1), easy administration (2.9±1.1).

Conclusions: Practical and cultural factors appear to be a limitation in prescribing anti-TNF alpha agents by Italian physicians. Improvement of logistics and knowledge is a must to allow the best management of IBD patients.

P575

AZA-related toxicity isn't aggravated by concomitant drugs in IBD patients

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Background: Thiopurine-methyltransferase (TPMT) polymorphisms have been investigated for decades, notably after the toxicity of azathioprine (AZA), a commonly used drug in the treatment of inflammatory bowel diseases (IBD), was recognized. Other genes have also been accused of AZA-related side effects, as well as concomitant therapy. The aim of our study was to investigate a relationship between the most common TPMT polymorphisms, AZA side-effects and concomitant therapy that is regularly applied in IBD, in a cohort of Croatian IBD patients.

Methods: The most prevalent TPMT-gene polymorphisms (TPMT*2, *3A, *3C) were investigated using validated Real-time PCR method, TaqMan[®] Drug Metabolism Genotyping Assays. The use of azathioprine, its side effect and the use of concomitant therapy (aminosalicylates, corticosteroids and anti-TNF) were assessed retrospectively, using patients' medical records. The statistical package "R" was used for the analysis. A statistical significance was set at p<0.5.

Results: 451 IBD patients were included in the study (48.7% female pts, 51.2% male pts; 66.51% MC pts, 33.48% UC pts). None of the patients was homozygous for any of the investigated TPMT polymorphism. 95.3% of patients had a wild-type gene, 0.4%, 3.3% and 0.9% of patients were heterozygous for TPMT*2, TPMT*3A and TPMT *3C, respectively. 58.3% patients received azathioprine therapy. 61.1%, 28.6% and 2.2% patients concomitantly received aminosalicylates, corticosteroids and anti-TNF therapy, respectively. 14.2% patients developed side-effects (13.68% myelotoxicity 7.6% hepatotoxicity and 8.3% pancreatic toxicity). In a regression model, with AZA-related side-effects as outcome vari-

able and TPMT genotype, diagnosis, gender, concomitant aminosalicylates, corticosteroids and anti-TNF therapy as predictive variables, only TPMT genotype was statistically significantly related to AZA side-effects (p=0.0372). Out of three investigated polymorphisms, in the post-hoc analysis only TPMT*3A appeared statistically significantly related to AZA side-effects (p=0.0036).

Conclusions: AZA-related toxicity is related to polymorphic versions of TPMT gene in a Croatian IBD cohort; statistically significantly to TPMT*3A allelic variant. We found no influence of concomitant therapy – either aminosalicylate, corticosteroid or anti-TNF – on AZA-related toxicity.

P576

Could the hyperbaric oxygen therapy be an effective adjuvant therapy for fistulising Crohn's disease?

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Background: Hyperbaric oxygen therapy (HBOT) is a treatment modality utilising 100% oxygen in a hyperbaric chamber, under increased pressure conditions. Blood hyperoxygenation provides better oxygen penetration into the tissues in accordance with the laws of physics [1], thereby reducing the inflammatory response by reducing the adhesion of leukocytes to the vascular endothelium of damaged tissues, reducing the production of Pro-Inflammatory Cytokines, stimulating angiogenesis, improving metabolism and antibacterial and antifungal action [2]. The aim of our observation is to prove that HBOT therapy may be an effective adjuvant therapy for fistulising Crohn's Disease (CD).

Methods: Observations were made in 7 patients with active perianal fistulising CD. Three patients (the first group) were in the course of biological therapy and immunomodulatory therapy, while the other four (the second group) were administered only standard immunomodulatory therapy. Both groups have undergone HBOT according to the following protocol: 30 session, 90 minutes each, with pressure of 2.5 standard atmosphere. Analysis of clinical disease activity was performed by means of CDAI scale, biomarkers (fecal calprotectin (FC), blood CRP) and imaging studies: endoscopy and magnetic resonance imaging (MRI) of the pelvis with contrast. Observational study was divided into 4 stages: stage I – prior to treatment, stage II-HBOT therapy, stage III-after completing the HBOT treatment, stage IV – 6 weeks after HBOT.

Regression of lesions confirmed in clinical evaluation and imaging studies was assigned as the end point.

Results: Analysis of the group of patients showed clinical improve-

Abstract P576 – Table 1

Patient No.	Age/Sex	CDAI		CRP (mg/l)		Fecal calprotectin (µg/g)		MRI	
		E I	E IV	E I	E IV	E I	E IV	E I	E IV
1	26/M	71	31	15.4	37.3	119	179	Active	Active/Regression
2*	40/W	179	110	1	1.1	>1800	964	Active	Active
3*	31/M	40	78	1	< 1.6	227	63	Active	Active/Regression
4	36/W	60	94	4	4	880	121	Active	Active/Regression
5	21/W	169	113	19.9	15.7	614	275	Active	Active
6*	28/M	352	78	51.8	1.4	831	429	Active	active/Regression
7	19/M	340	97	5.4	7.3	831	>1000	Active	Active/Regression

ment in CDAI in 2 out of 3 patients from the first group and in 3 out of 4 from the second group. Levels of FC decreased in all 3 patients from the first group and in 3 out of 4 from the second group, while the level of blood CRP decreased in one patient from the first group and one patient from the second group. Imaging studies (MRI, endoscopy) showed regression of lesions in 2 out of 3 patients from the first group and in 3 out of 4 patients from the the second group. The summary of results is presented in Table 1.

Conclusions: On the basis of the results recorded in both groups of assessed patients we can conclude that HBOT may be an effective way to support the treatment of CD by improving clinical improvement and significantly reducing the occurrence of inflammatory lesions in the imaging studies.

This is a preliminary report, as the study is ongoing.

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P577

“Treat to target” recommendations in ulcerative colitis in practice: clinician perceptions and potential barriers

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Background: A “Treat to Target” (T2T) approach has been proposed for ulcerative colitis (UC), with a target of combined clinical and endoscopic remission. This has yet to be evaluated in real-world care.

Methods: A multicentre, retrospective, cross-sectional review of patients with UC attending outpatient services in South Australia be-

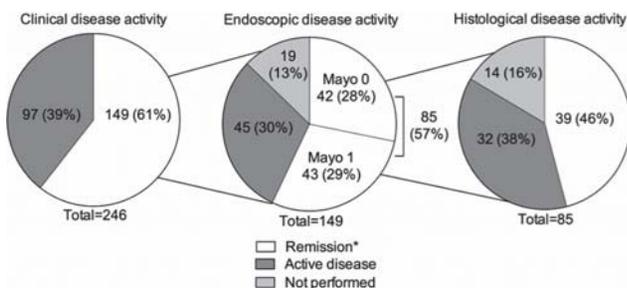


Figure 1. UC treatment targets achieved in real-world practice. *Clinical remission: normal stool frequency and absence of rectal bleeding. Endoscopic remission: Mayo endoscopic sub-scores of ≤1. Histological remission: Truelove and Richards Index remission.

tween Jul 2013 and Nov 2015 was conducted. Clinician assessment of disease activity and objective assessment (endoscopy, histology, and/or biomarkers) were recorded. An on-line survey of local Gastroenterologists evaluated their perceptions of T2T in UC. Multivariate logistic regression, Fisher’s exact tests and Kappa statistics were performed.

Results: Of 246 patients with UC, 61% were documented to be in clinical remission (normal bowel habit and no rectal bleeding), 35% documented to be in clinical and endoscopic remission (Mayo endoscopic sub-score ≤1), and 16% documented to be in concordant clinical, endoscopic and histological (Truelove and Richards’ Index) remission.

Table 1. UC treatment targets achieved in real-world practice. Overall proportions of patients in UC cohort (n=246) documented to attaining remission

Treatment target	n (% overall)
Clinical remission (Normal stool frequency and absence of PR bleeding)	149 (60.6)
Clinical remission + Endoscopic remission (Mayo endoscopic sub-score of ≤1)	85 (34.6)
	42 (17.1)
Clinical remission + Endoscopic remission + Histological remission (Truelove and Richards’ Index remission)	39 (15.9)

Rather than disease-related factors (extent/activity), clinician-related factors dominated outcome. The hospital location at which care was delivered and choice of therapy predicted combined clinical and endoscopic remission (OR 3.6, 95% CI 1.6–8.7, p<0.001; OR 3.3, 95% CI 1.1–12.5, p=0.04, respectively)

Table 2. Clinical factors associated with documentation of combined clinical and endoscopic remission. Logistic regression analyses, n=218 (endoscopy during follow-up). *p<0.05 statistical significance; ^Any therapy analysed in a separate model

Variable	OR	95% CI	p value	
Age	1.0	0.9-1.0	0.81	
Gender (male)	0.8	0.5-1.6	0.61	
Disease extent (E2/E1 vs. E3)	1.4	0.5-3.7	0.69	
Age of diagnosis of UC	1.0	0.3-3.6	0.99	
Disease duration	1.0	0.9-1.0	0.07	
Compliance with therapy and/or appointments	1.2	0.5-3.0	0.63	
Therapy	Any therapy^	3.3	1.1-12.5	0.04*
	5-aminosalicylic acid alone	3.5	1.1-13.3	0.04*
	Immunosuppressant therapy	4.8	1.3-20.4	0.02*
	Biologic therapy	2.3	0.3-14.8	0.39
	Oral prednisolone	0.6	0.1-3.3	0.61
Consultant vs. Registrar OPD review	0.9	0.4-1.8	0.72	
OPD Hospital	Hospital 1 (intercept)		< 0.001*	
	Hospital 2	3.6	1.6-8.7	
	Hospital 3	0.4	0.1-1.3	

Clinicians used C-reactive protein (CRP) more often than endoscopy as a biomarker for disease activity (75% vs 47%, p<0.001), despite observed random discordance between CRP and endoscopy (kappa 0.13, 95% CI 0.0–0.27). In the survey, 45/61 Gastroenterologists

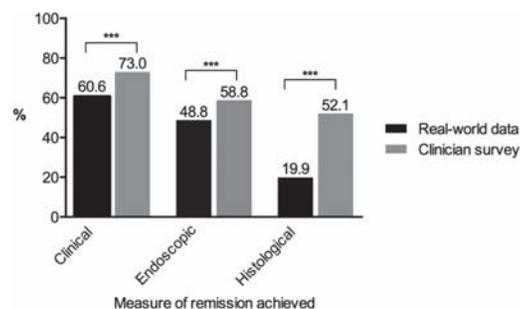


Figure 2. Clinician reported achievement of treatment targets in UC vs. real world data. Actual vs. expected proportions compared using a Fisher’s exact test. ***p value ≤0.001.

responded, with significant disparity between clinician estimates of targets achieved in practice and real-world data ($p < 0.001$ for clinical and endoscopic remission)

Conclusions: Most patients with UC do not achieve composite clinical and endoscopic remission in real-world practice. Clinicians overestimate their achievements and practice behaviour is a barrier to achieving stipulated targets.

P578

Evolution of Crohn's disease treatment in clinical practice: a 25 year single centre cohort study

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Background: The use of biologic agents, particularly anti-tumour necrosis factor (TNF) agents, is well established in Crohn's disease (CD). Historically, biologics were reserved for patients at surgical "risk". However, therapeutic goals have continued to evolve since their introduction from clinical to endoscopic remission and, subsequently, histological remission. The aim of this study was to assess changes in medical and surgical therapies for Crohn's disease over the past 25 years with special reference to biologic use and smoking.

Methods: Data were extracted from a prospectively maintained university hospital IBD database. We divided our population into 3 groups according to diagnosis date, 1) "Pre-biologic" cohort (1990–2002) (n=550), 2) "Early biologic" cohort (2003–2008) (n=308) and, 3) "Established biologic" cohort (2009–2015) (n=250).

Results: 1,107 patients were included in the study. 554 patients underwent their first major surgery during the follow-up period, 332 (60.4%) in cohort 1 (1990–2002), 174 (56.5%) in cohort 2 (2003–2008), and 48 (19.2%) in cohort 3 (2009–2015). The risk of first major surgery decreased over calendar time from cohort 1 to cohort 3 ($p < 0.001$, see Figure 1). The 1- and 5-year cumulative major surgical risk was 24.8% and 44.8% in cohort 1, 21.5% and 39.9% in cohort 2, and 14.3% and 22.1% in cohort 3. The cumulative probability of biologic use increased from cohort 1 to 3, with a 1 and 5-year cumulative risk of biologic use of 1.8% and 6.3% in cohort 1, 4.9% and 10.7% in cohort 2 to and 21.5% and 49.8% in cohort 3 ($p < 0.001$). The 5-year cumulative risk of either first major surgery or biologic use in cohort 1, 2 and 3 was 48.3% and 46.9% and 61.3% ($p = 0.003$). During the study period, smoking at diagnosis decreased from 38% in cohort 1 to 22% in cohort 3 ($p < 0.001$).

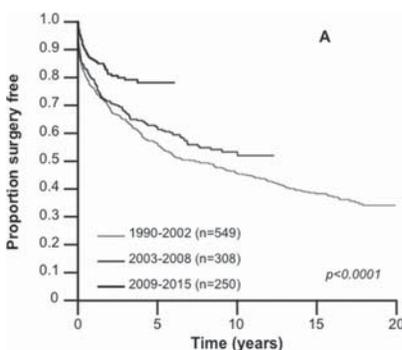


Figure 1

Conclusions: The large decline in major surgery in recently diagnosed Crohn's disease patients is mirrored by a substantial increase in biologic use and a decrease in smoking over the same period. Contin-

uous monitoring of therapeutic and social trends in clinical practice indicates substantial shifts in medical and surgical therapies and provides valuable data for service providers when planning future health care needs.

P579

Complete disease resolution after allogeneic hematopoietic stem cell transplantation in children with very early onset inflammatory disease and no identified monogenic mutation

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Background: Hematopoietic Stem Cell Transplantation (HSCT) may be curative in very early onset inflammatory bowel disease (IBD) when a monogenic defect is found. However, experience in paediatric patients without demonstrated underlying genetic defect is scarce. We present 4 children with severe IBD and unproven underlying monogenic disease who underwent reduced intensity conditioning HSCT.

Methods: Patient 1: A 3-year-old boy, born to consanguineous parents, presented with growth failure and chronic diarrhoea, investigations confirmed Crohn's disease (CD). He developed structuring gut disease, underwent colectomy and multiple ileal resections. He failed medical treatment including Infliximab and Basiliximab and became total parenteral nutrition (PN) dependent. He received HSCT from a matched family donor in 2008 at the age of 4. Patient 2: A 2-year-old girl presented with bloody diarrhoea. Histology confirmed unclassified IBD and she failed immunosuppressors and infliximab. At the age of 8 she developed a myelodysplastic syndrome and underwent a matched related donor HSCT for her hematologic condition in 2011. Patient 3: A 4-year-old boy born to non-consanguineous parents was found to have CD. He was refractory to standard medication, at age 6 he underwent colectomy and did not benefit from infliximab or adalimumab. He developed severe pyoderma gangrenosum. In 2013, at the age of 8 he received HSCT from a fully matched unrelated donor. Patient 4: A girl born to non-consanguineous parents had bloody diarrhoea and malnutrition at the age of 3. She had a paenteric granulomatous gut disease which did not respond to immunosuppressors and failed infliximab, adalimumab and sirolimus. She underwent a mismatched unrelated donor HSCT in 2014 when she was 9 years old.

Results: Post BMT. Patient 1: One year post HSCT, he was asymptomatic, started to thrive and was weaned off PN. He has been in clinical and histological remission to date. Patient 2: After 7 months, bone marrow was in remission and colitis had completely resolved. She remains disease-free until date. Patient 3: After 3 months, pyoderma gangrenosum healed. He achieved sustained remission after one year and until date. Patient 4: One year post HSCT, she had developed a chronic skin graft versus host disease but her gut disease went into remission which sustained until now.

Conclusions: This is the first report of paediatric HSCT for refractory early onset IBD without identifiable monogenic disorder. Our patients went into sustained remission after HSCT having failed all medical treatment before that. Our cases illustrate that HSCT may still be curative to some selected patients with early onset IBD who are refractory to medical treatment. Larger studies are needed to support this.

P580 Prognostic factors, effectiveness and safety of endoscopic balloon dilatation for *de novo* and anastomotic strictures in Crohn's disease – a multicenter “real life” study

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Background: Crohn's disease (CD) is a chronic inflammatory disease which is frequently complicated by obstructive symptoms secondary to development of intestinal strictures. The aim of this “real life” study was to assess the effectiveness, safety and outcome of endoscopic balloon dilatation (EBD) in *de novo* vs. anastomotic stenoses. **Methods:** Data of 144 endoscopic balloon dilatations in 63 CD patients were retrospectively analyzed. Technical success rate was defined as the ability of endoscope to traverse the stenosis after dilatation. Long-term clinical success rate was claimed if a patient remained asymptomatic and did not require surgery or further endoscopic dilatation following the technical success.

Results: 63.2% of strictures were *de novo* and 36.8% anastomotic. The elapsed time between diagnosis and the first balloon dilatation was 9.5 (0–35) years. 78.5% of dilatations were successful over a short-term period without serious complications. 44.4% of patients showed that endoscopic balloon dilatation is effective over a long-term period. Long-term success rate was 29.2% in the *de novo* group and 68.2% in the anastomotic group ($p=0.02$); moreover, less patients needed surgery in the anastomotic group (*de novo* group: 20.8% vs. anastomotic group: 9.1%; $p=0.07$). Biological therapy before or after dilatation, immunomodulatory therapy and the time between the diagnosis and the first dilatation had no influence on long-term effectiveness. Thirteen subjects required surgery due to strictures after balloon dilatation.

Conclusions: The results of this study highlight that endoscopic balloon dilatation is an effective therapy of short strictures in CD with low complication rate. Using this endoscopic method we can avoid surgical interventions in most of the cases. EBD of anastomotic strictures showed better outcome than that of *de novo* strictures.

P581 Highly purified eicosapentaenoic acid, as free fatty acid, reduces fecal calprotectin levels and prevents clinical relapse in ulcerative colitis patients: a double-blind, randomized, placebo controlled trial

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Background: The prevention of clinical relapse represents the major outcome in the treatment of ulcerative colitis (UC) patients. High fecal calprotectin levels indicate mucosal inflammation and have been shown to predict clinical relapse in many groups of UC patients. Epidemiological studies suggest that n-3 polyunsaturated fatty acids protect against the development of UC. Eicosapentaenoic acid, the major component of n-3 fish oil, has shown to have anti-

inflammatory and chemopreventive properties. Aim of this study is to define the effectiveness of highly purified eicosapentaenoic acid as free-fatty acid (EPA-FFA) in reducing fecal calprotectin levels and preventing recurrence in a group of asymptomatic UC patients at risk of clinical relapse, defined as fecal calprotectin level $\geq 150 \mu\text{g/g}$.

Methods: This is a double-blind, randomized, placebo-controlled study. Sixty UC patients with fecal calprotectin level $\geq 150 \mu\text{g/g}$ and Mayo endoscopic subscore ≤ 1 , in stable therapy for at least the 3 previous months, were randomized 1:1 to receive either EPA-FFA (500 mg sustained-release capsules, 2 bid) or placebo (500 mg sustained-release capsules of capric and caprylic acids, 2 bid) for a 6 month period. Fecal calprotectin levels, clinical and laboratory assessments have been performed at baseline, 3 and 6 months or at the time of clinical relapse, which has been defined as the occurrence of symptoms accompanied by an increase in the partial Mayo score > 2 and/or requiring a change in therapy. Patients who relapsed were referred for endoscopic evaluation.

Results: Cohort groups did not differ in clinical and demographic characteristics. Fecal calprotectin levels significantly decreased in the EPA-FFA group in comparison to the placebo group ($p=0.004$). At intention to treat analysis, 23.3% of patients in the EPA-FFA group and 50% of patients in the placebo group experienced a clinical relapse during the 6 months of follow up ($\chi^2 p=0.03$). At binary logistic regression analysis EPA-FFA treatment was the only factor affecting the number of patients who relapsed (HR 0.30, 95% CI 0.10–0.92, $p=0.03$). The cumulative 3 and 6 month relapse-free survival (RFS) was 86.7 and 76.7%, respectively, in the EPA-FFA group, compared to 80% and 50%, respectively, in the placebo group (Log-Rank test $p=0.04$) (Figure 1). Both treatments were safe and well tolerated, with no major side effects.

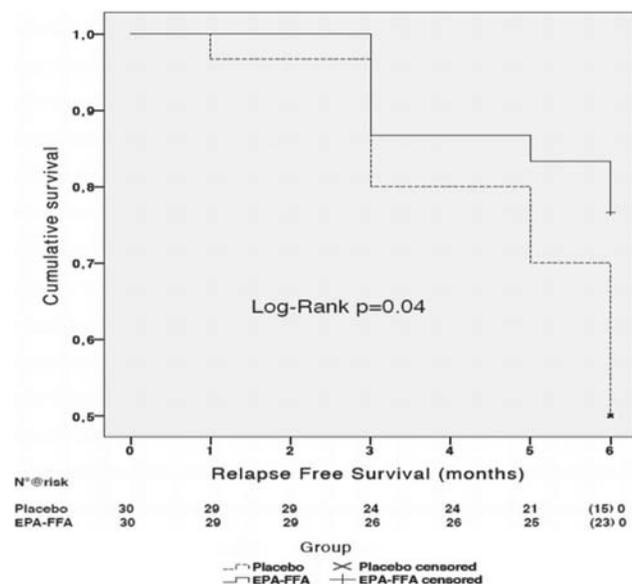


Figure 1. Kaplan-Meier life-table curves for patients remaining in clinical remission.

Conclusions: EPA-FFA decreases fecal calprotectin levels and is a safe and promising treatment to maintain symptom-free remission in UC patients.

P582
The pharmacoeconomic impact of biosimilar infliximab (CT-P13) in Europe from January 2015 to June 2016

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Background: CT-P13, a biosimilar of infliximab, has been approved by the US FDA and the European Medicines Agency. CT-P13 is offered at a lower price than the infliximab reference product (RP), therefore its use could reduce the economic burden associated with biologic therapy and increase access to treatment. This study analysed the real-world pharmacoeconomic effects of CT-P13 use in 5 European countries from 2015 to the end of the second quarter (Q2) of 2016. **Methods:** Surveys were conducted by IMS Health in France, Germany, Spain, Italy and UK to evaluate market share of CT-P13. Public prices for CT-P13 and RP in France, Spain, Italy and UK were used to evaluate costs. In Germany, prices were calculated using IMS Health sales data. Total cost savings were calculated as (Number of CT-P13 vials sold) x (RP price – CT-P13 price). The number of additional patients able to access biologic therapy was calculated as (Number of assessable vials[†]) x (100/3.75^{††})/365, where [†] was defined as (Cost saving in each country)/(CT-P13 price in each country), and ^{††} was the infliximab index from the WHO’s Anatomical Therapeutic Chemical (ATC) classification system with defined daily dose (DDD) (i.e. ATC/DDD).

Results: Market share of CT-P13 in the first quarter (Q1) of 2015 in France, Germany, Spain, Italy and UK was 0, 2.0, 4.4, 0.3 and 0.1%, respectively. By the end of Q2 2016 this had risen to 19.6, 25.3, 36.8, 55.2 and 72.6%, respectively (Figure 1).

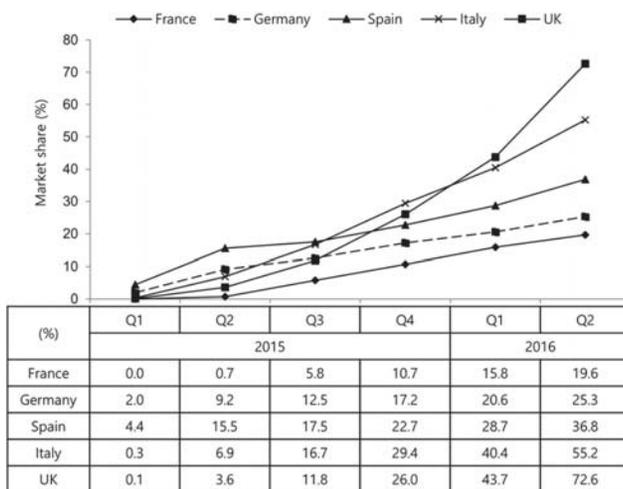


Figure 1. Market share (%)* of CT-P13 in 5 European countries from 2015 to the end of Q2 2016. *Market share (%) for CT-P13 = (CT-P13 vials sold/RP vials sold) x 100.

From 2015 to the first half of 2016, total cost savings associated with CT-P13 use in Germany, Spain, Italy and UK were €2,791,405, 12,233,004, 9,958,223 and 7,453,488, respectively. Public prices for CT-P13 and RP were the same in France; therefore, there were no cost savings. Use of CT-P13 in place of RP could enable an additional 369, 2222, 1699, or 1138 patients per year to access biologic therapy in Germany, Spain, Italy and UK, respectively.

Conclusions: In 4 of the 5 European countries in this study, use of CT-P13 instead of RP led to real-world cost savings. The lower cost of CT-P13 has ensured this biosimilar has rapidly entered into use, while the market share of RP has decreased. Even in France, where

the price of CT-P13 and RP is the same, use of the biosimilar has gradually increased. Competition between CT-P13 and RP may drive down costs of both. It is anticipated that as the market share of CT-P13 increases, the economic burden in each country will decrease, increasing access to biologic therapy.

P583
Trends in endoscopy management after surgery in a national cohort of Spanish Crohn’s disease patients. Results from PRACTICROHN study

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Background: Recurrence of Crohn disease (CD) after an ileo-colonic resection is predicted by the severity of endoscopic lesions during the first year after resection, hence guidelines recommend every patient to undergo endoscopy during the first year after surgery. The aim of our study was to describe the management and results of endoscopy after surgery in a population of CD patients between 2007 and 2010. **Methods:** PRACTICROHN was a study that included patients aged ≥18 years-old from 26 Spanish hospitals who underwent CD-related ileocolonic or ileorectal resection with ileocolonic or ileorectal anastomosis between January 2007 and December 2010. Clinical data was retrospectively collected from clinical charts during 5 years follow-up after surgery. Endoscopies were analyzed according to prophylactic treatment prescribed, year of surgery and hospital size. Categorical variables were compared with the χ^2 test or Fisher’s exact test Kaplan-Meier method was used to assess time to clinical recurrence and a log-ranktest to obtain statistical significance.

Results: 314 patients were analyzed (mean age 40 years [SD 13], 48% men). Of these, 52 (16.6%) had suffered more than one resection before the index surgery. In 143 (46.3%) a colonoscopy was performed during the first year after surgery. In 2007, only 24/75 patients (33%) underwent endoscopy in the first year, while in 2010 endoscopy was performed in 47/79 (59.5%) p=0.017 (Fig. 1).

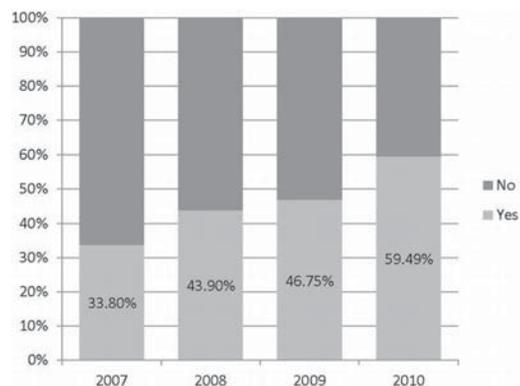


Figure 1. Frequency (%) of endoscopies in the first year by year of surgery.

Table 1

		Prophylactic treatment		p
		Yes	No	
Rutgeerts score	0i	54 (37.24)	15 (20.83)	0.005
	1i	18 (12.41)	11 (15.28)	
	2i	40 (27.59)	16 (22.22)	
	3i	12 (8.28)	18 (25.00)	
	4i	21 (14.48)	12 (16.67)	

During first year after surgery, 22 (7%) patients presented with endoscopic recurrence without symptoms. Along the five years follow-up 222 patients underwent colonoscopy. Rutgeerts score was ≥ 2 in 122 patients (55%). Rutgeerts score in patients that received prophylactic treatment was significantly lower than in patients without prophylaxis (Table 1).

The size of the hospital did not influence the percentage of endoscopies performed, being similar in hospitals <500 beds, between 500 and 900 and in hospitals with more than 900 beds.

Conclusions: From 2007 to 2010 there was a trend towards performing significantly more endoscopies after surgery in CD patients, as recommended by guidelines.

The number of endoscopic recurrence without symptoms in our study reinforces the importance of performing colonoscopies in high risk CD patients.

P584

A role for therapeutic drug-monitoring during infliximab induction treatment in inflammatory bowel disease?

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Background: Primary non-response (PNR) to infliximab (IFX) has been reported in up to one third of patients with inflammatory bowel disease (IBD) and represents a major therapeutic challenge. This study aimed to assess if IFX trough levels during induction therapy differed between patients with and without PNR to IFX and to calculate therapeutic thresholds.

Methods: Retrospective cohort study including all 166 IFX-naïve IBD patients (Crohn's disease (CD) n=93; ulcerative colitis (UC) n=72) who had received IFX induction therapy (5 mg/kg at weeks 0, 2 and 6) at a tertiary center since 2009. Corresponding to each infusion time point during induction therapy (weeks 2 and 6) and just after induction therapy (week 14) IFX trough levels were measured in a total of 322 blood samples using a validated automated immunofluorometric assay. Clinical response was defined as a reduction of >3 points in clinical scores from baseline (Harvey-Bradshaw Index or Partial Mayo Score) and was assessed at week 14. PNR was defined as no clinical improvement during IFX induction therapy resulting in discontinuation of IFX treatment.

Results: 18 patients (11%) (UC n=7; CD n=11) were classified as having PNR, whereas 148 (89%) responded to IFX induction therapy and were classified as responders. Patients with PNR had significantly lower IFX trough levels compared to responders at week 2 ($p<0.05$): Mean (SD) 17.2 (8.6) vs. 22.7 (8.1) $\mu\text{g/mL}$. The differ-

ence between the two groups was even more pronounced at week 6 ($p<0.05$): Median (IQR) 8.4 (4.3–16.4) and mean (SD) 17.9 (10.2) $\mu\text{g/mL}$, respectively. IFX cut-off values of 22.9 $\mu\text{g/mL}$ (area under the ROC curve (AUC) = 0.667, sensitivity=51%, specificity=80%) at week 2 ($p<0.05$) and 11.8 $\mu\text{g/mL}$ (AUC = 0.707, sensitivity = 72%, specificity = 77%) at week 6 ($p<0.05$) were associated with an overall clinical response to the induction therapy. In 8 patients with PNR, who had blood samples available also at week 14, IFX trough levels were compared to corresponding values from responders (n=58). Also at this time point IFX trough levels were significantly lower in patients with PNR compared to responders to the preceding IFX induction therapy (median (IQR) 0.5 (0.1–3.4) vs. 5.6 (3.0–10.0) $\mu\text{g/mL}$, $p<0.01$). An IFX cut-off value of 1.4 $\mu\text{g/mL}$ (AUC = 0.851, sensitivity = 91%, specificity = 75%) was associated with an overall clinical response ($p<0.01$).

Conclusions: IBD patients with PNR to IFX treatment have less circulating IFX than responders throughout the induction phase. This indicates a need for early dose intensification which is likely due to a high inflammatory load. Therapeutic drug monitoring may have value also during the IFX induction phase.

P585

Infliximab in moderate to severe ulcerative colitis: comparison between scheduled treatment strategy and bridge strategy

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Background: Ulcerative colitis (UC) is a potentially severe disease that carries an increased risk of complications and colectomy. Immunosuppressant and biological therapies are relevant tools for complex patients. The ACCENT study showed that in Crohn's disease (CD) scheduled infliximab (IFX) infusions vs. episodic are associated with greater efficacy. In UC, historical difficulties of economic access had conditioned to our IBD center, to use IFX in moderate to severe UC as a bridge to thiopurines in pts 6mp/aza naïve. In UC, the mentioned strategy was insufficiently compared with a regimen of scheduled IFX treatment, that currently we use. Aims: to compare (retrospectively) in moderate to severe UC the results of induction with IFX (in thiopurine naïve pts) continuing with 6mp/aza maintenance vs. similar induction followed by scheduled IFX maintenance strategy.

Methods: We included a cohort of moderate to severe UC treated with IFX in an IBD center (2006 to 2015) comparing results between IFX bridge followed by thiopurines (re-induction when available for moderate to severe relapse) vs. scheduled IFX (induction 0, 2, 6 wks and 8 wks' interval infusions maintenance). Optimization (by frequency of intervals) were allowed in both modalities. Comparisons: Kaplan Meier/Log rank test: a) Cumulative prevalence of colectomy, b) survival times relapse free, c) survival times corticosteroid free.

Results: We identified 135 UC (M 60, F 75, Age (mean \pm SD) 35.9 \pm 13.2, UC duration 5.8 \pm 5.9 yrs, Extent: extensive 58.5%, Left-sided 41.5%, Activity: severe 78.5%, moderate 21.5%, mean Mayo sc. 10.1 \pm 1.8. Primary no responders at week 12 (n 25; 18.5%) were not considered in maintenance comparisons, performed in 110/135 pts (follow-up 37.5 \pm 24.0 months) Groups: IFX bridge (n=51) and scheduled IFX (n 59) were not different in extent, age, UC duration, Mayo sc. Cumulative prevalence of colectomy was significantly

lower in the scheduled strategy (HR: 6.8805, 95% CI 1.7207 to 27.5133, $p=0.0349$), as well as survival times free of relapse (HR 3.1026, 95% CI 1.8368 to 5.2405, $p<0.0001$) and free of corticosteroids (HR 2.6057, 95% CI 1.5516 to 4.3757, $p=0.0003$). A proportion of UC significantly higher within the re-induced pts (IFX bridge) required a shift of biological drug compared with the scheduled strategy ($p=0.016$, Fisher), despite of similar rates of optimization. Infusion reactions needing definitive IFX suspension were more frequent as a tended ($p=0.06$) in re-induced pts.

Conclusions: similarly to was described for CD pts, in the CU, the scheduled IFX treatment strategy regimen, after a moderate-severe outbreak, seem to be associated with better long-term outcome regarding colectomy requirement, relapses, and need for corticosteroids, compared with a bridge IFX strategy followed by thiopurines.

P586

A novel approach to the implementation of biosimilar infliximab CT-P13 for the treatment of IBD utilising therapeutic drug monitoring: the Edinburgh experience

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Background: The introduction of biosimilar infliximab with CT-P13 offers substantial potential cost savings with opportunities of gain share to gastrointestinal units. Data on switching from Remicade to CT-P13 are only just emerging and were not available in early 2016. Therapeutic drug monitoring (TDM) is increasingly recognised as an effective means to optimize patient outcomes on anti-TNF therapy, but is not widely adopted in the UK. All bio-naïve patients in our unit scheduled for infliximab received CT-P13 from September 2015 ($n=73$), saving approximately £480,000 in year 1. Following discussions with hospital management, we took the opportunity to implement TDM whilst switching patients established on Remicade to biosimilar CT-P13.

Methods: A switch pathway was agreed (see Figure 1) and implemented June 2016, with all data collected prospectively. Routine

blood tests, disease activity scores (Partial Mayo/HBI), faecal calprotectin (FC) and serum for infliximab trough levels and antibodies to infliximab (ATI) were obtained. TDM was performed with the IDKmonitor[®] ELISA assay. Results were reviewed in a virtual biologics clinic (GI consultant/specialist pharmacist) and decision made on further management as per NICE DG-22 TDM algorithm. Clinical response was defined as a change in HBI ≥ 3 and Partial Mayo ≥ 2 . Clinical remission was defined as HBI < 5 and Partial Mayo < 2 . **Results:** 160/161 (99%) patients currently receiving Remicade agreed to our switch process. 86/160 (54%) patients were switched to CT-P13 with no dose change whilst 15/160 (9%) switched with dose escalation and 8/160 (5%) with dose de-escalation. 27/160 (17%) patients stopped biologic therapy altogether due to a combination of immunogenicity (infliximab trough levels $< 3 \mu\text{g/ml}$; ATI $> 8 \mu\text{g/ml}$), clinical and biochemical remission. 24/160 (15%) patients had immunogenicity with infliximab but were not in clinical and biochemical remission and therefore switched to an alternative biologic (adalimumab $n=18$; vedolizumab $n=6$). Data on trough levels and ATIs post switch (pre-infusion 3 and 6) are presently being analysed.

Conclusions: The local experience combining the sequential introduction of TDM with switching of Remicade to CT-P13 has not resulted in any immediate complications in our cohort of IBD patients. Health-economic evaluation of the switch process is on-going with a projected saving of approximately £710,000 in year 1.

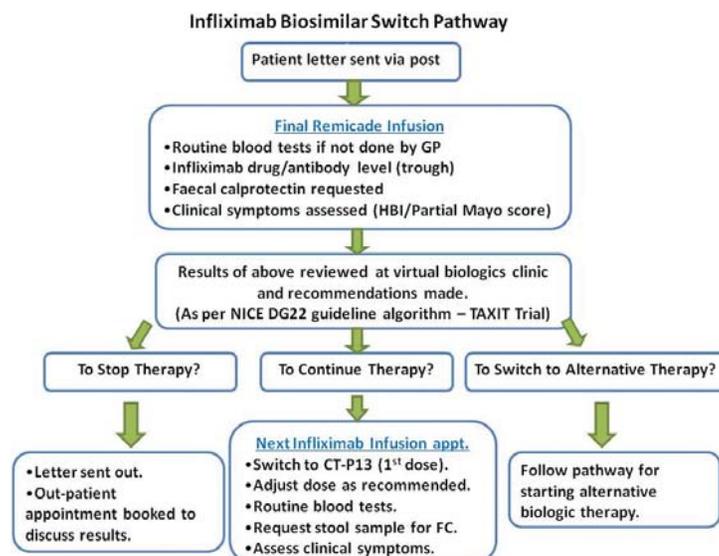
P587

Fermentation capacity of gut microbiota in patients with inflammatory bowel disease compared to healthy controls

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Background: Gut microbiota in the colon ferment undigested dietary



fibre to produce short-chain fatty acids (SCFA). SCFA have beneficial effects on colonic health. Differences in microbiota composition and metabolic activity have been described between IBD patients and healthy controls.

Methods: Fresh faecal samples were collected from IBD patients in clinical remission and healthy controls (HC). In vitro batch culture fermentations were carried out for 5 carbohydrate/fibres and for a mixture of these 5 fibres together (hi maize, pectin, raftilose, wheat bran, cellulose). Aliquots were taken at 0 and after 48 hours of fermentation. Faecal SCFA (butyrate, propionate and acetate) concentration ($\mu\text{mol/g}$) and their proportional ratio (%) were measured with Gas Chromatography.

Results: 39 IBD participants and 19 matched HC were recruited. Following 48h batch cultures, total SCFA from hi maize and raftilose in CD patients and from hi maize in UC patients were significantly lower than in healthy controls ($p=0.041$, $p=0.003$ and $p=0.003$ respectively) and for other fibre substrates tested: [Propionate, $\mu\text{mol/g}$, CD vs HC; wheat bran: 9.99 vs 7.77, $p=0.042$; raftilose: 14.4 vs 11.23, $p=0.005$]; [% Propionate, CD vs HC; raftilose: 9.84 vs 20.4, $p=0.016$]. UC patients also produced lower amounts of butyrate from mixed fibres and of acetate from hi maize fermentation compared to HC ($p=0.042$ and $p=0.045$ respectively). No significant differences were observed for acetate and butyrate concentration or the production profile (% proportional ratio) or SCFA.

Conclusions: These data suggest that the microbiota of IBD patients has a lower capacity to break down fibre, compared to healthy people. The findings of these work should be complemented with changes in microbiota composition using next generation sequencing.

P588

Ustekinumab for the treatment of Crohn's disease patients with TNF antagonist induced psoriasis. Real life experience from a tertiary referral center through week 54

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Background: Ustekinumab, a human antibody to IL 12/23p40 has recently been approved for the treatment of patients with moderate to severe Crohn's disease, who have had an inadequate response, lost response or were intolerant to either conventional therapy or TNF antagonists. Ustekinumab has already been approved for the therapy of patients with psoriasis and psoriatic arthritis. Psoriasis as a paradoxical inflammation of the skin can be seen by patients treated with TNF antagonists.

Methods: Patients with a TNF antagonist induced psoriasis and with loss of response to TNF antagonists were treated with ustekinumab. All patients had a chronic active disease course with a CDAI score >220 and <450 at the start of the ustekinumab therapy. Patients were treated with 90 mg ustekinumab subcutaneously every four weeks. CDAI, CRP and calprotectin were assessed at baseline and week 8, 12, 24, 36, 48 and 54 after treatment, when patients were seen again as part of standard clinical care. Sonography and ileo-colonoscopy was performed at baseline, week 12 and week 54. SES-CDEIS was assessed at baseline, week 12 and week 54. Response was defined as a >70 CDAI decrease and remission as a <150 CDAI.

Results: 85 patients were followed up. The median disease duration was 8.3yrs and mean baseline CDAI was 298. Mean baseline

fecal calprotectin was 483mg/kg, mean baseline CRP 9.8 mg/l. The median baseline SES-CDEIS was 13.5. 11 (12.9%) patients finished treatment before week 54 due to a loss of response or intolerance. At week 8 mean CDAI and CRP were 269 and 6.8 mg/l, calprotectin 359 mg/kg. Mean CDAI, CRP, calprotectin and SES-CDEIS at week 12 were 232, 5.1 mg/l, 278 mg/kg, 10.5. At week 54 mean CDAI, CRP, calprotectin and SES-CDEIS were 171, 3.3mg/l, 198 mg/kg and 5.9. 11 (14.9%), 40 (54.1%) and 45 patients (60.8%) had a response at week 8, 12 and 54. Remission was seen in 0 (0%), 6 (8.1%) and 30 (40.5%) patients at week 8, 12 and week 54, respectively. Psoriatic skin lesions were improved in 87.1% of the patients. No severe side effects were seen.

Conclusions: In this special cohort of patients with the TNF induced psoriasis and failure or loss of response of at least two TNF antagonists induction time of remission/response took longer than seen in clinical trials. This might be due to the fact that induction therapy with i.v. ustekinumab was not available at that time. But the therapy was well tolerated and maintenance treatment with ustekinumab was successful.

P589

Faecal microbiota transplantation for inflammatory bowel disease: a systematic review and meta-analysis

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Background: Given the importance of the enteric microbiota in the pathogenesis of the inflammatory bowel diseases, faecal microbiota transplantation (FMT) has been advocated as a potential therapeutic strategy, and has been the recent subject of increasing research. We thus performed a systematic review and meta-analysis to assess the effectiveness and safety of FMT in the treatment of inflammatory bowel diseases.

Methods: A systematic review of the literature was conducted up until the end of March 2016 in accordance with PRISMA and Cochrane recommendations. Electronic databases were searched, along with hand searching of major conference proceedings. Studies were excluded if patients had co-infection or if data was pooled across disease subtypes (ulcerative colitis (UC), Crohn's disease (CD), pouchitis) and could not be individually extracted. Clinical remission was established as the primary outcome; clinical response, endoscopic remission and safety were secondary outcomes. Pooled effect sizes and 95% confidence intervals were obtained using the random effects model. Heterogeneity, sensitivity and subgroup analyses were also performed.

Results: 5940 records were identified of which 82 articles were reviewed. Thirty eight studies were included (29 in UC [including 3 randomised controlled trials], 11 in CD, 3 in pouchitis) reporting on 371 UC, 73 CD and 22 pouchitis patients. Overall, 37.5% (139/371) of UC patients, 49.5% (36/73) of CD patients and 18% (4/22) of pouchitis patients achieved clinical remission during follow-

up. Among the cohort studies, the pooled proportion of patients that achieved clinical remission was 33% (95% CI 24%–44%) for UC with a moderate risk of heterogeneity (Cochran's Q, $p=0.121$; I² =31%) and 53% (95% CI 30%–75%) for CD with a moderate risk of heterogeneity (Cochran's Q, $p=0.081$; I² =49%). For the 3 RCTs of FMT in UC, there was borderline benefit in clinical remission (P-OR =2.37, 95% CI =0.91–6.19, $p=0.078$) with moderate heterogeneity (Cochran's Q, $p=0.168$; I² =44%). The controlled trial and cohort data suggest remission in UC is improved with increased number of FMT infusions and administration via the lower gastrointestinal tract. Most adverse events were transient minor gastrointestinal complaints. Microbiota analysis was performed in 16 studies, with many identifying a shift in recipient microbiota profile towards that of the donor post FMT.

Conclusions: There is a need for additional well designed controlled studies of FMT in IBD, especially in CD and pouchitis. FMT appears to be effective in the induction treatment of UC, particularly with increasing number of infusions. Long term durability and safety remain unclear.

P590

Reasons for discontinuation and switch of biologic therapy in IBD: findings from a large international observational study (03)

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Background: Data on reason for change of biologic therapy mostly comes from clinical trials and hospital case series. This interim analysis presents data on reasons for change of biologic therapy among participants in the vedolizumab Post Authorisation Safety Study (PASS).

Methods: The vedolizumab PASS study is a multicentre prospective observational cohort study of adult IBD patients starting or switching to a new biologic agent in 23 countries in North America and Europe. This analysis focused on patients recruited up to 30 September 2016, who at recruitment were biologic experienced and initiating a new biologic therapy. Changing from one anti-TNF α agent to a biosimilar of the same agent was not considered as starting a new biologic in this study. As part of baseline data collection, treating physicians reported the reason for discontinuation of previous biologic therapy for the study participants.

Results: 300 IBD patients in the cohort study had discontinued a previous anti-TNF α agent and started vedolizumab (n=231) or a new anti-TNF α agent (n=69). The majority had used only one previous biologic (68% of UC and 62% of CD patients).

Among UC patients switching to vedolizumab, the leading reasons for discontinuation of previous anti-TNF α treatment were lack of response (45%), loss of response (29%) and (28%). For UC patients switching to a new anti-TNF α agent, the leading reasons for discontinuation were also lack of response (32%), loss of response (23%) and intolerance/adverse event (14%).

Among CD patients switching to vedolizumab, the leading reasons for discontinuation of previous anti-TNF α agent were loss of response (32%) and intolerance/adverse event (19%). Among CD patients switching anti-TNF α agents, the main reasons for discontinuation of the previous agent were loss of response (28%), lack of response (21%) and intolerance/ adverse event (13%).

Concurrent thiopurine use was common in the study population, with 23–26% of patients on thiopurine medication when switching biologic agent.

Conclusions: This interim analysis of biologic use in clinical practice found the most frequent reason for discontinuation of previous anti-TNF α in UC was lack of response (primary non-response). Conversely in CD, the most frequent reasons for discontinuation of previous anti-TNF α were loss of response (secondary failure). Among patients changing from an anti-TNF α to vedolizumab, intolerance/adverse event was an important reason for changing therapy.

P591

Therapeutic drug monitoring in Paediatric inflammatory bowel disease on maintenance infliximab and adalimumab treatment improves clinical remission with a proactive approach

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Background: The anti-TNF antibodies Infliximab (IFX) and Adalimumab (Ada) are frequently used as maintenance therapy in Paediatric Inflammatory Bowel Disease (pIBD). However, the role and frequency of monitoring trough levels and anti-drug antibodies (ADA) during maintenance treatment remains unclear in children, with two regimens being considered, reactive vs. proactive approaches. Our aim was to investigate the trough levels of IFX and Ada, presence of ADA and identify correlation with inflammatory activity and clinical response.

Methods: Retrospective study of IBD patients on biologics (n=67, Crohn's disease [CD] (n=47), ulcerative colitis [UC] (n=11), inflammatory bowel disease unclassified [IBDU] (n=7), early onset IBD

[EOIBD] (n=2); male (n=43), age range 4 years 3 months–17 years; median 13 years 8 months). Biologic monitoring was started in 2013. Demographics, CRP/ESR/albumin and activity indices PUCAI/PCDAI were recorded. Ada was started after Infliximab was discontinued (various reasons). All patients were on concomitant immunosuppressive treatment. 42 patients were on IFX only, 25 on Ada and 6 on Vedolizumab. 8 excluded due to insufficient data. Maintenance TNF treatment was 3–66 months, median 18 months.

Results: Group 1 Infliximab converted to Adalimumab; n=25 patients, n=7 excluded as no data available (pre through level availability); CD n=15, UC n=3, IBDU n=5, EOIBD n=2. The lowest Ada trough levels in n=15 showed a median of 5.6, range 0.3–17; the highest a median of 9.1, range 3.7–12.7. ADA for Ada was negative in 16 patients, n=5 became positive over time, n=2 were positive at first measurement.

Group 2 Infliximab only; n=42; the lowest IFX through levels had a median of 1.4, range <0.8–32.5, with highest through levels median 5.2, range 0–45. ADA for IFX were negative in n=37, n=7 developed antibodies over time, median ADA of 61, range 10–>200. 50% (21/42) of patients with either low through levels and/or positive ADA received double doses to salvage treatment. Overall there was clinical improvement; this did not though correlate with a reduction of ADA. However in 81% (17/21) of patients, double dosing led to an incremented of through levels above >2, median 4.1, range 2.4–21.9. Although only 15/67 (22%) out of 67 patients had completely normal laboratory tests, 42/47 (89%) CD patients had normal PCDAIs, 10/11 (91%) UC patients had normal PUCAIs. 14/47 (30%) CD patients developed antibodies to IFX, 2/11 (18%) UC patients developed antibodies to IFX.

Conclusions: The vast majority of patients on Adalimumab or Infliximab had an excellent clinical response to treatment regarding therapeutic drug monitoring, thus enabling us to optimize their treatment and bring them into clinical remission. We therefore advocate proactive biologic drug monitoring in Paediatric IBD.

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Final results on immunogenicity profile and predictors of ADA development of biosimilar infliximab during the first 12 months of the therapy: results from a prospective nationwide cohort

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Background: Biosimilar infliximab CT-P13 received EMA approval in June 2013 for all indications of the originator product and its use is mandatory in all anti-TNF naïve IBD patients in Hungary since May 2014. In the present study we aimed to prospectively evaluate the immunogenicity profile of the biosimilar infliximab and predictors of TDM in IBD during the first year of therapy in a nationwide, multicentre cohort.

Methods: Demographic data were collected and a harmonized monitoring strategy was applied. Clinical and biochemical activity were evaluated at weeks 14, 30 and 54. Routine therapeutic drug monitoring (TDM) was applied. Trough level (TL) and anti-drug antibody (ADA) concentration were measured by ELISA (LT-005, Theradiag, France) at baseline and at 2, 6, 14, 30 and 54 weeks right before anti-TNF administration during the induction treatment.

Results: 353 consecutive IBD patients (209 CD patients and 144 UC patients) were included in the present cohort. 23.4% of CD patients and 19.4% of UC patients had received previous anti-TNF therapy. None of the patients had received infliximab within 12 months prior to initiation of the biosimilar infliximab. 60/51% of CD/UC patients received concomitant immunosuppressives at baseline.

Mean TLs were 18.9, 17.3, 7.4, 4.3 and 5.3 µg/ml at weeks 2, 6, 14, 30 and 54 in CD and 19.1, 11.8, 5.0, 3.9 and 4.5 µg/ml UC. Previous anti-TNF therapy was associated with lower early TL-s in both CD (week 2, 14, and 30, p<0.05) and UC (week 2 and 6, p=0.03).

ADA positivity rates were 4.3%, 12.0%, 20.9% and 28.6% in naïve patients at weeks 0, 14, 30 and 54 (n total=266, 312, 290 and 210). ADA positivity at week 14 was associated with lower TLs in all CD (week 2, 14 and 30, p<0.007 for all) and UC (week 6, 14 and 30, p<0.001 for all) patients.

Concomitant IS use prevented ADA formation in anti-TNF naïve patients (week 14, 30 and 54, p=0.01, 0.02 and 0.004) in CD but not in UC and did not affect clinical remission or response rates.

32 (8.9%) patients had infusion reactions during induction or maintenance treatment, of which 16 patients had received previous infliximab treatment.

Conclusions: Drug TLs and ADAs in IBD patients until week 54 were in line with results reported for the originator in previous studies. Patients with previous exposure to anti-TNFs had lower early TL coupled with ADA positivity and were more likely to develop infusion reactions. Concomitant IS use prevented ADA development in anti-TNF naïve patients.

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Hospital resource use and cost associated with first-line anti-TNF therapy in patients with IBD in the UK: comparison of subcutaneous (adalimumab) and intravenous (infliximab) therapies

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Background: UK National Institute for Health and Care Excellence guidance states that if more than one biologic therapy option is available for patients with IBD the least expensive option should be used.

However, limited economic data are available to inform these decisions.

Methods: Service evaluations (SE) were carried out in 2 UK hospitals between Feb and Sept 2016. The primary objective was to describe the overall cost of the first year of biologic therapy for patients with IBD treated with intravenous (infliximab [IFX]) or subcutaneous (adalimumab [ADA]) 1st-line anti-TNF therapy. SEs comprised a prospective time and motion evaluation of patient visits for anti-TNF treatment and a retrospective chart review of the resource utilisation associated with the first year of 1st-line anti-TNF-treatment in consenting patients with IBD treated with ADA or IFX for ≥12 months. Times for activities are reported as hh:mm:ss.

Results: For the time and motion study, 10 separate anti-TNF administration visits were observed for patients treated with ADA and IFX at each centre. The total time for all 10 administration visits in Centre 1 was 01:07:04 for ADA and 14:17:53 for IFX and in Centre 2 was 09:56:55 for ADA and 18:00:33 for IFX (see Table 1 for a breakdown of timings). The patient-reported time off work for anti-TNF administration visits was highest for patients treated with IFX at each centre (mean [SD] Centre 1: ADA 1.4 [1.5] hours/visit [n=9], IFX 3.3 [2.7] hours/visit [n=9]; Centre 2: ADA 3.7 [2.8] hours/visit [n=9], IFX 5.4 [3.1] hours/visit [n=8]). The total resource utilisation and related costs associated with the 1st year of anti-TNF therapy in Centre 1 (ADA n=16, IFX n=19) and Centre 2 (ADA n=19, IFX n=20) are summarised in Table 2. The drug cost/patient/year was similar for each anti-TNF at each centre (mean [SD] Centre 1: ADA £10,740.27 [445.43]/patient/year [n=16], IFX £11,319.08 [2,873.64]/patient/year [n=19]; Centre 2

ADA £11,398.22 [2,403.31]/patient/year [n=19], IFX £10,839.00 [2,626.54]/patient/year [n=20]).

Conclusions: The use of NHS resources associated with the use of ADA and IFX varies across the studied centres. The total cost/patient/year ranged between £363–£580 for ADA and £1563–£2067 for IFX. The total administration time of the anti-TNF ranged between 1 and 10h for ADA and 14 and 18h for IFX.

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Ustekinumab treatment effectiveness in clinical practice – a multicentre retrospective review of long-term outcomes in Crohn’s disease

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Background: Recently published data demonstrated the efficacy of Ustekinumab (USK) in the treatment of moderate-severe Crohn’s disease. This study aimed to evaluate the Irish experience of USK 2011–2016

Methods: A retrospective multicentre analysis of patients treated with USK was performed via the INITiative network, a national collaborative IBD research network.

Data collected from 5 centres included patient and disease characteristics, surgical history, concomitant therapies, induction and escalation of therapy, surgery post-treatment and sustained benefit at 12 months.

Results: 59 patients were included; data available n=54. Patient and disease characteristics as per Table 1.

Table 1. Patient demographics, disease characteristics and treatment history

Age (median; range)	39.5 years (19-74)		Failed ≥1 Anti-TNF n ;(%)	54 (100)
Gender n; (%)	Female 35 (64.8)		Failed ≥3 Anti-TNF n ;(%)	19 (35)
Disease duration (median; range)	11 years (1-32)		Prior surgery n ;(%)	32 (59.3)
Smoking history n;(%)	8 (14.8)		Perianal disease n;(%)	13 (24.1)
Montreal A n;%	A18 (14.8)	A2 39 (72.2)	A3 6 (11.1)	
Montreal B n;%	B1 25 (46.3)	B2 13 (24.1)	B3 16 (29.6)	
Montreal L n;%	L1 6 (11.1)	L2 18 (33.3)	L3 26 (48.1)	L4 4 (7.4)

Median duration of follow-up post-treatment = 17.4 months. 32/54 patients (59.3%) had prior Crohn’s-related surgery; 28% patients had >1 surgical procedure. All patients had been treated with ≥1 anti-TNF agent. 32 patients (59%) had failed therapy with 3 anti-TNF agents. Various induction regimens were utilised. All patients received sub-

Table 1: Time and motion study timings for administration of biologics by activity

Time for activity, hh:mm:ss	Centre 1		Centre 2	
	Adalimumab (n=10)	Infliximab (n=10)	Adalimumab (n=10)	Infliximab (n=10)
Mean (SD) time for drug reconstitution/preparation	00:01:05 (00:00:32)	00:03:11 (00:02:04)	00:04:52 (00:03:17)	00:11:20 (00:03:21)
Mean (SD) time for patient consultation/work-up	00:02:03 (00:01:01)	00:02:13 (00:01:59)	00:39:05 (00:09:51)	00:07:59 (00:03:51)
Mean (SD) time for drug administration	00:00:45 (00:00:23)	01:08:15 (00:13:45)	00:01:38 (00:00:32)	01:19:47 (00:11:22)
Mean (SD) time for post-administration monitoring	00:01:32 (00:04:51)	00:00:44 (00:01:18)	00:05:00 (00:08:28)	00:00:00 (00:00:00)
Mean (SD) time for administrative tasks/documentation	00:01:17 (00:02:14)	00:11:24 (00:08:26)	00:09:06 (00:03:05)	00:08:57 (00:11:13)
Total time taken for 10 patients	01:07:04	14:17:53	09:56:55	18:00:33

Table 2. Resource utilisation and related costs associated with first year 1st-line anti-TNF treatment

Total one year anti-TNF resource costs	Centre 1		Centre 2	
	Adalimumab (n = 16)	Infliximab (n = 19)	Adalimumab (n = 19)	Infliximab (n = 20)
Administration visits				
Total number of visits	66	153	19	157
Total HCP cost	£870.54	£21,089.95	£2,093.47	£29,005.55
Total consumables cost	£0.33	£1,930.60	£15.69	£3,857.55
Monitoring visits				
Total number of visits	40	52	68	63
Total HCP cost	£4,810.00	£6,284.00	£8,704.00	£8,002.00
Blood tests				
Total number	42	128	68	157
Total cost	£126.00	£384.00	£204.00	£471.00
Total annual cost	£5,806.87	£29,688.55	£11,017.17	£41,336.10
Total cost/patient/year (mean [SD])	£362.93 (104.47)	£1,562.56 (227.32)	£579.85 (140.25)	£2,066.80 (239.23)

HCP costs derived from www.pssru.ac.uk/project-pages/unit-costs/2015/index.php?file=full section 14 and NHS National Schedule of Reference Costs - Year 2014-15

cutaneous (sc) induction; median cumulative induction dose=225mg (range 135–270mg). 29.6% (n=16) were taking concomitant immunomodulators and 27.8% (n=15) concomitant steroids at induction.

Most patients received 90mg maintenance dose; median interval of 8 weeks (range: 2–8weeks). In 17 cases (31.5%) USK therapy was escalated, usually by increasing dose frequency. Of those patients who were escalated 13 (76.5%) had a sustained clinical benefit at 12 months.

12 month follow-up data is available for 44 patients; 10 patients continue USK with treatment duration <12 months. The median treatment duration=359 days (IQR 101–956 days).

25/44 (56.8%) had sustained benefit at 12 months; 18 patients (72%) continued USK at the time of last follow-up.

23 patients had endoscopic assessment before and after induction therapy. 39% (n=9) demonstrated improvement; 5 patients achieved mucosal healing.

13/54 patients (24%) had surgery while on USK; n=9 within 12 months of induction.

In a logistic regression model, failing to respond to 3 anti-TNF agents (primary non-response, loss of response, adverse event) was significantly associated with requiring surgery in the 12 months post-induction (p=0.017).

Conclusions: In this study, USK provided sustained benefit at 12 months to >50% patients with medically-refractory Crohn's disease. These data suggest that induction therapy with sc USK may be an alternative to iv induction. As with anti-TNF therapy, dose optimisation appears to be critical in inducing and maintaining response.

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The influence of vitamin D on expression of cytokines mRNA in IBD

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Background: The aetiology of Crohn's disease (CD) and ulcerative colitis (UC) is not known. Recent data suggest that vitamin D (VD) plays an important role in IBD. Pathways that are influenced by VD in IBD are poorly understood.

Methods: We performed a cross-sectional study. The cohort consisted of 87 IBD patients (47 CD and 40 UC) followed at the IBD centre of University Hospital Bratislava-Ružinov. We performed colonoscopy in each patient and took biopsies from inflamed and if applicable also from non-inflamed mucosa from sigma (CD, UC) and terminal ileum (CD). Serum concentration of 25(OH)VD was assessed in each patient at the time of colonoscopy. mRNA was extracted from mucosal biopsy samples for each cytokine and isolated by RLT buffer. mRNA was reversely transcribed. We normalized expression of the target genes to the expression of the house-keeping gene (GAPDH). Then we analysed the correlation between serum concentration 25(OH)VD and the expression of mRNA of inflammatory cytokines from biopsies samples.

Results: In CD we observed a positive correlation of serum concentration 25(OH)VD and mRNA expressions levels of TNF α (r2=0.41, p=0.04), IL-6 (r2=0.45, p=0.02), IL-10 (r2=0.44, p=0.03), IL-23 (r2=0.55, p=0.02), TLR 2 (r2=0.04, p=0.04) in inflamed mucosa of terminal ileum. A positive correlation was also observed

with CCR5 (r2=0.042, p=0.01) and CCR1 (r2=0.33, p=0.03) in non-inflamed mucosa from sigma. We also found a positive correlation between 25(OH)VD and IL-23 (r2=0.45, p=0.01), TLR4 (r2=0.42, p=0.02), CD 207 (r2=0.42, p=0.02), CCR1 (r2=0.52, p=0.002), CCR5 (r2=0.51 p=0.003) and CD 206 (r2=0.43, p=0.01) in non-inflamed mucosa of sigma in UC.

Conclusions: According to our results, VD significantly correlated with the levels of expression of several inflammatory cytokines including TNF α in colonic mucosa of patients with CD.

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FMT in patients with steroid dependant ulcerative colitis a single centre observational study

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Background: Ulcerative colitis is thought to arise from an aberrant immune response to a change in colonic environment in a genetically susceptible individual. Steroid dependant cases pose a significant challenge to clinicians. Fecal microbiota transplantation (FMT) has emerged as a novel approach to alter the colonic microbiome and has a promising future in emerging as a successfully treatment modality.

Methods: This observational study was conducted at the outpatient, indoor patients of Gastroenterology Department of DMC&H, Ludhiana. Two young healthy unrelated donors were screened with their 16 sRNA microbiome profiling done and subsequently enrolled. Fifteen patients suffering from ulcerative colitis (steroid dependant) were enrolled for the study. FMT was given twice a week for 1 month followed by once a week for 5 months with total duration of 6 months. Outcome was assessed at 4 months and 1 year follow-up according to rate of clinical response, remission and endoscopic remission. Safety and adverse effects were also recorded.

Results: Out of the 15 (100%) patients enrolled, mean age was 34.60+9.33 years (23–55) and there were 8 (53.3%) males. FMT therapy induced clinical remission in 73.3% at 4 months and in 93.3% patients at 1 year of follow-up. Clinical response was seen in all 15 (100%) patients at 4 months and 1 year follow-up. Endoscopic remission was in 26.7% patients at 4 month and in 73.3% at 1 year follow-up. There were no major side effects observed during the study.

Conclusions: FMT is effective in inducing clinical response, clinical remission and endoscopic remission in patients of steroid dependent ulcerative colitis. In view of toxicity profile of biological and steroids, it seems to have a promising future in the new era of clinical practice.

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Ustekinumab use in Crohn's disease: a tertiary centre experience

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Background: Efficacy of ustekinumab (UST) in Crohn's disease (CD) has been demonstrated in clinical trials. Real world symptomatic and endoscopic response is lacking. As opposed to intravenous (IV) induction, high dose subcutaneous (SC) induction has been proposed while the IV formulation is unavailable.

Methods: A retrospective, observational study of 2 different induction regimens was conducted. Standard dosing was 90mg SC at Week 0, 1 and 2; higher dose induction 270mg SC at Week 0 and 180mg SC at Weeks 1 and 2. Maintenance dosing was 90mg SC every 8 weeks for both induction regimens. Response assessed after 3 months (short term), and if remaining on therapy, after 6–12 months (medium term) and at least 12 months (long term). Symptomatic response defined as physician documentation of improvement of CD-associated symptoms, withdrawal of steroids and continuation of therapy. Endoscopic or radiological response defined as resolution or improvement in extent and severity of lesions.

Results: Seventy-nine patients commenced UST for CD from September 2012 to November 2016. (Figure 1) Five patients were lost to follow-up, with 74 patients remaining, including 39 induced with higher dose (Table 1). Maintenance dose escalation occurred in 17 patients (90mg every 4 weeks), of whom 13 and 4 had received standard and high induction. Symptomatic response assessed in 66 patients; 51% (17/33) in standard and 67% (22/33) in higher induction groups had short term symptomatic response. Biochemical response was seen in 64% (9/14) and 58% (11/19) of patients in standard and higher induction groups. Within the first 3 months, 29% (10/35) of standard and 8% (3/36) of higher induction groups ceased therapy. Symptomatic response was reported in 68% (15/22) of standard and 57% (13/23) of higher induction groups who continued on UST in medium term; in long term, 64% (14/22) and 80% (4/5) have an ongoing response. Endoscopic or radiologic response or improvement was achieved in 50% (10/20) and 71% (12/17) of standard and high induction groups. Of primary and secondary anti-TNF non-responders, 88% (14/16) and 56% (18/32) had short term symptomatic response.

Conclusions: Fifty-nine percent of patients had short term symptomatic response, with greater proportion receiving higher induction strategy, while primary non-response to prior anti-TNF was also associated with response. Fewer patients receiving high dose induction required dose escalation. Endoscopic or radiologic assessment also demonstrated greater improvement or response within this novel induction group. Results provide further encouragement for therapeutic benefit of UST in CD.

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Mucosal and transmural healing during anti-TNF therapy. Is fecal calprotectin a marker of therapeutic response?

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Background: Therapeutic response to Infliximab (IFX) and Adalimumab (ADA) in patients affected by Crohn's Disease (CD) has been assessed for many years by clinical indices of disease activity; however, recently it has been shown that a combination of both clinical and endoscopic remission leads to a better outcome. As CD involves the whole wall thickness, a transmural healing could be an even more important long-term target in order to reduce the risk of clinical relapse. A gold standard to assess transmural healing is still lacking. The primary aim of our study was to analyze if fecal calprotectin (FC) values correlates with mucosal and parietal healing evaluated

by Ultrasound Imaging (US) or Magnetic Resonance Imaging (MRI). The secondary aim was to evaluate mucosal and parietal healing in CD patients treated with anti-TNF with clinical response.

Methods: We enrolled 21 consecutive ileal CD patients who reached clinical remission at W6 with IFX or ADA. All patients performed colonoscopy, US and MRI at 1 year. Fecal calprotectin (FC) was evaluated at 6 months and at 1 year.

Absence of ulcers was considered as endoscopic healing. A bowel wall thickness (≤ 3 mm) was considered as transmural healing in MRI and in US. The value of 150mg/Kg of FC was considered the best cut off to identify patients at high risk of clinical relapse. Statistical analysis was performed by Fisher Exact Test.

Results: We recruited 21 CD patients (8M), 10 (48%) treated with IFX, 11 (52%) with ADA.

After one year of treatment, 9 (42%) patients showed mucosal healing, 7 (33%) patients showed transmural healing with US and 5 (23%) patients showed transmural healing with MRI. Five (23%) patients had FC values ≤ 150 mg/Kg at 6 months, 10 (48%) patients at one year. We found a correlation between FC values at 6 months and mucosal and parietal healing both with MRI and US.

Table 1. Correlation between calprotectin 6 months and MRI 12 months

	Thickness MRI >3 mm	Thickness MRI <3 mm	p
FC >150 mg/kg	15	1	0.004
FC <150 mg/kg	1	4	

Table 2. Correlation between calprotectin 6 months and endoscopy 12 months

	Non mucosal healing	Mucosal healing	p
FC >150 mg/kg	12	4	0.006
FC <150 mg/kg		5	

On the other hand, FC values at one year correlated with mucosal healing and with parietal healing with US, but not with parietal healing with MRI.

Conclusions: Our results showed that, even adopting restrictive criteria, a good response to anti-TNF therapy was observed both for mucosal and transmural healing. Above all, we found a correlation between FC values at 6 months and mucosal and transmural healing, suggesting that FC could be a prognostic marker of therapeutic response and a possible future target of therapy.

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Home testing for faecal calprotectin: follow-up results from the first UK trial

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Background: Faecal calprotectin (FCAL) is a useful test for monitoring of inflammatory bowel disease (IBD) activity. However, providing a stool sample in person to the hospital laboratory is anecdotally unpopular. A new FCAL kit (IBDoc™, Bühlmann) enables self-testing using a proprietary collection tube, camera smartphone and app. The aims of this study were to assess patients' adherence to and experience of using IBDoc™; to compare the assay to the standard laboratory test; and to determine if IBDoc™ can be used to predict a flare of disease within a four month period.

Methods: After focussed training, participants were asked to use IBDoc™ once a month for four months and provide a standard stool sample to be tested with standard ELISA (Bühlmann). The following

questionnaires were applied before and after testing: GAD-7 (anxiety), PHQ-9 (depression), IBD-control-8, Multi-dimensional Health Locus of control (MHLC) and Cognitive Behavioural Responses to Symptoms (CBSRQ). Patients were also asked to record their experiences and preferences for testing on a proprietary questionnaire. Electronic patient records and endoscopy and histopathology reports were retrospectively reviewed for patients who had FCAL results by both methods at one time point. A faecal calprotectin of $>100 \mu\text{g/g}$ was defined as a positive result.

Results: Overall, 54 patients (Crohn's: 23, UC: 31, mean age 36.0) were enrolled. Participants completed a median of 3 tests during the study with 19/54 (35%) completing all four set time points and 17/54 (32%) returning no samples. There was no difference in any of the questionnaire scores between compliant and non-compliant patients. Overall, 85% of respondents stated a preference for IBDoc™ of which 74% would want this to be in the context of prompt contact from the hospital team in the event of a positive result. There was moderate correlation of FCAL results between the two methods ($r=0.77$, $p<0.0001$). At least one paired laboratory FCAL and IBDoc™ result was available for 37 patients, of which 30 were in remission at the time of the test. To predict a flare within four months, the IBDoc™ FCAL had a sensitivity of 89%, specificity of 33% and NPV of 87.5%, compared with 78%, 57% and 86% respectively for the laboratory test.

Conclusions: There was reasonable uptake and adherence to a demanding testing regimen with 85% of respondents preferring the IBDoc™ test over other methods. The home testing kit results show only moderate correlation to laboratory results. A negative FCAL ($<100 \mu\text{g/g}$) by either method is a useful test to exclude a flare within four months, but positive results should be interpreted with caution and repeat testing would be advisable prior to treatment escalation.

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Infliximab trough levels for remission induction and long term therapy management of inflammatory bowel disease

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Background: Recent developments concerning the quantification of anti-TNF- α therapies and auto-induced antibodies screening are crucial in inflammatory bowel disease (IBD) treatment. The formation of anti-infliximab antibodies (AIA) are associated with poor disease control. We aimed to assess if higher infliximab trough levels correlate with long term remission status. We wanted to test the hypothesis of different infliximab trough levels cut-offs in early and chronic therapy. Our objective also concerned the relevance of AIA and the preponderance of different factors (such as use of immunomodulators) in its presence.

Methods: Retrospective cohort study based on IBD patients treated with infliximab that were submitted to trough levels and anti-drug antibodies measurement. Remission was defined by the absence of symptoms and a C-reactive protein value $\leq 0.5 \text{ mg/dl}$. Statistical work done with SPSS v. 20 (Chicago, IL USA), statistical significance assumed with p value <0.05 .

Results: 116 patients included, 56.8% women, mean age 39.4 ± 13.3 (18–74) years; 85 patients with Crohn's disease (73.3%), patients with indeterminate colitis were excluded. All included patients were being treated with infliximab for at least 3 months after first admin-

istration, 59.5% patients were being treated also with immunomodulator. Mean 45.7 ± 35.5 months of follow-up. For the entire group (116 patients) the isolated presence of AIA (in some cases temporarily) or the use of immunomodulators did not statistically significantly affect remission, but the infliximab trough levels ($p=0.009$) affected, $1.72 \mu\text{g/ml}$ cut-off (0.632 area under ROC curve, $p=0.016$, 95% CI 0.530–0.735). When adjusted for the follow-up, in the period 3–12 months after induction the trough levels were an excellent remission marker ($p=0.003$) with a $1.87 \mu\text{g/ml}$ cut-off (0.855 area under ROC curve, $p=0.006$, 95% CI 0.680–1.0). However, for the long term period (>12 months after induction) higher trough levels did not correlate with improved biochemical remission (0.576 area under ROC curve, $p=0.215$, 95% CI 0.460–0.692).

Conclusions: The infliximab trough levels showed good accuracy to optimize therapy in the period during or just after inducing remission but weren't very helpful in the period of maintenance. Our cut-offs for the trough levels were lower than the published before.

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Can Amitriptylin improve the quality of life in patients with Crohn's disease?

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Background: It is well known the fact that patients with inflammatory bowel disease (IBD) have an impaired quality of life (QoL) and up to 30% use antidepressants. Even though antidepressants are used in the treatment of irritable bowel syndrome few studies were made to evaluate their potential benefits on IBD patients.

Methods: We performed a double blind placebo study. We included 30 patients with Crohn's Disease (CD), in clinical remission or with a mild disease. The patients received either Amitriptylin 50 mg/day or placebo and were followed for 6 months (baseline, 3 and 6 months). The subjects completed IBDQ32 questionnaire for the QoL and provided blood and stool samples on each visit.

Results: Of the 30 participants, 15 were randomized to receive Amitriptylin and 15 placebo. 18 of the patients (60%) were male and the mean age was 39.2 years. Amitriptylin had statistical significant effect on the social (60% vs 20%), emotional (66% vs 26%) and systemic (40% vs 20%) function in comparison with placebo. There was no effect of Amitriptylin on CD activity or on the faecal calprotectin levels.

Conclusions: Patients with CD in clinical remission or with a mild disease could improve the QoL after the administration of Amitriptylin.

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Clinical/biochemical predictors of response to anti-TNF α therapies in a tertiary referral centre

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Background: Anti-tissue necrosis factor-alpha (TNF α) therapies have resulted in improved outcomes for patients with inflammatory bowel disease (IBD) reducing complications, hospitalisation rates, and need

for surgery. However loss of response (LOR), both primary and secondary is a concern and long-term predictive factors are not well understood.

The aim of this study was to assess response rates to anti-TNF α therapy, and to identify any predictors associated with loss of response.

Methods: A retrospective, observational study was designed at our centre. Inclusion criteria were all patients older than 17 years old with IBD who started treatment with anti-TNF drugs, either infliximab or adalimumab, between January 2014 to 2016. Treatment failure was defined as the need for dose intensification because of loss of response, surgery, or therapy removal for ineffectiveness/LOR. Patient data and demographics were obtained from patients electronic patient records. Results are shown as OR and 95% CI and analysed using the Chi-square test and multivariable logistic regression analysis.

Results: During the observational period, 99 patients commenced adalimumab therapy, 61 were on maintenance infliximab therapy. In terms of patient characteristics, for the cohort mean age was 40.5 years, female gender 89 (55.6%), smoking status at anti-TNF α induction 24 (15%). For adalimumab 80 (80.8%) had CD, 43 (70.5%) for infliximab. Mean duration of disease, was 8.09 years, for adalimumab, 11.43 years for infliximab. Response rates were greater overall for patients treated with infliximab versus adalimumab (65.6% v 52.5%, p value 0.05). There was no statistical differences in response rates, in terms of patient characteristics, disease behaviour, location, disease duration. Prior anti-TNF α exposure, was a risk factor for lack of response, 11/21 (52.4%) of infliximab non-responders versus 11/40 (27.5%) for responders, p=0.0327 (95% CI -0.52 to -0.02). Similarly for adalimumab 4/37 (10.8%) of non-responders had prior anti-TNF α exposure versus 0/43 (0%) for responders, p value = 0.0219 (95% CI -0.20 to -0.0). Mean CRP at week 14 was a good predictor of loss of response. For adalimumab non-responders, 21 (56.7%) had CRP >5, versus 5 (11.6%), p<0.0001 for responders, and a similar, though not statistically significant trend for infliximab, 35.7% versus 22%, p=0.19

Conclusions: Suboptimal or loss of response remains a concern for anti-TNF α therapy. Predictors of loss of response, like week 14 CRP and prior anti-TNF α exposure are useful to identify patients at risk of treatment failure, and to help develop strategies to overcome this.

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Hospitalisation risk and reintervention after ileocolonic resection with anastomosis in patients with Crohn's disease. Results from the PRACTICROHN study

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Background: 25% to 61% of patients with Crohn's disease (CD) will require intestinal resection during the first 5 years after diagnosis. In the follow-up can develop complications and require hospitalisation or new surgeries. The aim of this study was to determine the incidence of hospitalisations and reinterventions in patients with CD undergoing ileocolonic resection.

Methods: PRACTICROHN was a retrospective study, including patients with CD aged ≥ 18 years-old from 26 centres who underwent surgical resection with ileocolonic or ileorectal anastomosis between January 2007 and December 2010. Clinical data after surgery were retrospectively collected from medical records.

Results: 314 patients were analyzed (mean age 40 years [SD 13], 48% men). From 115 patients (36%) that were smokers at surgery only 30 (26%) quitted smoking during the first and second year after surgery, and 40 (34%) at 5 year follow-up. Median time from CD diagnosis to surgery was 6 years (IQR 1–12). Indication for surgery was: 147 (48%) structuring disease, 98 (32%) penetrating disease, 46 (15%) stricturing + penetrating and 14 (4%) refractoriness to medical treatment. 208 (68%) of patients received preventive therapy after surgery: 13% aminosallycates, 9% antibiotics, 46% immunomodulators (IMM) and 1% anti-TNFs. During follow-up, 56 (18%) patients required at least one hospitalisation during the first

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	1-12 months	13-24 months	25-36 months	37-60 months
Hospitalizations, n (%)	n= 314	n= 314	n= 314	n= 314
Total	56 (18)	74 (23)	82 (26)	94 (30)
Previous surgery complication	35 (44)	48 (41)	55 (37)	63 (31)
Recurrence, CD activity	36 (45)	56 (47)	72 (37)	100 (49)
Neoplasia related to CD	0 (0,0)	0 (0,0)	2 (1)	5 (2)
CD related infection	1 (1)	2 (1,6)	4 (3)	8 (4)
Other	7 (9)	12 (10)	16 (11)	27 (13)
Reinterventions n(%) Add total as for the above	23 (7)	33 (10)	37 (11)	45 (14)
Surgical Complication	18 (78)	25 (76)	28 (76)	33 (73)
Related to CD	10 (43)	15 (45)	17(46)	22 (49)
Penetrating complication	9 (90)	13 (87)	15 (88)	19 (86)
Abscess	5 (56)	5 (38)	6 (40)	6 (32)
Mass	1 (11)	2 (15)	2 (13)	4 (21)
Fistulae	5 (56)	8 (61)	9 (60)	11 (58)
Perforating	2 (22)	4 (31)	4 (27)	4 (21)
Stenosing	1 (10)	1 (7)	1 (6)	3 (14)
Resistance to treatment	1 (10)	3 (20)	3 (18)	6 (27)

year with a median stay of 10 days (IQR 6–15). The reasons for hospitalisation were: 36 (45%) for CD recurrence or active disease and 35 (44%) from surgical-related complications, 1 (1%) for infection and 7 (9%) for other reasons. At 5 years, 94 (30%) patients had required hospitalisation, mostly for recurrent active disease. 45 (14%) patients required reoperation within 5 years, with 23/45 (51%) during the first year, and the most common reason was surgical complications. (18/45, 40%). The median time to first reoperation was 228 days (IQR 133–527). At year 5, 22 patients needed reoperation due to CD activity, the most common reason was fistulae (11/22, 50%). No differences in the 5-year surgical recurrence were found in those with or without prophylaxis (Table 1).

Conclusions: During the CD related post-surgery evolution, around 20% of the patients will require hospitalisation for postoperative complications during the first year and 30% will require hospitalisation at 5 years follow-up due to disease recurrence. 14% will require a new reintervention after 5 years.

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Usefulness of stool hemoglobin and fecal calprotectin for detecting of mild to moderate ulcerative colitis

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Background: Ulcerative colitis (UC) is a major type of IBD with periods of waxing and waning. Intestinal blood loss is a major symptom in UC and stool Hb level correlated well with the endoscopic disease activity of UC patients. Fecal calprotectin (FC) level increases at gut inflammation and correlate well with endoscopic disease activity in UC. We evaluated the usefulness of FC, quantitative stool Hb (SHb), and CRP as a marker for reflecting UC disease activity

Methods: A total 106 UC patients who performed FC, SHb, CRP, and endoscopy at Korea University Hospital through March 2015 to August 2016 were retrospectively reviewed. UC disease severity was assessed using partial Mayo score (remission=0–1, mild=2–4, moderate=5–6, severe=7–9) and Mayo endoscopic score (remission=0, mild=1, moderate=2, severe=3). The ability of tests for reflecting disease severity was compared using Receiver Operator Characteristic–Area under the Curve (ROC-AUC) statistic.

Results: Among 106 patients, 26 patients have moderate to severe activity based on partial Mayo score. The area under the curve (AUC) in ROC analysis of SHb and FC to predict partial Mayo score more than 1 were 0.717 and 0.727 (AUC of CRP, 0.549). There was no significant difference between SHb and FC (PSHb vs CRP: 0.007, PFC vs CRP: 0.006, PSHb vs FC: 0.864). For detecting Mayo endoscopic score 1 or more, the AUC of SHb and FC were 0.956, 0.942 (AUC of CRP, 0.756, $p < 0.05$).

Conclusions: SHb and FC can effectively and noninvasively detect mild to moderate UC. Considering that SHb and FC reflects the status of mucosal inflammation and disease activity well, they might reduce the requirement for invasive endoscopic examinations.

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Rapid detection of anti-infliximab antibodies in inflammatory bowel disease patients treated with the reference biologic or the biosimilar CT-P13: performance comparison with ELISA

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Background: Therapeutic drug monitoring (TDM) of infliximab (IFX) and adalimumab is increasingly being used for the management of patients with inflammatory bowel disease (IBD) [1]. Enzyme-linked immunoassays (ELISA) is one of the most used techniques; however, often requires batching samples which can delay results, and be inconvenient in urgent situations where a quick action is needed. In this study we compare the performance of a new lateral flow (LF) rapid test to detect anti-IFX antibodies with ELISA in IBD patients treated with either Remicade® (RMC) only or CT-P13 only or switchers from RMC to CT-P13.

Methods: Serum samples from IBD patients who participated in BIOSIM01, an observational retrospective study, in which patients were treated with either RMC only, or CT-P13 only, or CT-P13 following a switch from RMC, were used. In this study a total of 564 consecutive trough sera (corresponding to 103 patients) were collected just before the infusion to all patients. All samples were frozen for subsequent testing with ELISA (Promonitor® Anti-IFX, Progenika, Spain) and the LF rapid test (Promonitor® Quick Anti-IFX, Progenika, Spain). The rapid test is an immunochromatographic qualitative kit based on LF technology to detect anti-IFX antibodies in patients treated with any IFX molecule in human whole blood (fingerprick or venous) or serum. Antibody test results were read visually at 30 minutes. ELISA quantitative results were categorized as positive or negative to allow comparisons with the rapid test.

Results: The rapid test allowed the detection of anti-IFX antibodies in a few minutes with just 15 µL of serum and showed an almost perfect agreement with the comparative ELISA method. Overall, positive and negative percent agreements between ELISA and the LF test were 97.9% (CI95: 96.3–98.8), 96.0% (CI95: 88.9–98.6) and 98.2% (CI95: 96.5–99.0), respectively. No significant differences in the detection of Anti-IFX antibodies against either drug in any of the three cohorts were observed (Table 1). All antibody positive patients showed no detectable IFX levels as measured with ELISA.

Table 1. Detection of anti-IFX antibodies in the different cohorts with the LF rapid test and ELISA

	Remicade only	Remsima (CT-P13) only	Inflectra (CT-P13) only	Remicade to CT-P13 switchers
Samples (patients)	192 (31)	209 (47)	24 (5)	139 (20)
ELISA Pos samples	29	11	1	34
LF Pos samples	29	14	1	37
PPA	100%	91%	100%	94%
NPA	100	98%	100%	95%

PPA, Positive Percent Agreement; NPA, Negative Percent Agreement.

Conclusions: The almost perfect agreement reported here between the LF and ELISA tests provides support to clinicians and laboratory personnel involved in biological drug monitoring in the use of the rapid test. The rapid test shows detection of antibodies against either the innovator or the biosimilar with comparable analytical sensitivity and offers a good solution in case a qualitative quick analysis of anti-IFX antibodies is required.

References:

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P606**Intestinal fatty acid binding protein parallels temporal changes in Harvey-Bradshaw Index and TNF α in response to infliximab in Crohn's disease**

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Background: Intestinal fatty acid binding protein (I-FABP) is an intracellular protein, with a low molecular weight of approximately 15 kDa, that plays an important role in the transportation and metabolism of long-chain fatty acids in the intestines. I-FABP is selectively expressed in the intestinal epithelium and indicates small intestinal barrier integrity.

The present aims were to determine if

1. I-FABP is elevated in active Crohn's disease (CD),
2. I-FABP parallels anti-TNF α antibody (infliximab) induced lowering of TNF α and Harvey-Bradshaw Index (HBI) as an indicator of mucosal healing, and
3. determine I-FABP distribution along the human gut.

Methods: Biobanked serum was analyzed from 10 CD patients collected during their first three consecutive infliximab treatments (years 2000–2005) with matched pre-treatment and follow-up samples one week after each treatment and corresponding HBI data. I-FABP reference range was established from 30 healthy subjects with normal gut permeability. CD patient TNF α was compared to an in-house reference range (61 healthy subjects). I-FABP and TNF α were measured by ELISA. Paraffin embedded healthy tissue sections were used for I-FABP immunohistochemistry in order to localize expression of I-FABP along the gastrointestinal tract.

Results: CD patient TNF α levels were 1.5 fold higher (2.34 \pm 0.22 vs 1.58 \pm 0.09 ng/L, p <0.001) than healthy subjects, while I-FABP was 2.4 fold higher (2.02 \pm 0.23 vs 0.86 \pm 0.17 μ g/L, p <0.001), with lower levels at first follow-up (p <0.05). Combining all infusion/follow-up pairs also gave a significant difference in I-FABP (p <0.005, n =30). Immunoreactivity to I-FABP was expressed solely in the epithelium of stomach, small intestine and colon, with highest expression in jejunum and ileum.

Conclusions: I-FABP is elevated in active CD with a magnitude comparable to TNF α . On treatment with infliximab temporal parallel falls of TNF α , HBI and I-FABP were found, with a subsequent rise over weeks until next infliximab treatment. Hence, I-FABP may be useful as an intestine-selective prognostic marker for mucosal healing.

P607**Post-operative mortality and predictive factors in a cohort of severe refractory ulcerative colitis patients from the ENEIDA Registry (1989–2013): a multicenter nationwide study**

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Background: Meta-analysis from population-based studies report mortality rates associated to colectomy in ulcerative colitis (UC) around 5% while the reported rate in tertiary centers is close to 0%. However, little is known about factors related to post-operative mortality in the subpopulation of patients with severe refractory (SR-UC). Aim: to evaluate the mortality rate over time together with related factors in patients requiring colectomy due to SR-UC.

Methods: Patients requiring colectomy due to SR-UC from 22 Spanish hospitals adhered to the ENEIDA Registry from 1989 to 2013 have been included. In addition, all investigators reviewed their hospital discharge registries using “colitis” and “colectomy” as search terms. The following variables have been analyzed: age, gender, disease duration and extent, rescue medical therapies, type of surgery (urgent vs elective; open vs laparoscopic), hospital complexity (tertiary vs secondary) and period (1989–2001 vs 2002–2013). Percentages were compared using the χ^2 or Fisher exact test as appropriate. Logistic regression analysis was used to evaluate predictive factors of death.

Results: A total of 424 patients have been included (253 male, age 42.3 \pm 16.4 years). Mortality rate associated to SR-UC flare was 6.4% (N=27/424). Causes of death were: infection 11, post-colectomy perforation 6, hemorrhage 4, multiorgan failure 4, others 2. Univariate analysis showed higher mortality in patients older than 50 years (p <0.0001) and in urgent colectomy (p <0.001). Colectomy rate was lower if SR-UC presented at diagnosis (p =0.02), if it was treated in tertiary centers (p =0.006) and in patients that received rescue medical treatment (p <0.001). There were no differences in mortality between periods (9.3% vs 4.8%; p =0.069). An age >50 [OR 26.0 (7.2–93.4)] and urgent colectomy [OR 13.2 (1.6–104.2)] were predictive factors of mortality whereas to be colectomized in a tertiary center [OR 0.2 (0.08–0.9)], after 2002 [OR 0.3 (0.1–0.9)] and to have a SR-UC at diagnosis [OR 0.1 (0.03–0.7)] reduced the risk independently.

Conclusions: Age, as surrogate marker of comorbidity, is the strongest factor related to post-operative mortality in SR-UC. Patients with SR-UC requiring colectomy should be operated in tertiary hospitals.

P608**New anti-migration extractible metal stents for Crohn's disease strictures: a nationwide GETAID-SFED cohort study**

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Background: In Crohn's disease (CD), strictures are frequent and may require surgical resection or endoscopic balloon dilation. Full covered metal stenting has been abandoned due to the high migration rate. A new anti-migration shaped self-expandable and extractable metal stent (SEEMS) is available. We evaluated its efficacy and safety in a real life cohort.

Methods: All GETAID and SFED centers were asked to collect retrospectively or prospectively all data on patients who had a SEEMS for a Crohn's disease stricture. The SEEMS (Hanarostent HRC-20-080-230 – MITech, distributed by Life Partner Europe) was maintained 7 days before its extraction during a second colonoscopy. Short- and long-term outcomes were evaluated.

Results: 38 patients were enrolled in the study between June 2015 and October 2016. Mean age was 47 years, and 61% were men. CD strictures were anastomotic and unique in 68% of cases. The median (\pm SE) length of the stricture evaluated by cross-sectional imaging and during colonoscopy was 3 ± 1.9 and 2 ± 1.4 cm, respectively. Immediate success (no obstructive symptom at day 30) was reported in 79% of cases. Among them, 6 (20%) and 4 (13%) patients needed a new balloon dilation or surgery during follow-up, respectively. 42% of patients were obstruction-free without any intervention after a mean follow-up of 18 months (range, 1–58). No perforation occurred and 2 migrations were observed (5%).

Conclusions: SEEMS is safe, with no perforation reported in this study, and has a very low migration rate. Whether SEEMS is superior to standard balloon dilatation will require additional investigation.

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A treat-to-target approach via a virtual clinic amongst inflammatory bowel disease patients with secondary loss of response to anti-TNF therapy improves clinical outcomes

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Background: Secondary loss of response to infliximab (IFX) or adalimumab (ADA) is common in inflammatory bowel disease (IBD). Therapeutic drug monitoring (TDM) identifies patients with sub-

therapeutic drug levels who are more likely to respond to dose intensification. Delivering dose-intensified therapy is resource-intensive and may benefit from a non-conventional decision making system such as a virtual clinic (VC). We sought to determine whether enrolment in a VC following a "treat-to-target" paradigm was effective in controlling disease activity in this complex cohort of patients.

Methods: Observational study of 37 IBD patients with secondary loss of response referred to our VC between September 2013-October 2016. Dose-intensification involved shortening the interval between ADA and IFX administration to weekly or six-weekly, respectively. Patients were reviewed in our VC every 6 months with scheduled C-reactive protein (CRP), faecal calprotectin (FC), intestinal ultrasound and IFX/ADA TDM using a drug-sensitive ELISA. Response was defined as maintaining improvements in biomarkers and physician global assessment for ≥ 12 months after initiation of intensified therapy, including those subsequently de-escalated to standard dosing. Patients failing intensified therapy were defined as non-responders. Receiver-operator characteristic analysis was performed to identify a threshold delta increase in drug level associated with response.

Results: 86% had Crohn's disease; 62% were treated with IFX. 22 (59%) responded, 55% of whom received IFX. 11 (30%) responders were de-escalated to standard dosing (median 12 months). 15 (41%) were non-responders (median 9 months). Considering the entire cohort, FC and CRP decreased after 12 months compared to baseline (450 vs. 80 μ g/g; $p=0.019$ and 8.5 vs. 3.5mg/L; $p=0.004$, respectively). Subgroup analyses of biomarker and TDM are shown in Table 1. Increasing IFX drug level $>3\mu$ g/mL from baseline best predicted response (area under curve 0.86, sensitivity 80, specificity 78%). No threshold was found for ADA.

Table 1. Responder vs. non-responder biomarker & drug levels (median; delta = difference between baseline & last test)

	Responders	Non-responders	p-value	n
Last FC (μ g/g)	44	566	< 0.001	34
Last CRP (mg/L)	3	7	0.024	37
Baseline to last IFX level (μ g/mL)	1–6.5	0.8–1.1	0.002; 0.109	10, 9
Baseline to last ADA level (μ g/mL)	2.8–12.7	1.7–11.9	0.002; 0.063	10, 5
Delta IFX levels (μ g/mL)	6.3	1	0.006	19
Delta ADA levels (μ g/mL)	9.4	7.9	0.514	15

Conclusions: A novel virtual clinic model to deliver intensified anti-TNF therapy enabled recapture of response in the majority of patients, with almost one-third de-escalated to standard dosing. IFX drug levels increased in responders compared with non-responders and a threshold increase of $>3\mu$ g/mL from baseline was associated with response. Non-responders treated with ADA showed similar increases in drug level to responders, suggesting that outcome was independent of ADA levels.

P610

Efficacy and safety of GLPG1205, a GPR84 antagonist, in ulcerative colitis: multi-centre proof-of-concept study

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Background: GPR84, a GPCR activated by medium-chain free fatty acids, is primarily expressed on white blood cells (polymorphonuclear, monocyte/macrophage). GLPG1205 is a potent and selective antagonist of GPR84, inhibiting GPR84-induced neutrophil migration *in vitro*. In a mouse IBD model (DSS), GLPG1205 dose-dependently decreased disease activity, histological activity, neutrophil influx as well as colonic MPO content.

Methods: The efficacy and safety of GLPG1205 in moderate-to-severe UC (Mayo score 6–12 with an endoscopic subcore of ≥ 2) was evaluated in an exploratory, double-blind study, in 63 patients (aged 18–75) treated for 12 weeks with 100 mg q.d. GLPG1205 or placebo (pbo) in a 2:1 randomization (NCT02337608). A stable background of 5-aminosalicylates, immunosuppressants or steroids was allowed. Mayo scores and biopsies for Geboes scores and myeloperoxidase (MPO) positive cells (immunohistochemistry) were collected at baseline (BL) and week 8. Fecal calprotectin (FC), subscores for partial Mayo and PK were evaluated at BL and week 4, 8 and 12.

Results: Baseline characteristics, including duration of disease (6.9 y), prior and concomitant medication, Mayo score, FC, MPO positive cells were similar in both groups. At primary endpoint (W8), there was no statistically significant difference in Mayo score, Mayo clinical response, clinical remission, mucosal healing, Geboes Index, and histological response (MPO) between GLPG1205 and placebo (see table). Over the total 12-week treatment period, no treatment difference was observed in the partial Mayo score, the Mayo subscores or FC changes. GLPG1205 was well tolerated. Worsening of colitis, leading to study discontinuation, was reported by 4 patients (3 GLPG1205, 1 placebo). Patients showed a good drug exposure with average plasma concentrations within the range of exposures observed in healthy subjects.

Outcome parameter	Time	Placebo (N=21)	GLPG1205 (100 mg QD) (N=40)	p-value
Mayo score (mean)	BL	8.7	8.7	0.5005
	Week 8	6.3	6.3	
Mayo response (%) ¹	Week 8	48%	40%	0.6143
Mayo remission (%) ²	Week 8	5%	5%	0.9084
Mucosal healing (%) ³	Week 8	10%	5%	0.6261
MPO positive cells (median)	BL	5%	7%	
	Week 8	5%	%	
Fecal calprotectin (median) (mg/kg)	BL	325	335	
	Week 8	189	264	

¹Decrease in Mayo score ≥ 3 points and $\geq 30\%$ and a decrease in rectal bleeding ≥ 1 or an absolute score 0/1. ²Mayo score ≤ 2 and no individual subscore > 1 . ³Endoscopy subscore 0 or 1. BL = baseline.

Conclusions: In this 12-week first-in-patient study with a GPR84 antagonist in patients with moderate to severe UC, GLPG1205 was well-tolerated. Compared to placebo, GLPG1205 had no effect on the clinical parameters or on the biomarkers related to the mode of action (FC or MPO). Therefore, our data suggest that inhibition of GPR84-mediated processes on inflammatory cells may not be relevant in the pathophysiology of active UC.

P611

Relapse risk and predictors for relapse in a real-life cohort of IBD patients after discontinuation of anti-TNF therapy

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Background: We aimed to investigate the incidence of relapse after anti-TNF withdrawal in a real-life cohort of Crohn's disease (CD) and ulcerative colitis (UC) patients in sustained clinical remission, to identify predictors for relapse and to assess the response to restart of anti-TNF retreatment.

Methods: CD and UC patients in clinical remission receiving infliximab (IFX) or adalimumab (ADA) treatment for ≥ 1 year and discontinued treatment were included. Clinical relapse was defined as recurrence of symptoms and the need to (re)start anti-TNF therapy, immunomodulators and/or corticosteroids. Relapse risk and predictors for relapse were studied using cox proportional hazard analysis.

Results: In total, 92 patients discontinued anti-TNF treatment (69 CD, 23 UC). Median duration of anti-TNF therapy at the time of withdrawal was 53 months (IQR 24–87) and the median duration of follow-up was 13 months (IQR 8–16). IFX and ADA were discontinued in 52 (57%) and 40 patients (43), respectively. So far, a total of 47 patients (51%) experienced relapse (CD 33, UC 14), with a median time to relapse of 7 and 4 months in CD and UC, respectively. Of patients that were retreated with the same anti-TNF agents, 83% showed a clinical response. A serum concentration at trough ≥ 2 $\mu\text{g/ml}$ (irrespective of the anti-TNF agent) within one year prior to anti-TNF discontinuation was associated with a significantly higher relapse rate (HR 3.6, 95% CI 1.2–10.6). Continuation of immunomodulatory treatment was not associated with a lower relapse rate in both CD and UC patients (HR 0.8, 95% CI 0.4–1.6; HR 0.6, 95% CI 0.2–1.7). Endoscopic remission in the previous year, bowel-related surgery, prior anti-TNF use, perianal disease, disease location, disease duration, duration of anti-TNF therapy and disease location were not associated with higher or lower relapse rates. Factors such as CRP and faecal calprotectin as predictors for relapse were not addressed, since they were within the normal range in most patients at the time of cessation of anti-TNF therapy.

Conclusions: Approximately 50% of patients in remission under anti-TNF treatment relapsed after anti-TNF withdrawal with a median time to relapse of 7 and 4 months in CD and UC, respectively. A trough level ≥ 2 $\mu\text{g/ml}$ prior to discontinuation of IFX and ADA therapy was associated with an increased relapse risk. Continuation of immunomodulatory treatment was not associated with a reduced relapse risk, which is in contrast to previous work. Retreatment with the same anti-TNF was successful in 83% of patients.

P612

Exclusive enteral nutrition in adults with active Crohn's disease is associated with decreased disease activity

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Background: Exclusive enteral nutrition (EEN) for 8–12 weeks, induces clinical remission in $\sim 70\%$ of children and adolescents with active Crohn's disease (CD), and is considered comparable to steroids. We aimed to evaluate the impact of EEN in adults with active CD.

Methods: Patients with active CD, referred for nutritional intervention with EEN in a tertiary inflammatory bowel disease (IBD) center, were enrolled. Baseline weight and nutritional needs were recorded. EEN was administered by oral polymeric formula with no other food

items allowed. Patients were treated for at least three weeks. Physician's Global Assessment (PGA), Harvey Bradshaw Index (HBI), biomarkers (blood count, C-reactive protein [CRP], and albumin), weight, and body mass index (BMI) were recorded at baseline and at the end of EEN course.

Results: A total of 33/42 patients with active CD (78%) who were offered EEN completed a full course. Eleven patients (33.3%) had newly diagnosed CD (<1.5 years), 16 (48.5%) were on stable-dose medications (immunomodulators and/or biologics), and two (6%) had no medical treatment. Disposition: male/female 25/8; mean age: 31.7±9.4 years; median disease duration – 7 (IQR 1–16) years. Montreal classification: L1 – 13 (39.4%), L2 – 1 (3%) L3 – 18 (54.5%); B1 – 15 (45.5%), B2 – 10 (30.3%), B3 – 4 (12.1%); P – 8 (24.2%). Baseline disease activity: PGA – mild 4, – moderate 20, and severe 8; mean HBI 6.7±4.7 points; median CRP 2.0 mg/dl (IQR 1.3–5.6). Mean EEN duration was 5.5 weeks (range 3–16). Baseline PGA improved after the EEN course in 31/33 patients (94%), this was in parallel to improvement in all activity indices: HBI 2.65±2.7 vs 6.78±4.7 vs ($p<0.001$); median CRP 1.01 (IQR 0.4–0.7) mg/dl vs 2 (IQR 1.3–5.6) vs mg/dl ($p<0.001$); mean albumin 4.2±0.4 mg/l vs 3.8±0.6 mg/l ($p=0.003$), respectively. There was no change in weight or BMI during EEN therapy. Notably, activity indices were also improved in a subgroup of long standing- CD patients: decrease in HBI 7.3±5.08 to 3.0±3.4 ($p<0.001$); CRP 4.66±5.7 mg/dl to 1.08±1.5 mg/dl ($p=0.005$). Finally, in 16 patients who received EEN as an add-on therapy to stable doses of their baseline therapy, HBI decreased from 6.5±5.8 to 2.4±3.3 ($p=0.001$) and CRP dropped from 3.5 (IQR 0.98–3.6) mg/dl to 0.88 (IQR 0.36–0.6)mg/dl ($p=0.023$).

Conclusions: EEN is an effective therapeutic modality for active CD in adults. EEN therapy is associated with decreased clinical and biologic inflammatory activity, and may benefit patients with longstanding and newly diagnosed CD in need of a bridge or an add-on induction treatment.

P613

Mycophenolate mofetil is a valid option in patients with inflammatory bowel disease resistant to TNF-alpha inhibitors and conventional immunosuppressants

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Background: Few studies evaluated the role of mycophenolate mofetil (MMF) in inflammatory bowel disease (IBD), and none of them had specifically focused on patients with previous multiple intolerances and/or nonresponses to conventional immunosuppressants and TNF-alpha inhibitors. The aim of this study was to evaluate efficacy and tolerability profile of MMF in patients with IBD and limited medical treatment options.

Methods: All consecutive patients with previous multiple intolerances and/or nonresponses to conventional immunosuppressants and TNF-alpha inhibitors who started an off-label treatment with MMF from January 2014 to February 2016 were entered in a prospectively maintained database. The steroid-free remission and the clinical response, this latter defined as a clear clinical improvement with a concomitant reduction of steroid dosage compared with baseline or discontinuation, were set as clinical end points.

Results: Baseline features of the study population (n=24) are summarized in Table 1.

Table 1. Baseline characteristics of patients

Variable	N=24
Age (years), mean ± SD/Male gender, n (%)	41.4±12.5/10 (41.7%)
Smokers, n (%) Never/Current/Ex	18 (75.0%)/2 (8.3%)/4 (16.7%)
Type of Disease, n (%) CD/UC	13 (54.2%)/11 (45.8%)
CD, n (%) Ileal/Ileocolic/Colic/UpperGI/Perianal	2 (15.4%)/9 (76.9%)/1 (7.7%)/1 (7.7%)/5 (41.7%)
UC, n (%) Proctitis/Left-sided/Extensive	0 (0.0%)/7 (63.6%)/4 (36.4%)
Behavior(CD), n(%) Inflammatory/Structuring/Fistulizing	3 (21.3%)/5 (38.3%)/5 (38.3%)
Previous resections (CD), n (%)	10 (76.9%)
Extraintestinal manifestations, n (%)	8 (33.3%)
Concurrent drugs, n (%) Prednisone/5-ASA/Biologics	21 (87.5%)/9 (37.5%)/4 (16.7%)

All patients had at least one previous nonresponse to IM or biologics. In particular, 15 (62.5%) were non responders to at least one IM, and 22 (91.7%) to at least one biologic agent; 12 (50.0%) were not responder to at least one IM plus at least one biologic. In addition, 20 (83.3%) had a previous intolerance to at least one IM, and 13 (54.2%) to at least one biologic. The median duration of total follow-up was 32 weeks (range 12–124). Four weeks after initiation of MMF therapy, a steroid-free remission was achieved in 4 patients (16.7%), while a clinical response in 13 (54.1%). At the end of follow-up, 12 patients (50.0%) remained on MMF. Six achieved and maintained steroid-free remission throughout the study period (25.0% of total), and a further 6 patients (25.0%) achieved a clinical response with complete discontinuation of steroids. Twelve patients (50.0%) were considered as treatment failure, and five of them underwent surgery. There was a trend towards a higher efficacy in patients with ulcerative colitis compared with Crohn's disease (63.6% vs. 38.5%, Figure 1), but this was not significant ($p=0.20$).

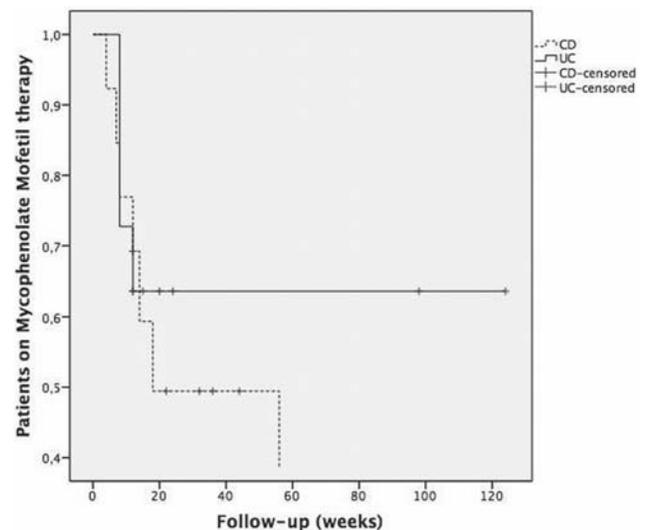


Figure 1. Time to treatment failure on mycophenolate mofetil among patients with Crohn's disease and ulcerative colitis (log-rank: $p=0.410$).

Conclusions: This is the first experience reporting a good efficacy and tolerability of MMF in patients with IBD and multiple previous failures to conventional immunosuppressants and/or TNF-alpha inhibitors.

P614

Anti-TNFs more frequently stopped due to loss of response in British Asians with Crohn's disease: a single centre retrospective analysis

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Background: The prevalence of IBD among British Asian populations matches that of British Caucasians within 2 generations of migration. However response to treatment within this population has not been reported. This study investigates whether indications for and response to anti TNF therapy vary with ethnicity.

Methods: The electronic records for patients under follow up between Sept 2015 and Sept 2016 at a large London IBD centre were studied, and patients ever prescribed anti-TNF were identified. Data collected included: disease onset & phenotype, indication for & time to first anti-TNF, and duration & indication for withdrawal (sustained remission, primary non response, loss of response>3 months or intolerance).

Ethnicity was ascertained as per UK standard coding and categories grouped as Caucasian, Asian or Black.

Results: 484 patients were identified from electronic records. 131 patients were excluded; 22 with mixed ethnicity, the remainder with incomplete records. Following exclusions, 223 Caucasian, 105 Asian and 25 Black patients remained (Total n=353). 245 received infliximab, 105 adalimumab, & 2 unspecified. The mean age was 33.3 years (16–74) with 59.2% (n=209) male and 41.8% (n=144) female. 77.6% (n=274) had CD, 19.2% (n=68) had UC, the remainder had IBD-U.

All UC and 63.91% (n=175) CD patients were treated for exclusively luminal disease; the remainder had luminal with either fistula or perianal disease. Indications did not vary with ethnicity (Chi sq. p=0.1697).

There was no difference in age at diagnosis with ethnicity for CD or UC.

The median (IQR) disease duration to first anti-TNF varied with ethnicity: Caucasians 7.8 (2.3–12.6) yrs; Asians 4.3 (2.0–7.3) yrs; Black 4.9 (2.1–9.7) yrs (Kruskal-Willis, p=0.0014, N=314). Asian patients with CD were prescribed anti-TNF a median 3.8 years earlier in disease course than Caucasians (Mann Whitney p=0.0002 N=229).

190 patients had stopped anti-TNF therapy at the time of review; 165 had a clearly documented stop and start date. Of these, the median (IQR) duration to stopping was 1.2 (0.5–2.3) yrs and did not vary with ethnicity (Kruskal-Wallis 0.9589).

The indication for stopping anti-TNF varied with ethnicity (χ^2

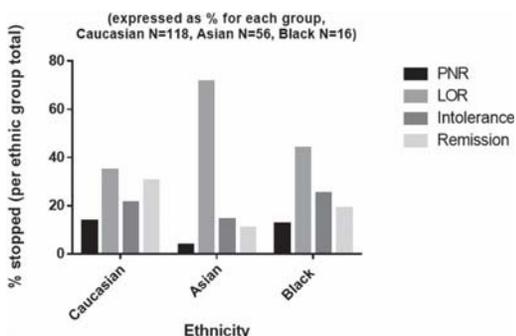


Figure 1. Indications for stopping anti-TNF

p=0.0010). Sub analysis of CD only showed that fewer Asians stopped due to sustained remission (Chi Sq with Yates correction p=0.0392). This trend was not seen within UC (p=0.1488)

Conclusions: Asian patients with IBD receive an anti-TNF sooner, but are more likely to have loss of response and are less likely to experience sustained remission.

P615

The unfinished symphony: golimumab is efficient in patients with refractory Crohn's disease

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Background: Golimumab is a fully human, IgG1k monoclonal antibody against anti-tumor necrosis factor alpha (anti-TNF) agent approved for the treatment of moderate-to-severely active ulcerative colitis. However, there have been no formal trials to date to assess its utility in Crohn's disease (CD). This study's aim was to assess the efficacy and safety of golimumab in patients with anti-TNF-refractory CD.

Methods: Consecutive patients with CD who were treated at a single IBD center with golimumab between March 2010 and September 2016 were included in a retrospective observational study. Clinical response was defined as a significant reduction in symptoms and biochemical markers of CD, with no requirement for surgery or introduction of immunomodulators. The outcome was assessed after 6, 12 and 36 months and at last clinical follow-up.

Results: Forty-five patients were included, with a median follow-up of 22 months (interquartile range 12–34) following initiation of golimumab. Induction regimens were often higher than the standard protocol with cumulative doses (week 0 and 2) of ≥ 400 mg and ≥ 600 mg in 75% and 21% of patients, respectively. All patients had previously failed at least 2 anti-TNF agents. In 64% of patients, anti-TNF failure was associated with loss of response and in 23% due to adverse effects. Clinical response at 6 months was achieved in 32/45 (71%) patients. The cumulative probabilities that patients maintained their clinical response for 12 and 36 months after the in-

Table 1. Demographic and clinical characteristics

	N = 45
Female, n (%)	28(60)
Age at induction (Median(IQR))	38 (43-29)
Disease duration (Median(IQR))	12.2 (20-8)
Duration of follow-up (Median(IQR))	22(34-12)
CD location (Montreal classification, n (%))	
Ileal (L1)	9 (20)
Colonic (L2)	6(13)
Ileocolonic (L3)	30 (67)
Proximal (L4)	13 (29)
CD phenotype (Montreal classification), n (%)	
Inflammatory (B1)	9 (20)
Stricturing (B2)	23 (51)
Penetrating (B3)	13(29)
Perianal	24 (53)
Smoker status, n (%)	
Non-smoker	42(93)
Current Smoker	3(7)
Previous intestinal resections, n (%)	32 (71)
Previous immunosuppressant, n (%)	38(84)
Previous anti-TNF, n (%)	45 (100)
Other previous biologics (non anti-TND agents), n (%)	12(27)
Concomitant immunosuppressant, n (%)	25(56)
Concomitant steroids, n (%)	21(47)
Elevated CRP (>5 mg/L)	33(73)

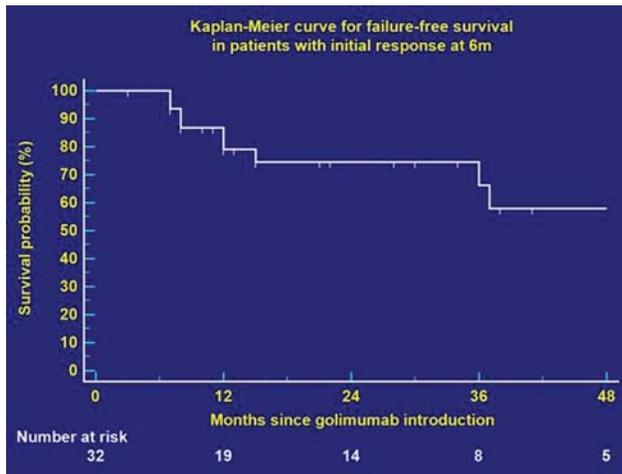


Figure 1. Kaplan-Meier curve for failure-free survival in patients with initial response at 6 months.

roduction of golimumab were 79% and 65%, respectively. Through most recent follow-up 59% remained on treatment. Endoscopic improvement and mucosal healing at 1 year were achieved in 73% and 47% of patients, respectively.

Conclusions: This study demonstrates the efficacy of golimumab in CD patients who were previously refractory to at least 2 anti-TNF agents. An initial response is successfully maintained in the majority of patients for up to 3 years. Future studies should be performed in CD to formally assess the efficacy of golimumab in a randomized controlled trial and to establish the optimal dosing regimen.

P616

Natural history and phenotype of inflammatory bowel disease with co-existent celiac disease

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Background: Inflammatory bowel disease (IBD) and celiac disease (CeD) have overlapping clinical features and may share some genetic risks. Under diagnosis and treatment of a concurrent disease can lead to persistence of symptoms and increase morbidity. We aim to characterize the natural history of patients with IBD and coexistent CeD. **Methods:** A retrospective case study was performed on all adult patients with IBD and CeD at our institution. A total of 447 patients were associated with the ICD-9 or ICD-10 codes for CeD and Crohn's disease (CD), or ulcerative colitis (UC). Of these, 107 patients met the diagnostic criteria for both IBD and CeD. Patient demographics, IBD location, phenotype, medication history, disease activity, CeD diagnostic methodology, and the need for hospitalizations, surgeries, and rescue corticosteroids were noted.

Results: A total of 107 patients (52.3% male) had IBD with coexistent CeD (Table 1). The majority of patients (n=69, 65.1%) were diagnosed first with IBD then CeD after a median 7.4 years (interquartile range [IQR] 1.5–12.8 years), while 28.3% (n=30) were diagnosed first with CeD then IBD after a median of 2.9 years (IQR 0.5–6.6 years). A small proportion (n=7, 6.6%) were concurrently diagnosed with IBD and CeD. The majority (n=69, 64.5%) of CeD was diagnosed based on both histology and serology. The median age of diagnosis for IBD was 29.2 years (IQR 19.7–40.0 years) and 35.0 years (24.8–49.2 years) for CeD.

The majority of patients with IBD had ulcerative colitis (UC) (77.8%

Table 1: Baseline Characteristics of Patients with Coexisting IBD and CeD

Characteristic		IBD-CeD N = 107
Age at IBD diagnosis, median (IQR)		29.2 (19.7 – 40.4)
Duration of IBD, years, median (IQR)		3.2 (0.03 – 8.7)
Age at Celiac diagnosis, years, median (IQR)		35.0 (24.8 – 49.2)
Male gender, N (%)		56 (52.3)
IBD type	Crohn's disease	32 (29.9)
	Ulcerative colitis	73 (68.2)
	Indeterminate colitis	2 (1.9)
Celiac diagnosis methodology	Serology and histology	69 (64.5)
	Histology alone	17 (15.9)
	Serology alone	11 (10.3)
	Clinical history	10 (9.3)
Order of diagnosis ^a	IBD before celiac	69 (65.1)
	IBD after celiac	30 (28.3)
	Concurrent	7 (6.6)
Time to celiac diagnosis after IBD, years, median (IQR)		7.4 (1.5 – 12.8)
Time to IBD diagnosis after celiac, years, median (IQR)		2.9 (0.5 – 6.6)
Crohn's disease location	Ileal	9 (29.0)
	Ileocolonic	13 (42.0)
	Colonic	9 (29.0)
Upper GI Crohn's disease ^b		6 (18.8)
Perianal Crohn's disease		5 (15.6)
Crohn's disease phenotype	Inflammatory	24 (75.0)
	Strictureing	4 (12.5)
	Fistulizing	4 (12.5)
Ulcerative colitis extent ^c	Proctitis	7 (9.7)
	Left-sided colitis	9 (12.5)
	Extensive colitis	56 (77.8)
5-ASA ever use		66 (61.7)
Corticosteroid ever use		45 (42.1)
Immunomodulator ever use		13 (12.2)
Biologics ever use		20 (18.7)
IBD-related hospitalization		33 (30.8)
IBD-related surgery		41 (38.3)

Footnote: a, missing data 1 case; b, upper GI only 1 case; c, extent unknown 1 case

extensive colitis) while 29.9% had Crohn's disease (CD) (42% ileocolonic, 75% inflammatory phenotype) (Table 2, see p. S395). Co-existent PSC was diagnosed in 22.4% of IBD-CeD patients (12.5% of CD, 61.6% of UC). At 5-years follow-up after initial diagnosis or initial presentation to our institution (if previously diagnosed elsewhere with IBD), 18.7% IBD-CeD had ever used biologics (50% of CD, 7.7% of UC), 30.8% had IBD-related hospitalizations (50% of CD, 23.3% of UC), and 38.3% had IBD-related surgeries (53.1% of CD, 31.5% of UC).

Conclusions: Patients with IBD and co-existent CeD were more likely to have had IBD diagnosed first, and those with CD compared to UC had more severe disease with a larger proportion requiring the use of biologics and in need for hospitalization or surgery.

P617

Extraintestinal autoimmune phenomena during treatment with vedolizumab

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Background: Extraintestinal side effects in patients receiving Vedolizumab, especially skin and joint reactions, have been described. Underlying mechanisms are unclear.

Methods: Four patients with extraintestinal symptoms under therapy with Vedolizumab were identified and clinical characteristics were analysed. In one patient with pulmonary symptoms, peripheral blood mononuclear cells (PBMC) were isolated, stained with anti-CD45, anti-CD3, anti-CD29 and anti-49d and assessed by flow cytometry.

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Table 2: Comparative characteristics of CD and UC with coexisting celiac disease on follow-up

Characteristic	CD N= 32	UC N= 73
Age at diagnosis, median (IQR)	27.7 (16.9 - 39.5)	29.8 (19.7 – 45.2)
Age at Celiac diagnosis, median (IQR)	35.5 (23.4 – 54.1)	34.9 (24.9 – 49.7)
Male gender, N (%)	11 (34.4)	45 (61.6)
Coexisting Primary Sclerosing Cholangitis	4 (12.5)	20 (27.4)
Baseline		
5-ASA ever use	17 (53.1)	49 (67.1)
Corticosteroid ever use	12 (37.5)	32 (43.8)
Immunomodulator ever use	4 (12.5)	8 (11)
Biologics ever use	10 (31.3)	9 (12.3)
1 year follow-up		
CD, N = 24		
UC, N = 54		
5-ASA ever use	8 (33.3)	31 (57.4)
Corticosteroid ever use	8 (33.3)	10 (18.5)
Immunomodulator ever use	5 (20.8)	9 (16.7)
Biologics ever use	7 (29.2)	5 (9.3)
Change in disease location/phenotype	7 (29.2)	-
Disease activity		
Remission	21 (87.5)	50 (92.6)
Refractory	3 (12.5)	4 (7.4)
2 year follow-up		
CD, N = 19		
UC, N = 48		
5-ASA ever use	4 (21.1)	25 (52.1)
Corticosteroid ever use	5 (26.3)	7 (14.6)
Immunomodulator ever use	5 (26.3)	6 (12.5)
Biologics ever use	7 (36.8)	6 (12.5)
Change in disease location/phenotype	5 (26.3)	-
Disease activity		
Remission	17 (89.5)	45 (93.7)
Refractory	2 (10.5)	3 (6.3)
5 year follow-up		
CD, N = 14		
UC, N = 26		
5-ASA ever use	3 (21.4)	12 (46.2)
Corticosteroid ever use	4 (28.6)	5 (19.2)
Immunomodulator ever use	4 (28.6)	2 (7.7)
Biologics ever use	7 (50)	2 (7.7)
Change in disease location/phenotype	6 (42.9)	-
Disease activity		
Remission	10 (71.4)	25 (96.1)
Refractory	4 (28.6)	1 (3.9)
IBD-related hospitalization	16 (50)	17 (23.3)
IBD-related surgery	17 (53.1)	23 (31.5)

Footnotes: 5-ASA, 5-Aminosalicylates; CD, Crohn's disease; IBD, Inflammatory bowel disease; UC, Ulcerative colitis

Results: All patients developed extraintestinal symptoms between the first and sixth dose, and the three patients receiving more than three infusions all responded well to the therapy regarding to their intestinal symptoms (decline in Harvey-Bradshaw-Index or modified Mayo-Score). One female patient with ulcerative colitis was diagnosed with thyroiditis de Quervain, a granulomatous inflammation of the thyroid, based on pathognomic ultrasound features after six doses. The second female patient developed vasculitis of the eye after receiving one dose of Vedolizumab for Crohn's disease (CD). Two male patients, both with Crohn's colitis, presented predominantly with pulmonary symptoms: One suffered from rapidly progressive acute respiratory distress syndrome requiring mechanical ventilation after receiving the fourth infusion; the other presented with dyspnoea and dry cough after the third dose. In both cases, CT-scan showed bilateral infiltrates and hilar lymphadenopathy. Extensive work-up identified no infectious or other specific cause (including repeat cultures and PCR for Mycobacterium tuberculosis complex DNA, Quantiferon assay, urine histoplasmosis antigen, HIV testing, negative autoantibodies; and soluble IL-2 receptor, ACE and CD4/CD8-ratio within normal range). In the latter case, lung tissue obtained during thoracoscopic wedge resection showed multiple characteristic non-caseating epithelioid-granulomas, highly suspicious for pleural and pulmonary manifestation of CD. Analysis of integrin-expression on PBMCs demonstrated a distinct CD29+ (i.e. integrin β 1+) population, an integrin necessary for lymphocyte homing into the lung. After treatment with prednisolone, both the β 1+ cells as well as pulmonary infiltrates vanished, along with complete resolution of clinical symptoms. Likewise, the other patients fully recovered after cessation of Vedolizumab plus administration of steroids, if needed.

Conclusions: Shifts in integrin-expression triggered by Vedolizumab and consequently altered migrational behaviour of immune cells into other organs than the gut might explain the excellent intestinal re-

sponse to the drug accompanied by extraintestinal manifestation of the disease in our patients.

P618

Rapidity of onset of response to adalimumab in luminal Crohn's disease. Data from RAPIDA trial

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Background: Rapidity of response to treatment in Crohn's disease (CD) is now considered a field of major interest, due to the importance of achieving the highest benefit in the shortest possible time. There are no studies specifically designed to evaluate the rapidity of

response to ADA neither other anti-TNF therapies. The aim of this trial was to evaluate the rapidity of onset of clinical response to adalimumab (ADA) therapy.

Methods: Adult anti-TNF naïve patients with active luminal (Harvey-Bradshaw Index (HBI) ≥ 8) moderate-to-severe CD (excluding penetrating and stricturing disease), with no response to a full and adequate course of therapy with corticosteroids and/or immunosuppressants, were enrolled in this interventional, prospective, open label, single arm and multicenter clinical trial. Patients received standardized ADA treatment (160 mg – 80 mg – 40 mg eow).

The HBI was evaluated to determine the response at day 4 and week 1; and clinical remission at weeks 2, 4 and 12. Response was defined as a decrease of, at least, 3 points in the HBI global score and remission was defined as HBI global score < 5 .

CRP (C Reactive Protein) and fecal calprotectin (FC) were analyzed at baseline, day 4, week 1, 2, 4, 12.

The modified intention to treat (mITT) population was the primary population for efficacy analysis and consisted of those patients enrolled in the study who had received at least one dose of ADA.

Treatment-emergent serious adverse events (AEs) were recorded to assess safety throughout the study until 70 days after last treatment dose. All patients who received at least one dose of ADA were included in the safety population.

Statistical analyses were performed by the t-test or the Wilcoxon signed rank test, as applicable. Time to clinical response was analyzed using a Kaplan-Meier survival analysis model.

Results: 80 anti-TNF naïve patients were analyzed. 62.5% and 71.3% of patients experienced a response at day 4 and week 1, respectively. Remission was achieved by 50.0% of patients at week 2, 62.5% at week 4 and 42.5% at week 12. The median time to obtain response was 4.0 days (95% confidence interval (CI): 1.0, 4.0) and the median time to remission was 7.0 days (95% CI: 4.0–18.0).

Table 1

	Median CRP levels (mg/L)	Median FC levels ($\mu\text{g/g}$)	p-value vs baseline for CRP and FC
Baseline	5.50	732	< 0.0001
Day 4	1.71	453	< 0.0001
Week 1	1.71	465	< 0.0001
Week 2	1.66	448	< 0.0001
Week 4	2.47	279	< 0.0001
Week 12	2.38	346	< 0.0001

37.50% of the patients suffered from any adverse event (AE) during the study. Only 1 patient (1.25%) showed a serious AE.

Conclusions: ADA produces rapid clinical remission and response

since day 4 in patients with moderate-to-severe CD unresponsive to therapy with corticosteroids and/or immunosuppressants.

P619 Tofacitinib for the treatment of resistant ulcerative colitis: the University of Chicago experience

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Background: Many inflammatory bowel disease (IBD) patients are unresponsive to medical therapy or lose response. Tofacitinib is a selective inhibitor of the Janus kinase (JAK) family, focused on JAK 1–3. Its effectiveness for rheumatoid arthritis and for induction and maintenance of remission of ulcerative colitis (UC) has been demonstrated in pivotal trials, but 2 separate phase 2 trials for Crohn's disease (CD) were negative. Here we describe our off-label experience with the use of tofacitinib for the treatment of anti-TNF refractory moderate to severe IBD patients.

Methods: This is a retrospective, observational study of the off-label use of tofacitinib for IBD. Patients with medically resistant IBD were treated with 5 mg twice daily or 10 mg twice daily. Clinical response and adverse events were assessed at 8 weeks and at subsequent visits until the last follow up encounter. Response to treatment was determined as defined by the patient's provider. Partial response was symptomatic improvement but not resolution and remission was defined as resolution of clinical symptoms.

Results: Between December 2014 and September 2016, 12 IBD patients (9 UC, 2 CD (colon), 1 IBD-U; 7 male; median age 36.5 years IQR 25.5) were treated with tofacitinib.

All patients had failed treatment with anti-TNF and anti-integrin previously. The initial dose for the patients was 5 mg PO twice daily. At 8 weeks of treatment, 8 patients (66.7%) had a clinical response to treatment. Of those, 3 achieved clinical remission. 3 patients (25%) did not respond to treatment and a single patient stopped treatment after 4 weeks due to an adverse event. Dose escalation to 10 mg PO twice daily was tried in 2 patients, with no clinical response in one patient and subsequent clinical remission in the other. The patients were followed for a mean 6.3 + 6.6 (range 2–23) months. No loss of response was noted in clinical follow-up. Two episodes of systemic infections were noted, both while on concomitant steroids: cellulitis and parainfluenza which required hospitalization and cessation of treatment. No other adverse effects were observed including changes in the levels of hemoglobin, neutrophil count, creatinine clearance,

Abstract P619

Table 1 Clinical and demographic characteristics of the patients

Gender (M/F)		7/5
Age at induction (median (IQR)), years		36.5 (25.5)
Duration of disease (median (IQR)), months		76 (158)
Previous medications (no. (percentile))	anti TNF	12 (100)
	thiopurines	8 (67)
	MTX	7 (58)
	vedolizumab	10 (83)
Concomitant medications	systemic corticosteroids (no. (percentile))	8 (67)
	prednisone dose (median (IQR)), mg	22.5 (15)
	azathioprine (no. (percentile))	1 (8)
	vedolizumab (no. (percentile))	1 (8)

lipid profile or liver enzymes. No episodes of herpes infections were noted during follow up.

Conclusions: In this cohort of medically-resistant IBD patients, 67% of them responded to off-label tofacitinib and none of these lost response during follow-up. Tofacitinib is an effective therapeutic option for this challenging patient population.

P620

Network meta-analysis of efficacy and safety of different intravenous iron compounds for the treatment of iron deficiency anaemia in patients with inflammatory bowel disease

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Background: Iron deficiency anaemia (IDA) is a frequent complication of inflammatory bowel disease (IBD) associated with reduced quality of life and increased hospitalisation rates. Not only has inflammation been shown to limit the absorption and efficacy of oral iron, but oral iron may exacerbate bowel inflammation in IBD. ECCO guidelines recommend intravenous (IV) administration of iron in IBD patients with IDA. IV Compounds currently approved for IDA in IBD are ferric carboxymaltose (FCM), iron sucrose/saccharate (IS), iron isomaltoside (ISM) and iron dextran (IDX).

Methods: We compared the efficacy and safety of different IV iron compounds approved to treat IDA in IBD patients using a network meta-analysis (NMA) and systematic review. In June 2016, PUBMED, SCOPUS, Web of Science and Cochrane databases were searched for trials with an observation time ≥ 4 weeks analysing IV iron therapy of IDA in IBD and published in English. Outcome measures were haematopoietic response (% of patients), defined as haemoglobin (Hb) normalisation or increase of ≥ 2 g/dL and no. of AEs as % of safety population. Bayesian NMA was performed after assessment of eligible studies using Cochrane's Risk of Bias tool in RevMan and expressed as ORs based on response rate with 95% credible intervals (CrIs). Analyses were conducted using R vers. 3.3.1 with package gcmc.

Results: From 1894 papers in total, after duplication removal and detailed review, 15 eligible studies were included: 6 RCTs (NMA) and 9 other studies (systematic review only). No eligible RCTs were found for IDX. Bayesian NMA was performed on the 6 eligible RCTs (1182 patients): Four RCTs compared FCM, IS or ISM vs. oral iron, one compared FCM vs. IS, and one IS vs. IS plus erythropoietin (IS+EPO). FCM was significantly more effective than oral iron (OR=1.9, 95% CrI [1.2;3.2]). For other IV iron, no statistical significance was found vs. oral iron (OR=1.3, 95% CrI [0.79;2.2] for IS, OR=1.3, 95% CrI [0.8;2.1] for ISM, OR=4.5, 95%CrI [0.71;43.0] for IS+EPO). Rank probabilities of the five treatments showed the most effective IV monotherapy to be FCM. IS+E combination therapy was most effective overall. The systematic review (1765 patients) showed overall response rates of 401/505 (79%) for FCM, 344/508 (68%) for IS, 147/219 (67%) for ISM and 33/78 (42%) for IDX. Drug-related AEs occurred at pooled rates of 12.0%, 15.3%, 12.0% and 17.0%, SAEs at 0.2%, 0.2%, 0.0%, 0.4%, for FCM, IS, IDX

and ISM, respectively. For oral iron, AE rate was 23.2% (82/353), and SAE rate 1.4% (5/353).

Conclusions: FCM was shown to be the most effective IV iron formulation as monotherapy, followed by iron sucrose. In addition, FCM tended to have a better safety profile than IS or ISM, with fewer AEs.

P621

Efficacy and safety of golimumab in ulcerative colitis. Preliminary data from a multicenter Italian study

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Background: Golimumab is an anti-TNF-alpha antibody approved for the treatment of Ulcerative Colitis (UC) patients. Its efficacy and safety were studied in randomized, double blind trials, but its effectiveness and safety in daily clinical practice are still little known.

The aim of the study was to assess the effectiveness and safety of Golimumab in daily clinical practice.

Methods: All UC patients from 14 centers treated with Golimumab, were consecutively enrolled starting from June 2015. Demographic information's (age, gender, smoking status) and clinical data (extension and duration of UC, previous therapies, comorbidities) at time of enrollment were collected. Clinical, laboratory and endoscopic data during the treatment with Golimumab were collected every three months.

Results: A total of 104 patients (39 males) were enrolled. The mean age at diagnosis and mean duration of disease were respectively 38.9 \pm 14.6 years, and 9.1 \pm 7.0 years. Sixty-four patients had a pancolitis (62%), 36 a distal colitis (35%) and 4 (4%) a proctitis. At enrolment, the median total and endoscopic Mayo score, ESR, C Reactive Protein and faecal calprotectin were respectively 8 (IQR 4–10), 2 (IQR 2–3), 25 (IQR 16.5–40), and 1 (IQR 0.3–2.35). Eighty-eight patients (87%) were never or ex smokers. Fifty-six patients (54%) were naïve to anti-TNF-alpha. Fifty-six patients (54%) were naïve to anti-TNF-alpha. The indications for Golimumab were: steroid-resistance in 17 pts (16%), steroid-dependence in 64 pts (62%), extraintestinal manifestations in 7 pts (7%), and anti-TNF-alpha failure in 16 pts (15%). Twenty patients (19%) were treated with concomitant immunosuppressants. After 3 months of therapy, a total of 48 patients (46%) were responder (reduction of at least 3 points of partial Mayo score), and 37 of them were in clinical remission (total Mayo score ≤ 2). After 3 months of therapy a significant

reduction of the median values of the total Mayo score (5; IQR 2–7, $p < 0.0001$), endoscopic Mayo score (1.5; IQR 2–2.25, $p < 0.0001$), ESR (18; IQR 12.5–30, $p < 0.01$), and CRP (median value 0.5, IQR 0.3–1.2, $p < 0.01$) was observed. At univariate analysis for predictive factors of response (gender, duration of disease, smoking status, previous therapies with anti-TNF, and combo therapy), only the naïve status to anti-TNF- α was associated with a better outcome ($p = 0.01$). A total of 7 adverse events (no serious) were observed. Six non-responder patients underwent to colectomy. All of them were refractory to other anti-TNF- α .

Conclusions: Golimumab is effective and safe in induction of response in UC patients in daily clinical practice.

P622
Efficacy of probiotics in inflammatory bowel disease: systematic review and meta-analysis

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Background: Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory bowel diseases (IBD). Evidence implicates disturbances

of the gastrointestinal microbiota in their pathogenesis. We performed a systematic review and meta-analysis to examine the efficacy of probiotics in IBD.

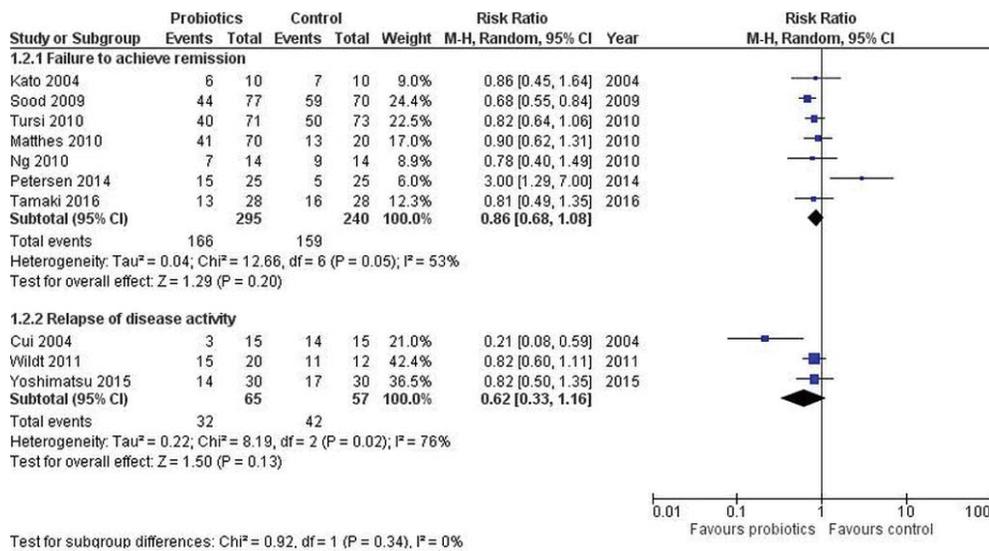
Methods: MEDLINE, EMBASE, and the Cochrane Controlled Trials Register were searched (up to November 2016). Eligible randomised controlled trials (RCTs) recruited adults with UC or CD, and compared probiotics with 5-aminosalicylates (5-ASAs) or placebo. Dichotomous symptom data were pooled to obtain a relative risk (RR) of failure to achieve remission in active IBD, or RR of relapse of disease activity in quiescent IBD, with 95% confidence intervals (CIs).

Results: The search identified 12,251 citations. Twenty-two RCTs were eligible. There was no benefit of probiotics over placebo in inducing remission in active UC (RR of failure to achieve remission = 0.86; 95% CI 0.68–1.08).

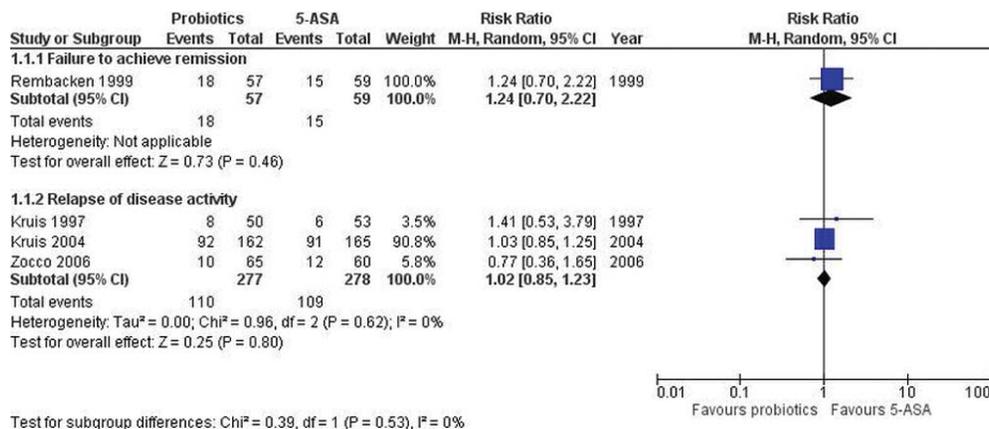
However, when only trials of VSL#3 were considered there appeared to be a benefit (RR = 0.74; 95% CI 0.63–0.87). Probiotics appeared equivalent to 5-ASAs in preventing UC relapse (RR = 1.02 (95% CI 0.85 to 1.23)).

There was no benefit of probiotics in inducing remission of active CD, in preventing relapse of quiescent CD, or in preventing endoscopic or clinical relapse of CD after surgically induced remission.

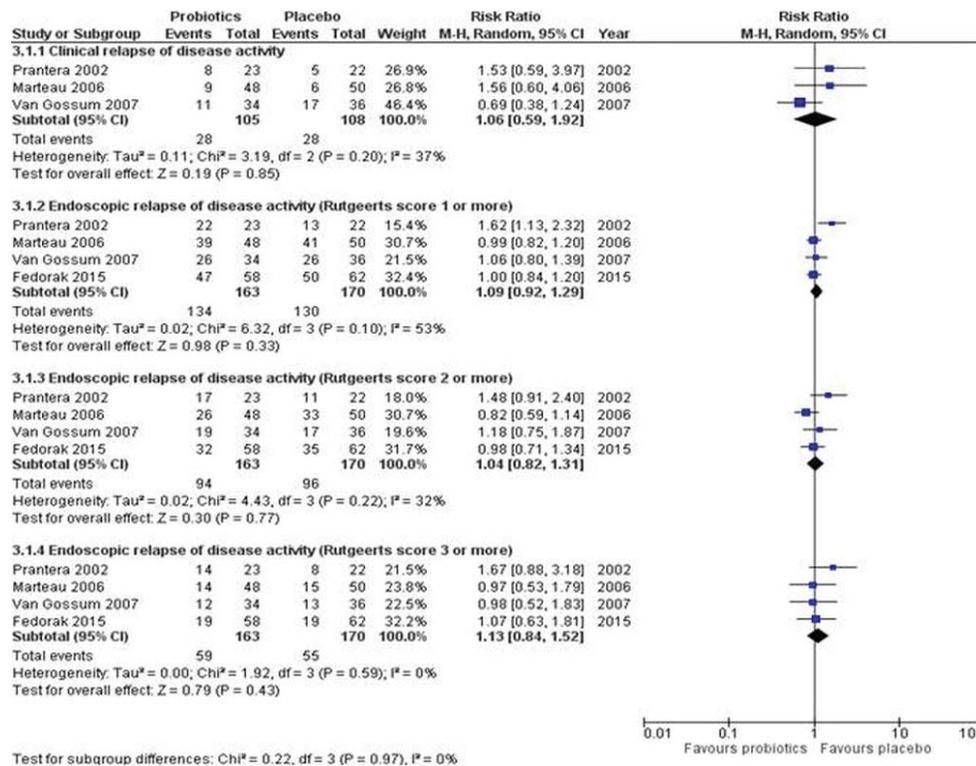
Conclusions: VSL#3 appears to be effective in inducing remission in active UC, and probiotics may be as effective as 5-ASAs in preventing relapse of quiescent UC. However, the efficacy of probiotics in CD



Abstract P622 – Figure 1. Forest plot of randomised controlled trials reporting the efficacy of probiotics versus placebo in inducing remission in active UC, or in preventing relapse in quiescent UC.



Abstract P622 – Figure 2. Forest plot of randomised controlled trials reporting the efficacy of probiotics versus 5-aminosalicylates in inducing remission in active UC, or in preventing relapse in quiescent UC.



Abstract P622 – Figure 3. Forest plot of randomised controlled trials reporting the efficacy of probiotics versus placebo in inducing remission in active CD, or in preventing relapse in quiescent CD.

remains uncertain, and more evidence from RCTs is required before their utility is known.

P623

Therapeutic preferences and outcomes in newly diagnosed patient with inflammatory bowel diseases in the biological era in Hungary. A nationwide study based on the National Health Insurance Fund database

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Background: Accelerated treatment strategy, including tight disease control and early aggressive therapy with immunomodulators (IM) and biological agents has become increasingly common in IBD. The aim of the present study was to estimate the early treatment strategy and outcomes in newly diagnosed IBD patients between 2004–2009 and 2009–2015 in Hungary in the administrative database of the National Health Insurance Fund (OEP).

Methods: We used the nationwide administrative database of the National Health Insurance Fund (OEP), the only nationwide state-owned health insurance provider in Hungary. Patients were identified through previously reported algorithms using the ICD-10 codes for Crohn's disease (CD) in the out-, inpatient (medical, surgical) non-primary care records and drug prescription databases between 2004–2015. Patients were stratified according to the year of diagnosis and maximum treatment step during the first 3-years after the diagnosis. **Results:** A total of 6173 newly diagnosed CD patients with physician-diagnosed IBD were found in this period. Rate of maxi-

imum treatment step did not differ before and after 2009 (5-ASA: 12% vs. 14%, Steroid 31% vs. 31%, IM 44% vs. 44%, biological 13% vs. 12%). Probability of hospitalizations in the first 3-years after the diagnosis according to the maximal treatment step was different before and after 2009 (at 12-months: anti-TNF: 63% vs. 57% (p=0.03) IS: 56% vs. 50% (p=0.002), steroid: 32% vs. 58% (p<0.001)), respectively. In contrast, surgery rates were not significantly different in patients diagnosed before and after 2009 according to the maximum treatment step (at 12-months: anti-TNF 9% vs. 13%, IS: 56% vs 49%, steroid 36% vs. 34%, 5-ASA 27% vs. 26%). **Conclusions:** The rate of maximal treatment steps and surgery rates did not differ in patients diagnosed before and after 2009. Hospitalization rates during the first 3-years after the diagnosis decreased in all – but the steroid- treatment groups, suggesting a change in the patient management.

P624

Chromoendoscopy and narrow band imaging versus conventional white light endoscopy for detection of neoplasia in ulcerative colitis – a systematic review and meta-analysis

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Background: an increased risk for development of colorectal can-

cer (CRC) in patients with ulcerative colitis (UC) was confirmed in multiple studies. In light of this, professional authorities recommend surveillance of CRC in patients with long-standing UC, favoring chromoendoscopy (CE) with targeted biopsies of identified lesions over white light endoscopy (WLE). Narrow-band Imaging (NBI) has been evaluated in several studies, however it is still unclear whether this modality can be considered an equally accurate alternative.

The aim of the study was to compare the diagnostic yield of WLE, CE and NBI for detection of neoplasia in UC patients.

Methods: We performed a meta-analysis of prospective trials comparing the accuracy of CE, WLE or NBI for detection of neoplasia in patients with IBD MEDLINE and EMBASE search were performed using the search terms “ulcerative colitis”, “chromoendoscopy”, “narrow band imaging”. We compared the diagnostic accuracy for detection of any neoplasia individual patient examined, as well as per number of neoplastic lesions per patient.

Results: The search yielded eleven studies eligible for analysis. Five studies compared CE to WLE. CE (n=361 patients) was found to be superior to WLE (n=358 patients): per-patient analysis odds ratio (OR)-2.05 (95% CI 1.26,3.35; p=0.004; I2=0%); per lesion analysis OR-2.79 (95% CI 2.08,3.73; p<0.00001; I2=22%). In four studies Comparing NBI (n=305 patients) to WLE (n=305 patients), no difference was found: Per-patient analysis OR-0.97 (95% CI 0.62,1.53; p=0.91; i2=0%); per lesion analysis OR-0.94 (95% CI 0.63,1.4; p=0.68; i2=0%). Two studies compared CE (n=104 patients) to NBI (n=104 patients) and were not statistically significant different: per-patient analysis OR-1.0 (95% CI 0.51,1.95; p=0.73; i2=0%); per-lesion analysis OR-1.29 (95% CI 0.69,2.41; p=0.93; i2=0%).

Conclusions: Our results suggest that CE has a superior DY for detection of neoplasia in patients with UC. NBI was not significantly different to either WLE or CE, but due to the low number of studies, further evaluation is needed.

P625

Ustekinumab use in Crohn's disease: effectiveness of dose escalation

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Background: Efficacy of ustekinumab (UST) in Crohn's disease (CD) has been demonstrated in clinical trials. In the absence of therapeutic drug monitoring, empirical dose escalation has been considered as a strategy to optimize response in patients with either primary or secondary non-response. Efficacy and safety of UST 90mg subcutaneous (SC) every 4 weeks is not known.

Methods: A retrospective, observational study of compassionate use of UST in CD was conducted at a Canadian tertiary centre. A subset of patients in whom dose escalation (90mg SC every 4 weeks) had occurred was identified. Symptomatic response, defined as physician documentation of improvement of CD-associated symptoms and continuation of therapy, following dose escalation was assessed, as was biochemical or endoscopic response if available.

Results: Ustekinumab was dose escalated in 16 patients (9 males) of median age 47 (IQR 34–54); disease duration of 12.5 years (IQR 8–18) and location of ileal (4); colonic (4) and ileocolonic (8), with accompanying perianal involvement in 8 patients. All patients were anti-TNF experienced. Fourteen patients had been induced with standard SC dosing (90mg Weeks 0, 1, 2) and 4 with higher SC dosing (270mg Week 0; 180mg Weeks 1 and 2). Dose escalation occurred for primary and secondary nonresponse to UST in 7 and

9 patients respectively. Nineteen percent (3/16) of patients had a response to dose escalation, while 10 patients have ceased therapy. A myopathy developed in one patient and was considered possibly related to UST; dose has been subsequently de-escalated. No additional significant adverse events were reported in the remaining patients who received dose escalated UST.

Conclusions: In this subset of real-life experience of UST use in patients with CD, maintenance dose escalation to 90mg every 4 weeks had a modest benefit in achieving a clinical response. This may be suggestive of the mechanism of loss of response to UST being driven by factors other than low bioavailability due to processes such as rapid clearance. Further assessment in larger cohorts as well as the use of therapeutic drug monitoring will be important to evaluate the usefulness of dose escalation for patients on UST.

P626

Ustekinumab for the treatment of perianal fistulas in patients with Crohn's disease

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Background: Ustekinumab (UST), an interleukin-12/23p40 inhibitor, is effective in Crohn's disease (CD). Little is known on its efficacy in perianal fistulizing disease. To date, perianal outcomes using UST have been reported in only 18 patients. We report on the efficacy of UST on perianal fistulizing disease in CD. We also describe UST trough concentration, clinical, biomarker and endoscopic response in CD patients with perianal fistulas.

Methods: Anti-TNF refractory CD patients treated with UST (2013–2015) at the McGill University Health Centre were recruited. All patients were induced with UST 90mg SC at week 0, 1, 2 then maintained with UST 90mg SC every 4 or 8 weeks. At 6 months 77.4% were receiving UST every 4 weeks. The primary endpoint was >50% reduction from baseline in the number of draining fistulas. The secondary endpoint was closure of all fistulas. Outcomes were assessed for longitudinal patients and cross sectional patients ≥6 months. A combined cohort was analyzed at ≥6 months, when available. UST and UST antibody concentrations were assessed using a liquid phase assay (HMSA, Prometheus Laboratories, San Diego, CA, USA).

Results: Sixty-two patients were recruited. 17 patients had a history of perianal fistulizing disease. 6 patients had actively draining fistulas prior to initiating UST. At ≥6 months, 66% (4/6) of patients had a >50% reduction from baseline in the number of draining fistulas, and 33% (2/6) patients had closure of all fistulas. At ≥6 months, of the 6 patients who had active fistulas at commencement of UST, 3/6 (50%) attained clinical response while 2/6 (33%) attained clinical remission as determined by HBI assessment (HBI<5). 2/6 (33%) achieved steroid free clinical remission. Endoscopic response was attained in 3/6 (50%) patients while 2/6 (33%) attained endoscopic remission. Mean UST trough concentration at ≥ week 26 was 4.85 ug/ml. In those with >50% reduction in draining fistulas (n=4) mean UST trough concentrations were 5.0 ug/ml compared to 4.6 ug/ml in those without (n=2).

Conclusions: UST was effective in achieving reduction in perianal fistulas in a small series of anti-TNF refractory CD patients. Given the limited information on this subject, this series adds to the exist-

ing data on response of perianal fistulas with UST. However, larger studies are required to confirm these findings.

P627

Surrogate markers of mucosal healing in Crohn's disease patients in clinical remission under biological/immunomodulator treatment

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Background: Mucosal healing is a desired endpoint in both clinical trials and “real-life” practice as it has been associated with better outcomes in patients with IBD. Lower GI endoscopy is required to determine the presence or absence of mucosal healing. Our aim was to assess specific biomarkers that could accurately predict (either alone or in combination) the presence of mucosal healing in Crohn's disease (CD) patients under long-term anti-TNF and/or immunomodulator treatment.

Methods: Eligible patients were those with CD who were on clinical remission for at least 6 months under stable treatment with anti-TNF and/or immunomodulators. Prior to endoscopy all patients were subjected to thorough workup every two months with recordings of Harvey-Bradshaw index score and selected laboratory tests that included fecal calprotectin and serological inflammatory markers. After the end of this 6 month period, colonoscopy was performed and mucosal healing was determined as present [complete (no inflammatory lesions) or partial (minimal inflammatory lesions)] or absent. The predictive value of several clinical and laboratory markers for the presence of mucosal healing was investigated.

Results: Twenty-three patients have been recruited so far (Male=9, Age: 40.8±14.3, 19–70, mean ± SD, range, in years). Fourteen patients (60.8%) achieved mucosal healing as evidenced by lower gastrointestinal endoscopy. Patients in the “no healing” group had significantly higher fecal calprotectin values when compared to patients with mucosal healing at 2 months prior to endoscopy [“no healing” group 554 µg/gr, 235–1800 (median, interquartile range) vs. mucosal healing group 83, 33–330.5, p=0.012], 4 months prior to endoscopy (“no healing”, 600, 338–600 vs. mucosal healing 134, 22.5–272, p=0.009), as well as at 6 months prior to endoscopy respectively (“no healing”, 265.0, 142–482.5 vs. mucosal healing 64, 13.8–199, p=0.039). No significant differences between the two groups were observed regarding CRP levels. Moreover, higher amylase values were found in the “no healing group” in comparison to the healed mucosa group at 6 months prior to endoscopy (91.1 IU/L ± 24.8 vs. 63.1±27.2, mean ± SD, p=0.02). Finally, smokers had less often mucosal healing (p<0.0001) and higher CRP and fecal calprotectin values as well, than non-smokers.

Conclusions: Fecal calprotectin is a better predictor of mucosal healing than CRP in patients with CD in clinical remission. Its use in clinical practice may improve patient management by allowing the identification of patients at higher risk for disease flare, who may require closer follow up and earlier endoscopy.

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P628

Anti-TNF therapy in refractory pouchitis and Crohn's disease-like complications of the pouch after ileal pouch-anal anastomosis following colectomy for ulcerative colitis: a systematic review and meta-analysis

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Background: Pouchitis and secondary Crohn's disease (CD)-like complication of the pouch are the most common complications after ileal pouch-anal anastomosis following colectomy for ulcerative colitis. Data about the effectiveness of anti-TNF agents in these two entities remains sparse.

We aimed to perform a systematic review and meta-analysis to evaluate the efficacy of anti-TNF therapy in differentiating patients with chronic refractory pouchitis and CD-like complications.

Methods: Systematic literature search was performed in MEDLINE and from international meetings abstracts. The search process, selection of manuscripts, and data extraction were performed independently by two physicians according to PRISMA statements.

Prevalence and 95% confidence interval (CI) were estimated using random-effects models assuming between and within study variability. Statistical heterogeneity between results was assessed by examining forest plots, CI and using I² and sensitivity analyses were conducted.

CD-like complications of the pouch were defined as the presence of non-anastomotic fistula and/or non-anastomotic stenosis and/or prepouch ileitis. Chronic refractory pouchitis was defined as inflammation limited to the pouch.

The short term and the long term responses were evaluated at 8 weeks and 12 months, respectively.

Results: We identified 21 articles and three abstracts including 313 patients treated either with infliximab (IFX) (n=194) or adalimumab (ADA) (n=119) for inflammatory complications of the pouch.

The rate of complete response (CR) after anti-TNF induction therapy for inflammatory complications of the pouch was 0.51 (95% CI [0.39–0.64]; I²=0.56). The rate of short-term CR was 0.57 (95% CI [0.38–0.75]; I²=0.36) for IFX-treated patients compared to 0.38 (95% CI [0.08–0.72]; I²=0.50) for ADA-treated patients (p=0.20). The long-term rate of CR in patients treated with anti-TNF therapy was 0.52 (95% CI [0.39–0.65]; I²=0.59), with 0.59 (95% CI [0.45–0.72]; I²=0.30) for IFX-treated patients compared to 0.30 (95% CI [0.15–0.46]; I²=0.00) for ADA-treated patients (p=0.19).

The rate of CR after anti-TNF induction therapy seemed to be higher for CD-like complications of the pouch 0.64 (95% CI [0.5–0.77]; I²=0.18), compared to refractory pouchitis 0.10 (95% CI [0.08–0.35]; I²=0.00) (p=0.06). The rate of long-term CR in patients treated with anti-TNF was 0.57 (95% CI [0.43–0.71]; I²=0.32) for CD-like complications of the pouch compared to refractory pouchitis 0.37 (95% CI [0.14–0.62]; I²=0.47) (p=0.57).

Conclusions: Despite wide heterogeneity of the data, anti-TNF agents have a clear trend to have higher and faster efficacy in CD-like complications of the pouch compared to refractory pouchitis, highlighting the need to differentiate these two entities in clinical practice.

P629

Efficacy, safety and economic impact of the switch to biosimilar of infliximab in inflammatory bowel disease patients in clinical practice: results of one year

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Background: The first biosimilar (BS) of infliximab (IFX) was approved for the same indications as the biological reference in inflammatory bowel disease (IBS). After its commercialization we have results of efficacy and safety in IBD, however, data on the switch to BS are still limited. On the other hand, economic impact studies are needed in real life.

We aimed to evaluate the efficacy and safety of the switch BS in patients with IBD in clinical practice and analyze the economic impact of this strategy.

Methods: Observational and retrospective study. All the patients of the monographic consultation of IBD in maintenance treatment with IFX at the time of introduction of the BS were included. The clinical activity at the time of change to BS, at 6 and 12 months was analyzed using the Harvey Bradshaw index for Crohn's disease (EC) and partial Mayo score for ulcerative colitis (UC). Adverse effects, flares, intensification or withdrawal of treatment were recorded. The total amount in milligrams of IFX administered per patient was calculated and the milligram drug price was established based on the real sales price of the original IFX and BS vial.

Results: We included 72 patients (62 EC/10 CU; 47% male; mean age of 46 years (± 13 years)). The mean time to treatment with baseline IFX before switching to BS was 51 months (± 38.83 months). At the time of the switch, 86% of the patients were in clinical remission (62/72), with remission at 12 months maintaining 80.5% (58/72). Nine patients required treatment with steroids, 10 needed intensification and 8 urgent surgery (4 laparotomy and 4 perianal disease). Treatment was withdrawn in 9,72% of the patients (7/72), in 4 of them due to loss of secondary response. Adverse effects were recorded in 10 patients, 13,8% (mostly infections), without any withdrawal or treatment modification. A mean of 2780mg (DS 1092.29) of BS per patient was administered during one year, the total cost was 746150 € gross, which meant a saving of 248716 € gross annuals compared to the estimated expenditure with IFX before being marketed BS.

Conclusions: The switch to BS in IBD is effective in maintaining clinical remission at 12 months. No relevant adverse effects have been reported during the study period, one year. This strategy supposes a relevant reduction in the annual pharmaceutical expenditure in IBD patients.

P630

The long-term efficacy of adalimumab on Crohn's disease comorbid with perianal lesions and poor prognostic factor analysis

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Background: Patients with Crohn's disease (CD) are often comorbid

with perianal lesions (especially in Asian countries). Perianal lesions in CD are generally characterized by pathological complications and a high incidence of relapse. The long-term efficacy of adalimumab (ADA) on CD, especially with perianal lesions, is still unclear. We retrospectively analysed Japanese CD cases with perianal lesions to evaluate the efficacy of ADA treatment.

Methods: We enrolled 83 CD patients who underwent scheduled maintenance treatment using ADA from 2010 to 2015 in the Coloproctology Centre at Takano Hospital, Japan. The long-term effectiveness of ADA on CD with perianal lesions and the prognostic factors for relapse were analysed. Relapse was defined using a IOIBD score of ≥ 2 , CRP > 0.3 mg/dl or occurrence of a new pathological lesion.

Results: There were 56 male (67%) and 27 female (33%) patients with a mean age of 33.3 years at the first administration. The mean duration of disease was 8.8 years and the mean follow-up period was 40 months. The number of patients who experienced prior infliximab was 26 (31%) and 58 (68%) patients experienced anal lesions. Clinical remission was achieved in 76 patients (91%) using ADA induction treatment. Persistence rate of ADA treatment during a 6 year follow-up period was greater than 80% (See Figure).

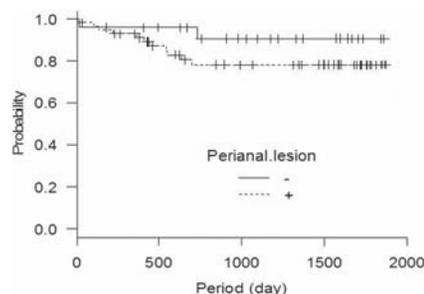


Figure 1. Persistence rate of ADA treatment for patients with Crohn's disease.

Multivariate analysis revealed that complications due to perianal lesions (OR=4.58, 95% CI: 1.01–20.7, $p < 0.05$) and prior surgical treatment for perianal lesions (OR=46.6, 95% CI: 3.79–573, $p < 0.01$) are significant independent risk factors for relapse.

Clinical improvement of perianal lesions was achieved in 50 patients (86%) within 8 weeks and clinical remission of perianal lesions was achieved in 28 patients (48%) within 20 weeks. Furthermore, patient history of antibiotic use (OR=0.12, 95% CI: 0.022–0.697, $p < 0.05$) and surgical treatment for perianal lesions (OR=0.03, 95% CI: 0.005–0.172, $p < 0.0001$) were significant risk factors for relapse. Moreover, the relapse-free survival curve analysis ($p < 0.01$, Kaplan-Meier) also revealed that prior surgical treatment for perianal lesions was a risk factor for the relapse of perianal lesions.

Conclusions: ADA treatment showed high and long-term efficacy on CD with perianal lesions in this retrospective study. Moreover, surgical treatment for perianal lesions may be a poor prognostic factor for disease progression.

P631

Results and predictors of outcome of endoscopic balloon dilation of colonic strictures in inflammatory bowel diseases

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Background: Endoscopic balloon dilation represents a valid thera-

peutic alternative in patients with inflammatory bowel disease that have colonic symptomatic strictures whether they occur before or after surgery. The aim of this study was to analyze the outcomes and to identify the predictors of success of endoscopic colonic dilation.

Methods: Inclusion criteria: Patients having inflammatory bowel disease with colonic stenosis treated by endoscopic balloon dilation from 2000 to 2015 were enrolled. Patients with a follow up lower than 6 months were excluded.

Technique: Dilation was performed with hydrostatic with variable diameters and pressures, adjusted depending on the stricture type. Procedure was performed under sedation and scopic control. All patients were hospitalized during 24 hours after procedure in order to detect possible complications.

Criteria defining dilation failure: Failure of endoscopic balloon dilation was defined by the need to recourse to a second session or to surgery within six months after the first session of dilation.

Statistic study: Univariate and multivariate analysis were performed SPSS 18/0) in order to identify independent predictors of outcome of endoscopic balloon dilation.

Results: During the study period, a total of 31 dilations have been performed among 18 patients (mean age 49.6 years old and sex ratio of 1,2).

Three patients had ulcerative colitis while fifteen had Crohn's disease since an average duration of 10 years.

Endoscopic treatment was successful in 72% in our cohort after a follow up of 18 months (6–48 months). Six patients needed more than one dilation (2–5 dilations), while 2 needed a surgical removal of the stricture. No complication occurred in our study.

In univariate analysis, predictors of outcome of endoscopic balloon dilation were: the age lower to 60 years, an inflammatory stricture, a disease that has been evolving for less than 5 years, a high balloon pressure, the association to a systemic treatment and an elevated level of the C reactive protein. In multivariate analysis, no factor was identified as an independent predictor of outcome of endoscopic balloon dilation.

Conclusions: Endoscopic balloon dilation of stricture during inflammatory bowel disease represents a safe alternative to surgery with a success rate of 72%. It should be privileged in young patients with an inflammatory stricture. It has a better outcome when done with a high balloon pressure and when associated to other therapeutic measures (immunosuppressive treatment). However, larger study should be performed in order to identify independent predictors of outcome of endoscopic balloon dilation.

P632

Comparative analysis of the pharmacokinetics of Inflectra[®] biosimilar with Remicade[®] in the induction phase of remission in patients with Crohn's disease

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Background: We have increasing evidence on the efficacy, pharmacokinetics, immunogenicity, safety, interchangeability and behavior of biosimilars, similar to the reference product in patients with inflammatory bowel disease (IBD). Although low, biosimilar infliximab pharmacokinetics studies on induction and maintenance show similar behavior to the original IFX.

Goal: Compare prospectively the pharmacokinetics of Infliximab biosimilar (Inflectra) with Remicade during induction of remission in Naïve anti-TNF patients with IBD.

Methods: We have performed prospective pharmacokinetic analysis in 9 patients with IBD during the induction phase of remission. Samples were taken at week 4 and week 14 to determine the baseline levels of Inflectra[®]. At the same time plasma albumin levels were determined in the same sample. Pharmacokinetic analysis (central distribution volume, peripheral, plasma clearance, biological half-life and AUC) was performed. All patients were on a normal level of albumin and taking conventional IMMs (AZA/MTX). The results obtained were compared with the registration of our population pharmacokinetic model with Remicade[®]. Serum analysis obtained pre-infusion of IFX trough levels by ELISA (Promonitor).

Results: 13 patients with Crohn's disease (4 M; 5 F). Average age: 38.6 years (95% CI 30–47). Albumin levels: 4.17 g/dl (95% CI 3.99–4.25). Inflectra[®] trough levels: 9.72 mcg/mL (IC95% 7,19–12,26) similar of Remicade[®] in our cohort of patients 8.19 mcg/ml (95% CI 6.98–11.96) (p=NS). In Table 1 the individual pharmacokinetic analysis is expressed and in Table 2 the average values of Inflectra[®] and Remicade[®] series.

Limitations of the analysis: sample size.

Table 1. Pharmacokinetics of patients treated with Inflectra

Central volume (L)	Peripheral volume (L)	Clarification (L/d)	Biological half-life d ⁻¹	AUC (mg·d/L)
3.79	1.34	0.4	11.12	937.5
3.07	1.2	0.26	14.05	1096.15
3.8	1.35	0.31	13.6	1217.53
3.82	1.34	0.38	11.65	1000
2.9	1.7	0.29	16.75	913.79
3.92	3.05	0.32	22.59	1328.13
3.76	1.46	0.45	10.78	828.36
3.99	1.64	0.32	14.81	1133.54

Table 2. Pharmacokinetics of Inflectra and Remicade

Central volume (L)	Peripheral volume (L)	Clarification (L/d)	Biological half-life d ⁻¹	AUC (mg·d/L)
3.63 (3.29–3.97)	1.63 (1.14–2.13)	0.34 (0.28–0.39)	14.41 (11.18–17.65)	1056.87 (916.63–1197.12)
3.52 (3.35–3.70)	1.31 (1.25–1.37)	0.35 (0.31–0.36)	12.55 (11.5–13.4)	1062.44 (963.75–1161.14)

Mean values (95% CI).

Conclusions: The pharmacokinetic behavior of Inflectra[®] biosimilar is comparable to Remicade[®].

P633

Antibodies to infliximab in patients treated with either the reference biologic or the biosimilar CT-P13 show identical reactivity towards biosimilars CT-P13 and SB2 in inflammatory bowel disease

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Background: The recent approvals of the infliximab (IFX) biosimilars, CT-P13 (Remsima[®]/Inflectra[®], Celltrion/Hospira) and SB2 (Flixabi[®], Biogen) by EMA were based on robust biosimilarity comparisons that demonstrated their equivalent efficacy and comparable

safety and immunogenicity with the reference biologic (Remicade®, RMC, Merck). However, concerns about inter-switching patients between the three brands were understandably raised in the absence of cross reactivity data between the antidrug antibodies against each molecule with the other two. We aimed to determine if antibodies to IFX (ATI) in IBD patients cross-react with CT-P13 and SB2.

Methods: Sera from patients who participated in BIOSIM01 (an observational retrospective study in which patients were treated with either RMC only, or CT-P13 only or RMC followed by a switch to CT-P13) were used. Based on previous ATI status 34 (13 RMC, 9 CT-P13, and 12 switchers) out of the 103 patients (59 CD and 44 UC) enrolled, were selected. Additionally, 28 IFX-naïve patients were tested as controls. In total, 180 samples were analysed. ATI trough levels were measured in parallel with 3 different bridging ELISA: a) Promonitor-ANTI-IFX kit (Progenika, Spain) which uses RMC to crosslink patient anti-IFX antibodies; b) the same assay but using CT-P13, and c) the same assay but using SB2. Spearman's coefficient and percent of agreement were used to study the correlation and association between assays.

Results: In total, 76 samples out of 152 IFX-treated patient samples were tested positive with Promonitor-ANTI-IFX (30 RMC, 14 CT-P13 and 32 switchers). All were ATI-positive when either CT-P13 or SB2 bridging assays were used. Positive and Negative Percent Agreements were 100% and 100%, respectively, when they were compared either with CT-P13 or SB2 bridging assays. No significant differences were found among ATI level determined by the three assays, with Spearman's coefficients ranging between 0.98 to 1.0 for all the three groups of patients ($p < 0.0001$) (Table 1).

Table 1. ATI cross-reactivity results

Patient cohort / (No samples, No patients)		ELISA bridging assay		
		Promonitor-ANTI-IFX (RMC)	CT-P13	SB2
Remicade-only (60, 13)	ATI-Positive samples, n	30	30	30
	Median ATI level (AU/mL)	140	171	163
	p (ANOVA)		$p=0.224$	
CT-P13-only (28, 9)	ATI-Positive samples, n	13	13	13
	Median ATI level (AU/mL)	91	110	133
	p (ANOVA)		$p=0.738$	
Switchers (64, 12)	ATI-Positive samples, n	32	32	32
	Median ATI level (AU/mL)	203	216	228
	p (ANOVA)		$p=0.902$	

Conclusions: ATI of RMC-, CT-P13- or RMC to CT-P13 switch patients show full cross-reactivity with SB2 and with CT-P13 [1,2]. No significant differences are observed in ATI levels determined with either drug, suggesting that immunodominant epitopes in the reference and CT-P13 drugs are equally present in SB2, and are responsible for exactly the same degree of reactivity. Results also demonstrate that Promonitor-ANTI-IFX test can be used to monitor antibodies to CT-P13 or SB2 in biosimilar-treated patients.

References:

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P634

Long term risk of relapse after anti-TNF discontinuation based on mucosal healing in inflammatory bowel disease

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Background: To investigate the risk of relapse and the need of restarting biological treatment in patients affected of inflammatory bowel disease (IBD) in whom Anti-TNF drugs were discontinued after mucosal healing was proved, and the influencing factors on it.

Methods: Retrospective study including 100 patients affected of IBD (70 Crohn's disease, 28 ulcerative colitis, 2 unclassified IBD) in whom biological treatment was stopped between June 2009 and May 2016, after mucosal healing had been proved.

We have recorded the IBD characteristics, the biological treatment which reached mucosal healing, analytical and histopathological data, as well as the other IBD treatments used, and the needing of anti-TNF dose intensification at any time.

We have analyzed the risk of relapse after discontinuation, the needing of restarting biological therapy, and the clinical response to it.

Results: Anti-TNF (61 Infliximab, 37 Adalimumab) had been indicated after immunomodulators had failed in 65 cases. Steroid-dependence was the indication in 66 patients, and steroid-refractoriness in 32. 8 of them had needed dose intensification at any time. After anti-TNF withdrawal, 83 patients kept on receiving immunomodulator therapy.

After discontinuation of anti-TNF drugs, 41 patients suffered disease relapse (average follow-up of 25 months); 34 of them needed to take up anti-TNF drugs again, and 28 of them achieved clinical response. Risk of retreatment on months 12, 24 and 36 was 21%, 42% and 48%, respectively.

Univariate analysis showed lower risk of relapse in Crohn's disease with L2 extension (29% vs 54%, $p 0.04$) whereas it was higher when the indication was steroid-dependence (48% vs 25%, $p 0.02$), in the case of anti-TNF start up after immunomodulator had failed, and when there had been dose intensification needing (86% vs 36%, $p 0.005$). The same factors determined the future need of anti-TNF resuming, although the only factor achieving statistical significance was previous fail to immunomodulator drugs (49% vs 26%, $p 0.02$). In multivariate analysis, only previous fail to immunomodulators, and intensification, predicted the relapse and the need of restarting anti-TNF drugs (not significant: $p 0.07$ and 0.05).

Conclusions: At long term, about half of the patients need to restart biological therapy after discontinuation because of mucosal healing, with good response to it in more than 80% of the cases.

In patients in whom immunomodulator therapy fails prior to biological therapy, and in those who need anti-TNF dose intensification to reach mucosal healing, risk of relapse is higher. Nevertheless, the frequent good response to restarting biological therapy allows us to test discontinuation. Histological healing is not associated to better prognosis.

P635

Enteral nutrition in the treatment of young adults with active Crohn's disease

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Background: Exclusive enteral nutrition (EEN) is commonly used to induce disease remission in children, but not adults, with active Crohn's disease. Partial enteral nutrition (PEN) has been shown to improve symptoms in children and adolescents but is inferior to EEN

in achieving mucosal healing. The aim of this study was to investigate the feasibility and effectiveness of EEN and a novel PEN regimen to achieve disease remission in young adults with active Crohn's disease. **Methods:** Adults aged 16–40 years with active Crohn's disease involving the ileum were referred into an open label prospective intervention study comprising of two interventions: eight weeks of EEN or PEN with a polymeric formula. The PEN regimen comprised of two weeks of EEN followed by six weeks of enteral nutrition plus one small meal per day of usual foods. Patients had serum, faecal and anthropometric assessments at baseline and fortnightly during treatment. Disease activity was assessed at baseline and treatment completion using the Crohn's disease activity index.

Results: Patients referred for treatment with EEN (n=25) or PEN (n=13) had similar baseline characteristics. Fourteen patients (56%) completed EEN and nine (69%) completed PEN treatment. Patients withdrew from the study for various reasons. Intention to treat and per protocol analysis found that disease activity significantly reduced consequent to both treatments ($p < 0.03$). Disease remission was achieved by 93% and 78% of patients who completed treatment with EEN and PEN respectively ($p > 0.05$). Per protocol analysis found that median serum C-reactive protein decreased in both groups ($p = 0.09$) and median insulin-like growth factor-1 improved consequent to EEN ($p = 0.048$) and PEN ($p = 0.20$). Body mass index decreased during EEN ($p = 0.008$) and PEN treatment ($p = 0.152$). Faecal calprotectin fell in the EEN group to a median of 587 $\mu\text{g/g}$ (micrograms per gram) ($p = 0.091$) and in the PEN group to a median of 773 $\mu\text{g/g}$ (micrograms per gram) ($p = 0.910$).

Conclusions: EEN and PEN effectively induce disease remission in young adults with small bowel Crohn's disease and a novel PEN treatment may be a feasible alternative treatment in this cohort. PEN treatments should be explored further in a larger cohort of adults with active small bowel Crohn's disease but the impact of the inclusion of usual foods on mucosal healing needs to be assessed.

P636

Reproducibility of the main prognostic factors for postoperative recurrence in a cohort of patients with Crohn's disease under anti-Tnf therapy

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Background: Up to half of the patients with Crohn's disease require at least one surgery during their life-time. Without therapy, recurrence is expected to occur in up to 50%, and is higher in patients meeting specific unfavorable prognostic factors (ex. smoking, structuring or penetrating behavior). Anti-TNF therapy has proven to be the most effective therapy in preventing postoperative endoscopic and clinical recurrence. However, the weight of the different prognostic factors in patients under anti-TNF has not been adequately assessed. Our aim was to study the predictors of anti-TNF failure in postoperative Crohn's disease.

Methods: Patients with Crohn's disease under anti-TNF therapy for prevention of postoperative recurrence were retrospectively reviewed. Clinical recurrence was defined as the need to escalate or discontinue therapy. A logistic regression analysis was performed to evaluate potential predictors of surgical recurrence.

Results: A total of 240 patients with Crohn's disease were evaluated. Anti-TNF therapy included Infliximab in 160 patients and Adali-

mumab in 80 patients. The median follow-up was 5.4 (0–19.1) years. Clinical recurrence occurred in 106 patients (44.2%) and surgical recurrence in 30 patients (12.5%). Predictors of surgical recurrence included active smoking (OR 7.429 95% CI 1.006–54.851, $p = 0.049$), upper gastrointestinal disease (OR 2.61 95% CI 0.99–6.9, $p = 0.05$), structuring or penetrating disease (OR 4.39, 95% CI 1.54–12.49, $p = 0.005$), perianal disease (OR 2.69 95% CI 1.14–6.37, $p = 0.024$) and clinical recurrence (OR 4.79, 95% CI 1.90–12.07, $p = 0.001$). Each additional risk factor increased the risk of surgical recurrence by 103% (OR 2.798 95% CI 1.85–4.23, $p = 0.000$). Surgical recurrence occurred in 2.3% of patients with one or fewer risk factors but in 46.7% of those with four or more risk factors ($p = 0.000$). A model including all 5 risk factors would predict surgery with 87.1% accuracy (AUC 0.902, 95% CI 0.862–0.942, $p = 0.000$).

Conclusions: Response to anti-TNF therapy is influenced by disease location, behavior, perianal disease and clinical recurrence. Patients presenting all these factors are potential candidates for non-anti-TNF driven therapies.

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Anti-infliximab antibody concentrations guide therapeutic decision-making in patients with Crohn's disease losing clinical response

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Background: Loss of clinical response (LOR) to infliximab (IFX) maintenance therapy in patients with Crohn's disease (CD) may necessitate treatment intensification. We explored the pharmacokinetics and effectiveness of infusion interval shortening (IS) and dose doubling (DD) and whether IFX and antidrug antibody (ADA) trough concentrations (TC) can guide therapeutic decision-making. **Methods:** A retrospective cohort study was conducted, including 93 patients with CD who received a double dose IFX (10 mg/kg body weight) and/or a next infusion after a shortened interval following LOR during maintenance therapy. IFX TC and ADA were measured at consecutive time points just before (at T0) and after (at T+1) the treatment intensification. ADA were quantified using an in-house developed drug tolerant assay (1). We compared the short-term evolution of IFX exposure, immunogenicity, clinical (based on physician global assessment) and biological (based on CRP) response during DD, IS and combined DD+IS.

Results: Overall, treatment intensification significantly increased the IFX TC from 1.2 $\mu\text{g/mL}$ to 3.6 $\mu\text{g/mL}$ (93 paired samples, $p < 0.0001$) (Table 1). An ADA concentration below 481 ng/mL eq. predicted a therapeutic post-treatment TC (3 $\mu\text{g/mL}$, 100% specificity, 51% sensitivity, AUROC 0.83, $p < 0.0001$). When ADA were undetectable, all treatment intensification interventions significantly increased the IFX TC and DD+IS resulted in a larger TC increase compared to DD alone (Table 1). When ADA were detectable but below the 481 ng/mL eq. cut-off, only DD significantly increased the IFX TC. When ADA were above the 481 ng/mL eq. cut-off, neither treatment intensification intervention was effective for increasing the IFX TC.

A significant TC increase was associated with clinical response in patients undergoing IS, only when they had no detectable ADA (from

Abstract P637 – Table 1. Course of the IFX pharmacokinetics during treatment intensification

	Total		IS		DD		DD+IS	
	T0	T+1	T0	T+1	T0	T+1	T0	T+1
IFX TC	1.2 [0.3–3.6] (n=93) p<0.0001	3.6 [0.5–10.2] (n=93)	0.8 [0.3–3.4] (n=35) p<0.0001	1.7 [0.3–5.5] (n=35)	2.0 [0.3–4.7] (n=45) p<0.0001	4.0 [1.0–10.9] (n=45)	1.2 [0.3–1.7] (n=13) p=0.0005	6.1 [4.7–11.1] (n=13)
IFX TC when ADA are undetectable	2.4 [1.1–5.4] (n=49) p<0.0001	7.4 [3.0–12.6] (n=49)	3.1 [0.7–5.7] (n=17) p=0.0002	5.4 [1.9–15.6] (n=17)	3.4 [1.3–6.0] (n=25) p<0.0001	5.5 [2.9–11.8] (n=25)	1.7 [1.2–2.2] (n=7) p=0.02	10.7 [8.3–13.7] (n=7)
IFX TC when ADA are low	0.8 [0.3–1.8] (n=26) p<0.0001	3.8 [1.0–8.6] (n=26)	0.7 [0.4–1.1] (n=9) p=0.1	1.2 [0.4–2.3] (n=9)	1.5 [0.4–3.7] (n=12) p=0.002	7.2 [3.3–13.5] (n=12)	0.3 [0.3–0.7] (n=5) p=0.06	5.2 [2.8–5.9] (n=5)
IFX TC when ADA are high	0.3 [0.3–0.3] (n=17) p=0.6	0.3 [0.3–0.3] (n=17)	0.3 [0.3–0.3] (n=8) p=0.3	0.3 [0.3–0.4] (n=8)	0.3 [0.3–0.3] (n=8) p=1.0	0.3 [0.3–0.3] (n=8)	0.3 [0.3–0.3] (n=1) –	0.3 [0.3–0.3] (n=1)

All values are median [IQR], g/mL.

2.3 µg/mL [0.7–4.4] to 4.9 µg/mL [1.7–12.1], n=15, p=0.009). Even when ADA were detectable but below the 481 ng/mL eq. cut-off, a significant TC increase was associated with clinical and biological response and remission in patients undergoing DD (biological response: from 1.5 µg/mL [0.4–3.1] to 6.0 µg/mL [3.3–13.5], n=8, p=0.02; biological remission: from 1.7 µg/mL [0.3–3.4] to 4.0 µg/mL [3.2–13.7], n=7, p=0.03; clinical response: from 2.0 µg/mL [1.0–6.2] to 9.2 µg/mL [4.4–13.5], n=8, p=0.008).

Conclusions: DD is more effective than IS for restoring therapeutic TC and clinical and biological response and remission in patients with low ADA titers. When ADA titers are high, neither treatment intensification strategy is effective.

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Release of 5-aminosalicylic acid from mesalazine formulations: a novel dynamic dissolution model simulating gastrointestinal pH changes

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Background: Various oral mesalazine formulations are available for treatment of IBD, but dissolution behaviours for each formulation in a physiological-based pH gradient considering the rapid fall in caecal pH (especially in ulcerative colitis) remain unclear.

Methods: In vitro release of 5-aminosalicylic acid (5-ASA) from different mesalazine formulations was assessed by a novel dynamic dissolution model simulating physiological-based gastrointestinal pH gradient prepared from compendial media. Dissolution profiles of one time-dependent (pH-independent) release formulation (Pentasa 500 mg tablets) and of two pH-dependent release formulations (Salofalk 500 mg granules, Mezavant 1200 mg tablets) at different pH values (1.2, 6.0, 6.8, 7.2, 6.0 or 5.5, 7.0) were determined. The pH drops to 6.0–5.5 in the caecum was taken into consideration.

Results: The time-dependent release formulation (Pentasa) lost 49% of 5-ASA in conditions simulating the stomach and small intestine at pH values of 1.2, 6.0, 6.8 and 7.2 (4 h) with 75% cumulative 5-ASA release in the caecum and colon (pH 6.0, 7.0; 7 h). Salofalk granules started to release mesalazine only at pH ≥6 and demonstrated 39% 5-ASA release in the small intestine (pH 6.0, 6.8 and 7.2; 3 h) with 100% cumulative 5-ASA release in the caecum and colon (pH 6.0, 7.0; 7 h). Mezavant started to release 5-ASA at pH 6.8 with 15% 5-ASA release in the small intestine (pH 6.8 and 7.2; 2 h) with 59%

cumulative 5-ASA release in the caecum and colon (pH 6.0, 7.0; 7 h). Surprisingly, after pH drops to 6.0 or to 5.5 in the caecum 5-ASA release from all formulations (including pH-independent Pentasa) was slowed down. The following pH rise to 7.0 (distal colon) resulted in 5–15% increase in the release of 5-ASA.

Conclusions: Significant variations were observed between the dissolution profiles of various mesalazine formulations examined in a novel dynamic model simulating physiological-based gastrointestinal pH changes. The time-dependent release formulation (Pentasa) lost 50% of 5-ASA in the small intestine and released only 25% in the caecum and colon suggesting that it is not enough to create a high concentration of mesalazine in the distal colon. We suppose that the pH-dependent release formulation (Mezavant, pH >7) might not fully release *in vivo*, as the gastrointestinal pH might not reach 7 and the rapid fall in caecal pH can slow down the release of 5-ASA. Salofalk granules (pH ≥6) revealed an optimal dissolution profile corresponding to the physiological gastrointestinal pH gradient, supporting its therapeutic use in distal ulcerative colitis. The reduction of 5-ASA release due to pH drops in the caecum should be considered when choosing oral mesalazine formulation for patients with distal ulcerative colitis.

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Switching from originator-infliximab to biosimilar-Infliximab in IBD-patients does not lead to significant changes in infliximab trough levels

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Background: Clinical use of biosimilar-infliximab (CT-P13) in inflammatory bowel diseases (IBDs) is based on extrapolation of indication from clinical studies performed in rheumatoid arthritis and ankylosing spondylitis. Only few data exist of behavior of infliximab trough level (TL) and anti-drug antibodies (ADA) during switching. The objective of this study was to evaluate the changes in TL and ADA after switching from originator-infliximab to biosimilar one during IBD maintenance therapy.

Methods: In this single-center observational study, all IBD patients receiving maintenance infliximab therapy were switched to biosimilar-infliximab. Serum samples for measurements of TL and ADA were taken before the last originator-infliximab infusion (baseline samples) and before the third biosimilar-infliximab infusion

(follow-up samples). TL and ADA were measured by ELISA Data of laboratory values, demographic data, clinical disease activity (HBI or partial Mayo score) and concomitant medication were collected from patients records.

Results: Baseline TL and ADA were available of 78 patients (45 males, 37 UC, 38 CD and 3 IBUD). The baseline low or high TL led to change in infliximab dosing in 16 patients and these were excluded from final analysis. No significant changes in TL occurred after switching (p=0.05): The mean baseline TL was 6.55 mg/l (SD 3.53) and follow-up TL was 5.73 mg/l (SD 3.21). ADAs were detectable in one sample at baseline. Two patients developed ADAs after switching (titer 12 AU/ml and 35 AU/ml, respectively). Mean baseline partial Mayo score was 1.19 (SD 1.73) and mean follow up Mayo score 0.77 (SD 1.26), mean baseline HBI was 1.25 (SD 2.31) and mean follow up HBI 1.19 (SD 2.25). The disease activity during switching neither in UC or in CD showed no statistical difference, p=0.07 and p=0.89.

Conclusions: These data suggest that switching from originator-infliximab to biosimilar-infliximab does not cause any statistically significant differences in infliximab trough concentrations. No safety concerns occurred during 16 weeks following switching.

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Serum ustekinumab levels achieved with a subcutaneous induction regimen correlate to clinical outcome – a prospective study

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Background: Recently published randomised controlled trials of

ustekinumab (USK) in Crohn’s disease used intravenous induction therapy, achieving median USK concentrations of 3.6ug/ml. Unlicensed USK has been on-going in Ireland for several years with induction protocols which rely exclusively on subcutaneous (sc) USK. The aim of this study was to assess USK drug levels achieved with sc induction regimen and the relationship to clinical outcomes.

Methods: Patients commencing treatment with USK in a single academic centre were recruited. Patients received sc USK 180mg at Week 0 and 90mg at Weeks 1, 2 and 8. The standard maintenance dose of 90mg sc 8 weekly could be changed at the discretion of the treating physician. Prospective data, including patient demographics, Harvey-Bradshaw Index, body mass index (BMI), C-reactive protein (Crp), serum Albumin (Alb) and trough serum USK levels was collected at Weeks 0, 1, 2 & 8.

Results: 12 patients were recruited from June 2016; median HBI at inclusion=6 (Range 0–9). Patient and disease characteristics are included in Table 1.

The median duration of follow up=118 days. Median values for Crp, Alb and HBI as per Figure 1.

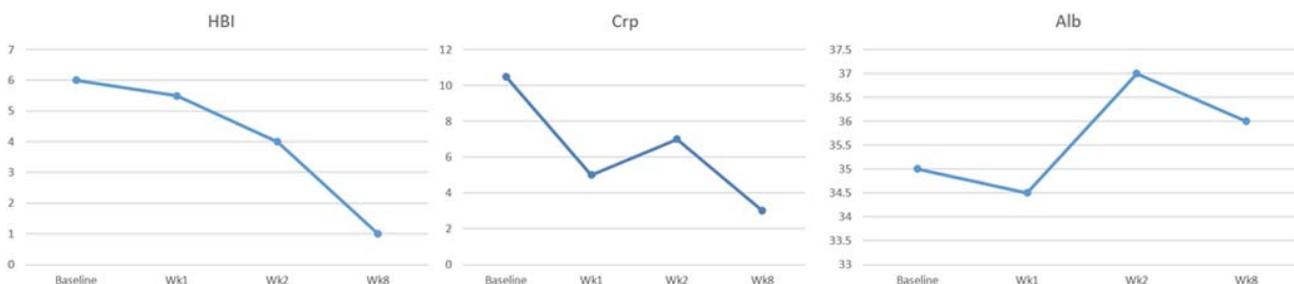
11 patients completed the study induction protocol and continued maintenance USK. At Week 8, 83% (n=10) patients were in clinical remission (HBI score ≤4). The median Crp at Wk 8 was 3mg/L and median change in HBI was -2 (range -7 to 2). There was a significant correlation between change in HBI and BMI (r=-0.754; p=0.019).

The median trough levels were 15 ug/ml (IQR 13–22ug/ml), 20 ug/ml (IQR15.25–29.25 ug/ml) and 4.5 ug/ml (IQR 3.9–9.9) at Weeks 1, 2 and 8 respectively. 86% were found to have Wk 8 USK trough levels >3.6ug/ml, which has previously been associated with higher rates of clinical remission. There was a significant correlation between trough USK levels at Wk 2 and trough USK levels at Wk 8 (r=0.906; p=0.005). There was a significant correlation between Wk 1 USK levels and Wk 8 HBI (r=0.803; p=0.05).

Conclusions: Optimal therapeutic USK levels have yet to be defined. Recent data suggest that higher serum USK levels following iv induction are associated with better outcomes. This may also apply in the case of a novel modified sc induction regimen. Our data suggest a relationship between early USK levels and clinical outcomes at Wk 8.

Abstract P640 – Table 1. Patient demographics and disease characteristics

Age (median; IQR)	35 yrs (28.5-51)				
Gender n; (%)	F 11 (91.6%)				
BMI (median; IQR)	20.1 (18.1-27.6)				
Disease duration (median; IQR)	15 yrs (5.9-22.3)			Perianal n; (%)	3 (25%)
Montreal A n; (%)	A1: 3 (25%)	A2: 8 (66%)	A3: 1 (8.3%)		
Montreal B n; (%)	B1: 3 (25%)	B2: 4 (33%)	B3: 5 (41.6%)		
Montreal L n; (%)	L1: 3 (25%)	L2: 2 (16.6%)	L3: 7 (58.3%)	L4: 0	



Abstract P640 – Figure 1. Median HBI, C-reactive protein (mg/L) and serum Albumin (g/L) at baseline, Wk 1, 2 & 8.

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Long-term outcome of adalimumab therapy and predictors of response in 254 patients with Crohn's disease: a hospital-based cohort study from Korea

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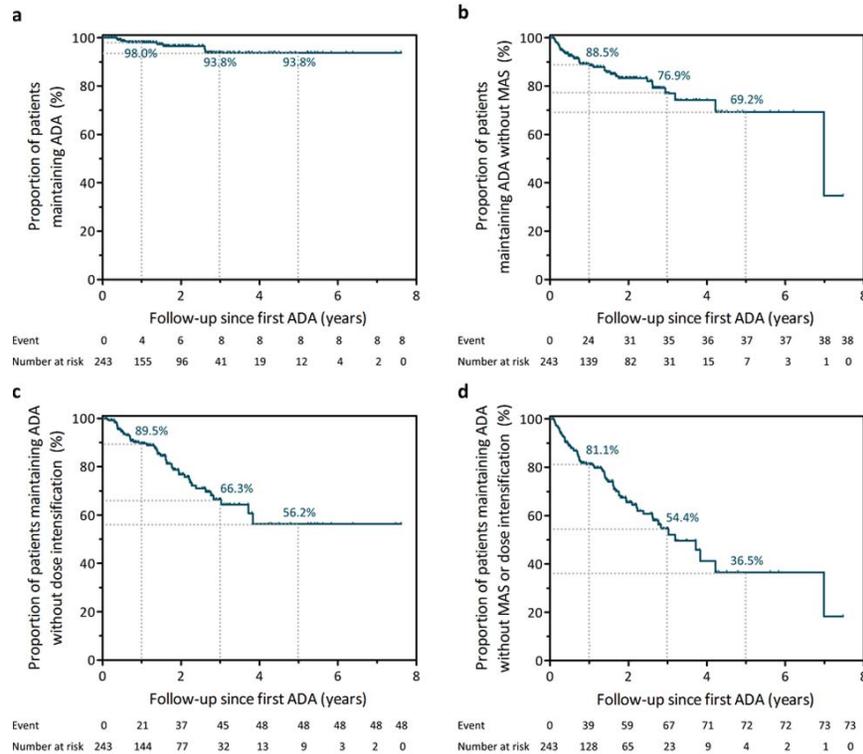
Background: Large scaled-studies regarding long-term outcomes of adalimumab (ADA) treatment in Korean patients with Crohn's disease (CD) are still lacking.

Methods: We retrospectively analyzed long-term outcomes of ADA treatment in Korean CD patients who started to be given scheduled ADA treatments at Asan Medical Center between November 2008 and July 2016. Clinical responses were defined as maintaining ADA therapy without major abdominal surgery (MAS) or dose intensification.

Results: Among 254 patients who received at least two doses of ADA by 2-weeks interval as an induction therapy, 250 (98.4%) patients had a primary response at week 4. Among primary responders, 243 patients were followed up for longer than 4 weeks and were included for further analysis. The median (interquartile range, IQR) duration of ADA maintenance therapy was 19.0 (6.4–32.2) months. At the end of the follow-up, 31 patients (12.8%) experienced MAS after a median (IQR) of 8.9 (2.8–18.7) months and 45 patients (18.5%) required dose intensification after a median (IQR) of 16.8 (7.3–23.4) months. Finally, 161 (66.3%) patients were still receiving ADA without MAS or dose intensification. The cumulative survival for maintenance of ADA without MAS or dose intensification was 81.1% at 1 year, 54.4% at 3 years, and 36.5% at 5 years (Figure 1).

Multivariate analysis using Cox proportional hazard model identified the previous exposure to infliximab (p=0.018, hazard ratio 1.79, 95% confidence interval 1.10–2.89) and an elevated level of C-reactive protein (>5 mg/dL) at the initiation of ADA (p=0.014, hazard ratio 2.34, 95% confidence interval 1.19–4.58) as independent predictors of a poor long-term response to ADA (Table 1).

Conclusions: The long-term outcome of ADA in a large, real-life cohort of Korean patients with CD appears to be comparable to that in previously published Western studies.



Abstract P641 – Figure 1. The cumulative survival for a) maintenance of adalimumab (ADA), b) maintenance of ADA without major abdominal surgery (MAS), c) maintenance of ADA without dose intensification, d) maintenance of ADA without MAS or dose intensification.

Abstract P641 – Table 1. Predictors of a poor response to adalimumab in Korean patients with Crohn's disease

Variables	Univariate analysis		Multivariate analysis		
	Hazard ratio	P value	Hazard ratio	95% CI*	P value
Disease duration prior to the first adalimumab (> 4 years)	1.71	0.060	Not retained		
Active perianal fistula at diagnosis	0.59	0.084	Not retained		
Previous exposure to infliximab	1.81	0.015	1.79	1.10-2.89	0.018
Elevated level of C-reactive protein at the first adalimumab (> 5 mg/dL)	2.53	0.007	2.34	1.19-4.58	0.014

* CI: confidence interval

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Impact of histological and endoscopic remission in clinical recurrence and recurrence-free time in ulcerative colitis

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Background: Resolution of clinical symptoms and mucosal healing constitute the therapeutic goals in ulcerative colitis (UC). Although a Mayo Endoscopic subscore (MSe) of 0 is the optimal target, there is insufficient information to recommend it for all patients and a MSe of 1 should be a minimum target. Moreover, histological healing is not a target in UC because of limited evidence for its clinical utility in UC.

This study aims to determine the impact of the definition of endoscopic remission (MSe 0–1) and histological activity in the recurrence of UC and the time free of recurrence.

Methods: Patients with UC in clinical remission (partial Mayo Score [MSP] ≤ 1) and endoscopic remission (MSe ≤ 1) who underwent colonoscopy with biopsies between 03/2010–12/2013 were included. The validated Nancy score was used to evaluate histological activity, which considers inactivity if 0–1 and activity if 2–4. The recurrence-free time was evaluated and recurrence was defined as MSP ≥ 2, therapy to induce remission, hospitalisation or colectomy. Predictive factors associated with recurrence were determined. Statistical analysis: X², Student's t-test, Kaplan-Meier survival curves, Log-rank test, logistic regression and Cox regression. Significance: p < 0.05.

Results: Sixty patients were included, 58.3% (n=35) were women, with a mean age of 52.7 years. MSe=0 was observed in 53.3% (n=32) and MSe=1 in 46.7% (n=28). Histological activity occurred in 61.7% (n=37). Clinical recurrence occurred in 31.7% (n=19) of patients, with a cumulative risk of 17.1%/24.5%/26.7%/40.1% at 12/24/36/48 months, respectively. MSe=1 (p=0.02) and histological activity (p=0.007) were significantly associated with recurrence. Of these, only histological activity (p=0.03) was an independent predictive factor of recurrence. Patients with MSe=1 (p=0.02) and with histological activity (p=0.01) had a significantly shorter recurrence-free time in univariate analysis. In multivariate analysis, only histological activity (p=0.02) was an independent predictive factor of lower recurrence-free time.

Conclusions: Patients with UC in clinical and endoscopic remission experienced a global recurrence of 31.7% (n=19), reaching 40.1% in 48 months. The presence of histological activity represents an independent predictive factor of recurrence and time to recurrence, which was not verified with MSe 0–1.

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Therapeutic thresholds for infliximab trough levels during maintenance treatment in patients with inflammatory bowel disease

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Background: Clinical use of therapeutic drug monitoring (TDM)-based strategies for infliximab (IFX) treatment is limited by lack of

validated and well-defined cut-off points for IFX trough levels distinguishing between therapeutic and sub-therapeutic drug levels. This study aimed to identify serum IFX levels associated with clinical remission and biochemical remission during maintenance therapy to facilitate TDM-guided IFX therapy in patients with inflammatory bowel disease (IBD).

Methods: Retrospective cohort study including 149 IFX-naïve IBD patients (Crohn's disease (CD) n=83; ulcerative colitis (UC) n=66) who received IFX induction therapy followed by maintenance therapy every 8 weeks. Using a validated immunofluorometric assay IFX trough levels were measured in 647 blood samples which have routinely been collected prior to scheduled infusions from all anti-TNF treated IBD patients at a tertiary center from 2009 onwards. Treatment outcomes were assessed at the time of each infusion. Clinical remission was defined as Harvey-Bradshaw Index < 4 or Partial Mayo Score < 2. Blood C-reactive protein (CRP) < 10 µg/mL defined biochemical remission. Results are based on data from serial blood samples at different time points throughout one year of follow up.

Results: Significantly higher IFX trough levels were observed in patients in clinical remission compared to those with active disease: Weeks 14 (p<0.0001), 22 (p<0.01), 30 (p<0.001), 38 (p=0.06), 46 (p<0.01) and 54 (p<0.01). At all time points during maintenance therapy, receiver operation characteristic (ROC) analyses showed that median IFX levels ≥ 3.5 µg/mL (cut-off value) were associated with clinical remission. Patients in biochemical remission also had significantly higher circulating trough levels of IFX as compared to those with active disease: Weeks 14 (p<0.01), 22 (p<0.01), 30 (p<0.001) and 38 (p<0.05), but not at weeks 46 and 54, likely reflecting a type 2 error. ROC analyses revealed that median IFX levels ≥ 2.1 µg/mL were associated with biochemical remission.

Conclusions: IFX blood trough levels ≥ 3.5 µg/mL is associated with beneficial treatment outcomes during the entire first year of IFX maintenance therapy. This therapeutic threshold can be used to support TDM-based treatment decisions when optimizing IFX treatment in IBD.

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Factors and salvage surgery for treatment of pouch failure after restorative proctocolectomy for ulcerative colitis – a single-institution study

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Background: For many patients with ulcerative colitis (UC), total colectomy and pouch surgery (ileal pouch-anal canal anastomosis (IACA), ileal pouch-anal anastomosis (IAA)) are performed, improving the quality of life (QOL). However, pouch failure occurs in some patients, markedly reducing their QOL. In this study, we examined the course of patients with pouch failure.

Methods: Of 1,156 patients who underwent total colectomy and pouch surgery under a preoperative diagnosis of UC between 1992 and 2015, the subjects were 26 patients (2.2%) in whom pouch-associated complications led to pouch failure (ileostomy state for 2 years or more or pouch resection). Total colectomy was indicated for 14 patients with refractory UC, 12 with severe UC, and 1 with cancer/dysplasia. Concerning techniques, IACA was selected for 21 patients, and IAA for 5. The median age at the time of pouch surgery was 31 years. The median interval from surgery until the appear-

ance of complication-related symptoms was 19.5 months. The median follow-up period from pouch failure was 60 months.

Results: Among complications causing pouch failure, fistulae from the anastomotic site accounted for 38% (10 patients), the highest percentage. In 4 of these, suture failure was noted as an early complication. In addition, anal canal-associated complications were observed in 34% (9 patients: 7 with anal fistulae, 1 with a vaginal fistula, and 1 with a pouch fistula (5%)). The final outcomes consisted of anal and pouch excision in 11 patients (after re-ileal pouch anal anastomosis in 2), pouch vacant in 14, and redo ileal pouch anal anastomosis in 1 (12%, 3/26). Of these, 1 required additional ileostomy. Finally, concerning the pouch function after stoma closure, the frequency of defecation was 10 to 15 times/day in both patients, facilitating rehabilitation.

Conclusions: In UC patients with pouch failure, the incidence of complications related to fistulae from the anastomotic site was high, suggesting the possibility of early suture failure. For 92% of the subjects, permanent ileostomy was selected. However, redo ileal pouch anal anastomosis was possible in some patients, and closure was possible after temporary ileostomy in others. Treatment methods must be examined in accordance with individual patients.

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The introduction of infliximab therapeutic drug level monitoring for is associated with cost savings in a cohort of patients in a large district general hospital

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Background: Infliximab is a chimeric monoclonal antibody directed against TNF- α , with proven efficacy in IBD. Reported loss of response is 15–40% per year. There is evidence to suggest that the development of anti-infliximab antibodies plays a major part in this. Antibodies may develop and not be associated with failure, however in this setting it is thought that infliximab does not have ongoing efficacy for maintaining remission. Whilst therapeutic drug level monitoring could optimise anti-TNF use, it could also be associated with cost savings, but the long-term cost savings are unknown. Not only this, it is likely that it will optimise the use of anti-TNF therapy and guide on future therapies improving long-term patient outcomes.

Our aim is to show that the use of therapeutic drug level and antibody monitoring is associated with cost savings by stopping unnecessary anti-TNF, or dose de-escalation of therapy.

Methods: By interrogating our local IBD database and searching patient records we identified all patients receiving anti-TNF therapy, the indication for performing therapeutic drug and antibody levels. We identified patients in which results of the drug levels and antibody status alone influenced the future treatment strategy, then calculated the costs and cost savings made when treatment was altered. Maintenance therapy with biosimilar Remsima costs £3510 per year, calculations were based on the assumption that all patients were receiving Remsima.

Results: 104 patients receiving infliximab between 2013 and 2016 had infliximab levels checked at a total cost of £7280.

26 (25%) patients were identified as having their treatment changed as a direct result of the drug levels and antibody status.

18 (69%) patients in remission with positive antibodies and undetectable trough levels had infliximab withdrawn with an annual cost saving of £63,180.

6 patients in remission had the Remsima dosing interval lengthened to 12 weeks due to high trough levels of infliximab with a cost saving of £7020 per annum.

2 patients had the Remsima interval reduced to 6 weeks based on low drug trough level at an increased cost of £3510 per annum.

No patient had a change in biologic drug based on drug levels alone. The total annual cost saving from the introduction of therapeutic drug level and antibody monitoring was £59,410 based on using Remsima. This cost saving would be increased to £140,920 if originator infliximab had been used.

Conclusions: The use of therapeutic drug monitoring at a district general hospital leads to significant cost savings in the use of infliximab therapy.

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Low FODMAPs diet as a magic bullet in reducing symptoms in different gastrointestinal diseases

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Background: Several recent studies have shown FODMAPs (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols) free diet is efficient in subjects with Irritable Bowel Syndrome (IBS). Patients with Inflammatory Bowel Diseases (IBD) and celiac disease (CD) can experience functional gastrointestinal symptoms not related to inflammation, but data about the use of low FODMAPs diet in these settings are still scarce.

Aim: To evaluate the usefulness of a low FODMAPs diet in patients with IBS, IBD and CD on gluten-free diet (GFD).

Methods: We performed a dietetic interventional prospective study evaluating the effect of a low FODMAPs diet in patients with IBS, CD following at least a 1-year-GFD and IBD without signs of active inflammation, who experienced functional symptoms. Each subject was submitted to a low FODMAPs diet, after filling out questionnaires on quality of life and symptoms (IBS-SSS and SF-36), and was re-evaluated after 1 and 3 months.

Results: 127 subjects were enrolled: 56 with IBS, 30 with IBD and 41 with CD. The analysis of the IBS-SSS explained if the symptomatology reported by the patient was mild (score <175), moderate (score 175–300) or severe (score 300–500) before starting the diet (T0) and one month (T1) and three months (T3) after prescription of a low FODMAPs diet. The overall average score of the study population was 250±113 SD at T0, 146±68 SD at T1 and 81±50 SD at T3 (p<0.001).

Furthermore, by analysing the SF-36 questionnaire, we did not observe any significant difference between the groups in terms of response to diet (p=NS), even if we observed a clinical improvement from T0 to T3 after the start of the diet for the most of the questionnaire's domains.

Conclusions: A low FODMAPs diet could be a valid tool to contrast functional disorders in patients with IBS, non-active IBD and CD on GFD, thus improving the quality of life and the social relations.

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Tuberculosis in patients treated with vedolizumab: clinical trial and post-marketing case series

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Background: Treatment with anti-tumour necrosis factor-alpha (anti-TNF α) agents has been shown to increase the risk of reactivating latent infections, especially tuberculosis (TB) [1]. Vedolizumab (VDZ) is a humanised monoclonal antibody that targets $\alpha_4\beta_7$ integrin and selectively blocks gut-specific lymphocyte trafficking. This gut selectivity may be associated with a lower risk of reactivating latent infections compared with anti-TNF α agents, which cause systemic immunosuppression. Here we describe the frequency of TB with VDZ therapy in clinical trials and the post-marketing (PM) setting.

Methods: Safety data from the GEMINI 1 and 2 studies (VDZ vs placebo, in ulcerative colitis [UC] and Crohn's disease [CD], respectively), the ongoing GEMINI open-label extension (OLE) study (VDZ only, both UC and CD; data cut-off: 21 May 2015) and PM data from the VDZ Global Safety Database (May 2014–31 August 2016) were assessed. TB infections were classified according to MedDRA.

Results: In GEMINI 1, 2 and OLE, 6 TB events were reported in 5 patients (serious: n=4; non-serious: n=1; Table 1), with 4 TB events considered treatment-related. Patients with TB were in the Czech Republic (n=1), India (n=1), Republic of Korea (n=1), Russian Federation (n=1) and Slovakia (n=1). All TB events resulted in treatment discontinuation, as per study protocol. In the context of ~66,390 patient-years of VDZ therapy in the PM setting, 5 patients (Table 2) reported TB (serious: n=4; non-serious: n=1): 2 patients perma-

Table 1. TB cases in clinical studies*

Study in which case was reported	Treatment group in GEMINI 1, 2 or 3 [†]	MedDRA preferred term	Country of occurrence (Total VDZ exposure for country in PY)
Adverse events			
GEMINI OLE	GEMINI 3 PLA	Latent TB [‡]	Slovakia (56.2)
Serious adverse events			
GEMINI 2	GEMINI 2 VDZ/VDZ Q4W	Latent TB [‡]	Czech Republic (314.9)
GEMINI OLE	GEMINI 1 VDZ/PLA [§]	Pulmonary TB	Republic of Korea (110.4)
GEMINI OLE	GEMINI 2 PLA/PLA [¶]	Two events of pulmonary TB	India (145.0)
GEMINI OLE	GEMINI 2 VDZ/VDZ Q8W**	Pulmonary TB	Russian Federation (170.1)

*Patients were excluded if they had active or latent TB at screening, evidenced by a history of TB, a positive diagnostic TB test 1 month prior to enrollment or a chest X-ray within 3 months of enrollment for which active or latent TB could not be excluded

[†]GEMINI 3 was a phase 3, 10-week, placebo-controlled, induction study in patients with CD

[‡]Not part of the patient's concomitant or previous medical history (diagnosed after the start of treatment with vedolizumab)

[§] Patient received VDZ at Week 0 and Week 2 in the induction phase of GEMINI 1, and PLA in the maintenance phase for up to 52 weeks

[¶] Patient received PLA at Week 0 and Week 2 in the induction phase of GEMINI 2, and PLA in the maintenance phase for up to 52 weeks

**Patient received vedolizumab at Week 0 and Week 2 in the induction phase of GEMINI 2, and vedolizumab in the maintenance phase for up to 52 weeks

MedDRA, Medical Dictionary for Regulatory Activities; PLA, placebo; PY, patient-years; OLE, open-label extension; Q4W, once every four weeks; Q8W, once every eight weeks; TB, tuberculosis; VDZ, vedolizumab

Table 2. TB cases in the PM setting

Indication	MedDRA preferred term	Country of occurrence (Total VDZ exposure for country in PY)
Haemorrhagic rectocolitis*	Disseminated TB	France (~3,471)
UC	Latent TB [†]	United States (~38,102)
CD [‡]	Cutaneous TB	Germany (~8,894)
NR	TB	United States (~38,102)
UC	TB	United States (~38,102)

*VDZ is not approved for use in this indication
[†]Not part of the patient's concomitant or previous medical history (diagnosed after the start of treatment with VDZ)
[‡]Patient had previous cutaneous TB (healed in the past)
 CD, Crohn's disease; MedDRA, Medical Dictionary for Regulatory Activities; NR, not reported; PM, post-marketing; PY, patient-years; TB, tuberculosis; UC, ulcerative colitis; VDZ, vedolizumab

nently discontinued treatment, 2 discontinued and later restarted, and 1 was not reported (discontinuation recommended in product label). Of the 5 patients in the PM setting, 2 had previously received anti-TNF α agents (infliximab: n=1; adalimumab: n=1). The PM TB events occurred in the US (n=3), France (n=1) and Germany (n=1).

Conclusions: The frequency of TB in VDZ clinical trials and the PM setting was low. Clinical trial events occurred in countries where TB incidence is higher than in the US, while the origin of PM reports is likely to be explained by the greater exposure in those countries. Limitations associated with PM safety reporting (e.g. incomplete comorbidity and co-medication data), which make confirming a causal association between drug and event difficult, must be considered when interpreting the PM results.

References:

- [1] Solovic I, Sester M, Gomez-Reino JJ, et al. (2010), The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement, *Eur Respir J*, 1185–26

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The impact of infliximab therapeutic drug monitoring on decisions made in a virtual biologics clinic for IBD

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Background: Virtual biologics clinics (VBC) are used in Leeds to review annually all patients receiving biological therapy and those who have lost response or had treatment complications. Decisions on continuing, switching or stopping therapy are documented based review of clinical symptoms, disease history and laboratory investigations Therapeutic drug monitoring (TDM) of infliximab trough levels (ITL) and anti-drug antibodies (ADA) can aid decision making but has previously not been universally available in the UK. The aim of this study was to assess whether access to therapeutic drug and antibody levels influences decision making within the VBC.

Methods: All IBD patients receiving Infliximab maintenance therapy were reviewed and two treatment decisions were recorded. The first decision was based on assessment of all clinical details but clinicians remained blinded to ITL and ADA data (Biohit assay). After documenting the first decision an administrator then revealed the ITL and ADA data and clinicians formed a second decision incorporating TDM data. Decisions were standardised to the following format:

A – continue without change B – shorten infusion interval/increase infliximab (IFX) dose C – lengthen infusion interval D – stop IFX E – other.

Results: Of 201 patients reviewed TDM data were available for 191 (mean 40y old, 57% male). Diagnoses were Crohn's disease in 160, ulcerative colitis in 18 and IBD-U in 13 cases. Mean duration of IFX treatment was 4 years (minimum 6 months), 57% received combination therapy with an immunomodulator and 38% were on shortened infusion intervals. Disease activity was remission in 70%, mild in 19%, moderate in 10% and severe in 1%.

ITL were sub-therapeutic in 25% (<1.8 mg/l), therapeutic in 61% and supra-therapeutic in 14% (>7 mg/l); mean ITL was 3.85 mg/l. ADA were detected in 30% and were >50 AU/ml in 14%. Blinded treatment decisions were changed on unblinded review of ITL and ADA in 56 cases (29%, see table 1, chi-square test: $p < 0.0001$). <https://planner.smart-abstract.com/ecco2017/submission/en/abstract/3000/content#> Knowledge of ITL & ADA led to 7 patients receiving higher dose IFX or more frequent infusions whereas 33 patients were able to dose de-escalate or stop IFX therapy.

Conclusions: TDM has a significant impact on decision making in VBC. Basing decisions on TDM rather than clinical acumen alone led to change in 29% of cases. Notably, an additional 23 patients (11% of the IFX-treated cohort) discontinued therapy due to undetectable ITL and high ADA. This represents a considerable cost saving and reduces the exposure of patients to potentially toxic therapies with no ongoing therapeutic benefit. Routine TDM should be considered as an integral part of the annual biologics assessment

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Does switching to low dose thiopurine and allopurinol prevent IBD patients with evidence of hypermethylation on standard dose thiopurines from developing hepatotoxicity and drug side effects?

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Background: It is accepted that low dose thiopurine and allopurinol (LDTA) therapy is effective in those who develop side effects or abnormal liver functions tests (LFTs) to standard dose therapy. Some units switch to LDTA if there is evidence of hypermethylation (6MMPN:6TGN ratio >11:1) even without side effects or abnormal LFTs due to concern that these may develop with time. To our knowledge there is no evidence that this practice is beneficial. In our unit 1 clinician switches all patients with evidence of hypermethylation and another does not.

Aim: Compare outcomes at 1 year in IBD patients with evidence of hypermethylation who remained on standard dose thiopurine against those who were switched to LDTA.

Methods: A prospective database of IBD patients is maintained at our hospital. We identified patients with hypermethylation between weeks 4 and 6 who had started standard dose thiopurine

Results: 72 patients were identified, 24 (33%) had abnormal LFTs. 7 (29%) continued standard dose azathioprine (LFTs normalised in subsequent weeks), 3 had drug reactions, 2 switched to mercaptopurine (MP), 1 switched to methotrexate (MXT), 1 reduced dose of thiopurine, 1 stopped due to myelosuppression, and 2 stopped due to evidence of hypermethylation and a desire to conceive.

14 of 72 developed side effects; nausea, vomiting, fatigue, abdominal

pain, joint pain, sore throat headaches. In 4 symptoms resolved on starting LDTA, 1 developed pancreatitis and switched to MXT, 1 switched to MP, 3 had ongoing symptoms on LDTA, 4 did not try LDTA (2 refused, 1 stayed on infliximab monotherapy, and 1 on 5-ASA).

At one year 20 of 29 (68.9%) who continued LDTA were in remission. 3 (10.3%) commenced biologics whilst on LDTA due to disease activity, 2 (6.9%) switched to IFX monotherapy, 1 (3.5%) started MXT, 1 (3.5%) had abnormal LFTs after 9 months, 2 (6.9%) stopped due to myelosuppression. 5 (17.2%) had abnormal LFTs after 1 year on LDTA: 3 (10.3%) stayed on LDTA, 1 (3.5%) stopped LDTA and 1 (3.5%) switched to IFX monotherapy.

At 1 year of those who remained on standard dose thiopurine 21 of 30 (70%) were in remission. 3 (10.3%) commenced biological co-therapy, 2 (6.7%) started biological monotherapy, 1 (3%) stopped due to skin cancer risk, 1 (3%) lost to follow up, 1 (3%) switched to LDTA, 1 (3%) stopped due to anaemia.

3 of 30 (10.3%) on standard thiopurine dose developed raised LFTs; 2 (6.7%) mildly elevated ALT so no changes to thiopurine, 1 (3%) significantly raised ALT 65 therefore switched to LDTA.

Conclusions: At one year switching patients with evidence of hypermethylation to LDTA did not reduce the risk of hepatotoxicity, drugs side effects or reduce the number of patients requiring biologic therapy.

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The prognostic impact of radical resection margins on the Recurrence of Crohn's disease

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Background: Up to 85% of Crohn's patients will undergo surgical resection during the course of their disease. The majority of these resections involve ileocecal resection. Smoking, fistulizing disease, and young age have been identified as risk factors for clinical and surgical postoperative recurrence. The prognostic impact of radicality of resection has been a matter of debate for decades, but so far current guidelines do not specifically recommend performing a radical resection. In contrast, they only emphasize the importance of a limited resection. The aim of this study is to analyze the prognostic impact of pathological findings in the resection margins of ileocecal resection specimens in Crohn's disease.

Methods: A consecutive series of 43 patients with Crohn's disease undergoing primary ileocecal resection for medically refractory disease between 2006 and 2009 at the Academic Medical Center (AMC) in Amsterdam were included. Resection margins were histologically scored for several inflammatory parameters (e.g. architectural changes, eosinophils and neutrophils in lamina propria, crypt destruction, erosions and ulcerations, granulomas, and fissures). The score was based on the adjusted Geboes score. Pathological findings were correlated to clinical results that have been collected in a prospectively maintained database. Clinical recurrence was defined as endoscopic recurrence necessitating medical treatment.

Results: There were 12 men and 31 women with a median age of 33.3 years. Median follow-up time was 71 months, with a minimum of 58 months. A radical resection was performed in 65.1% of patients. No association between clinical parameters and non-radical resection could be demonstrated. Overall clinical recurrence rate was 41.9%, with a lower recurrence rate in the radically resected group (32.1% versus 67.9% in the non-radical group, $p=0.06$ log-rank).

Kaplan Meier curves showed that the median time to recurrence was 18 months for both groups. The incidence of surgical recurrence was too small (n=1) to perform statistical analysis.

Conclusions: The presence of active microscopic inflammation in the resection margin after ileocecal resection seems to be related to recurrent Crohn's disease. The high incidence of clinical recurrence in the non-radical group (68%) justifies a renewed discussion about the clinical importance of a radical surgical resection in these patients.

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Barriers to clinical research in children with inflammatory bowel disease: the patients' perspective

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Background: Recruitment for clinical research in paediatric inflammatory bowel disease (IBD) could be difficult. Patients' willingness to participate in clinical research is affected by several factors including research-related, patient-related and disease-related factors. Understanding the nature of barriers to recruitment for clinical studies is important for better planning of future research. Data on barriers to recruiting children with IBD to clinical studies are limited. The aim of this study was to examine possible barriers for clinical research in children with IBD from patients' perspective

Methods: In a cross-sectional single center paediatric study, children with IBD or their care givers when appropriate were surveyed via a questionnaire that addressed patients'/parents' willingness to participate in clinical studies and factors that may influence patients' willingness to participate. Univariate logistic regression analysis was used to examine any possible effect of factors such as disease nature, type of biological samples, and parental education on willingness to participate in clinical research.

Results: Out of 96 children with IBD (mean age 13.9± 2.78 years, 53 boys, 49 Crohn's disease (CD)) who were consecutively recruited in the Pediatric IBD clinic, Winnipeg Children's Hospital, Winnipeg, Manitoba, 84 (87.5%) were "definitely or probably" willing to participate in clinical research while 12 (12.5%) were neutral or unwilling to participate (p<0.01). Factors associated with increased willingness to participate included providing research blood (OR=2.1, 95% CI 1.2–4.1, p=0.03) and urine (OR=2.04, 95% CI 1.03–4.1, p=0.04) samples but not stool samples (OR=1.3, 95% CI 0.73–2.47, p=0.3) or endoscopy (OR=1.45, 95% CI 0.83–2.56, p=0.19). Patients with CD were more willing to participate (OR=3.27, 95% CI 1.11–9.66, p=0.03). Parents' education, income, age at diagnosis, money incentive, disease activity and medications such as immunosuppressive or biological medications at the time of the survey did not have any significant effect on willingness to participate.

Conclusions: The majority of children with IBD are willing to participate in clinical research especially in studies that include blood and urine sample collection but not stool samples or endoscopy. Children with Crohn's disease are more likely to participate in research studies.

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Unmet needs of physicians managing inflammatory bowel disease. A Survey of the Italian Group for Inflammatory Bowel Disease (IG-IBD)

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Background: It is known that patients affected by Inflammatory Bowel Disease (IBD) present several unmet needs about the management of their illness and its consequences on their Health Related Quality of Life. However, little is known about the unmet needs of physicians caring IBD patients. The aim of the study was to investigate the difficulties and the problems of Italian physicians managing IBD. **Methods:** A questionnaire was submitted to physicians attending the National Congress and the Residential Courses of IG-IBD.

Results: 280 physicians (156 men) completed the questionnaire. Mean age ± SD was 44.4±10.7 years; 95 (33.9%) were working in Academic hospitals. On a 5-point Likert scale, the most problematic issues in managing IBD patients were: increasing bureaucratic charge (3.9±1.2), lacking of extra-gastroenterological IBD expertise (3.4±1.4), lacking of diagnostic techniques (3.1±1.4), budget limitations (2.9±1.3), drugs safety (2.9±1.2), difficulties in guidelines application (2.7±1.2), pharmacy's limitations (2.2±1.1). Ranking from 0 to 9 the most lacking extra-gastroenterological IBD specialist figures led to the following classification: surgeon (2.5±2.5), nobody (3.3±3.4), rheumatologist (3.8±2.3), nutritionist (3.8±2.0), psychologist (3.8±2.2), dermatologist (4.2±2.0), pathologist 4.3±2.5), radiologist (4.8±2.6), stoma therapist (5.4±2.4). Ranking from 0 to 9 the most lacking techniques led to the following classification: nothing (1.6±1.8), anti-drug antibody and trough levels assays (2.7±3.0), enteroscopy (3.1±2.0), exploration under anesthesia of perianal disease (3.2±2.1), entero-MR (3.2±2.4), bowel ultrasonography (3.3±2.8), videocapsule endoscopy (3.9±2.1), entero-CT scan (4.4±2.1), fecal calprotectin (4.7±3.0).

Conclusions: In Italy, several situations appear to potentially limit the best management of IBD patients. However, most of them appear to be correctable.

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The efficacy and safety of stem cell therapy for Crohn's disease: a meta-analysis

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Background: Stem cell therapy (SCT) for the treatment of Crohn's disease (CD) is still in its infancy, whether SCT is associated with improved outcomes is unclear. We performed a meta-analysis to evaluate the efficacy and safety of patients receiving SCT.

Methods: Electronic database were searched for eligible studies. Raw data from included studies were pooled for effect estimates. The primary endpoint was clinical remission. Secondary outcomes included proportions of patients who were clinical response, endoscopic remission or fistula healing. Subgroup analyses were performed for exploration of heterogeneity regarding all outcomes.

Results: We analyzed 36 studies comprising 588 patients with ac-

tive CD. A random-effects meta-analysis of studies of SCT as systemic infusion showed 63% (95% CI, 48%–76%, n=182) of patients achieved clinical remission. Similarly, a random-effects pooled rate of clinical response and endoscopic remission were 62% (95% CI 41%–80%, n=164) and 30% (95% CI 14%–54%, n=66), respectively. A random-effects meta-analysis of all perianal CD studies showed that 57% (95% CI, 45%–67%, n=271) of patients had healed fistula with SCT. The pooled rate of clinical recurrence was high of 23% (95% CI 16–31, n=216) with a follow-up >12 months. The pooled rate of severe adverse events (SAEs) and SAEs related to SCT were 14% (95% CI 8%–22%) and 10% (95% CI 5%–18%, n=427), respectively. A funnel plot and Egger's test suggested no existence of publication bias.

Conclusions: SCT was associated with improved clinical and endoscopic remission or response, as well as fistula healing. SCT is therefore emerging as an alternative treatment for active CD.

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Mucosal healing with a second anti-TNF- α in patients with ulcerative colitis after the failure of the previous anti-TNF- α treatment

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Background: Anti-tumor necrosis factors (TNF)- α agents represent an effective treatment for ulcerative colitis (UC) patients. Indeed, infliximab (IFX), adalimumab (ADA) and golimumab (GOL) have demonstrated in clinical trials to obtain not only clinical remission but also mucosal healing (MH) in UC patients with significantly higher rates compared to placebo. However, in patients not-naïve to anti-TNF- α treatment the efficacy of a second agent of the same pharmacological class has not been properly assessed. Aim of this study was to evaluate in a cohort of UC patients the rate of MH obtained after the switch to a different anti-TNF- α agent.

Methods: UC patients consecutively treated with two different anti-TNF- α agents were considered. Only patients who underwent to at least three colonoscopies in order to assess endoscopic activity and MH were included. In detail, the first colonoscopy was performed before starting the first anti-TNF- α (baseline), the second during the first anti-TNF- α course (1st MH assessment) and the third colonoscopy during the second anti-TNF- α course (2nd MH assessment). When more than a colonoscopy was performed after the start of the anti-TNF- α agent course the earlier exam was considered for assessing MH. Endoscopic activity was assessed by means of Mayo endoscopic score. MH was defined for a Mayo score of 0 or 1.

Results: During the study period, 42 UC patients were treated with two different anti-TNF- α agents. Of these, 14 resulted eligible for the study according to the inclusion criteria. Eight patients were males, mean age was 30 years old (range 16–49), 11 patients had pancolitis and 3 left colitis. At baseline colonoscopy all patients had endoscopic activity: 6 Mayo score 2 and 8 Mayo score 3. For 13/14 patients (93%) the first anti-TNF- α used was IFX and in 1 patient GOL. After the first course of anti-TNF- α 2/14 patients (14%) improved the endoscopic appearance, but only 1 obtain MH. The indication for switching to the second anti-TNF- α was primary non response in 3 pts (21.4%), loss of response in 6 (42.8%) and intolerance to treatment in 5 (35.7%). The second anti-TNF- α agent used was ADA for 10 patients, GOL for 3 and IFX for 1. After the second course with a different anti-TNF- α , 4/14 (28.5%) patients obtained MH (3 with

ADA and 1 with GOL). Of the patients with MH 2 were intolerant to the first anti-TNF- α (2/5, 40%) and 2 had loss of response before switching (2/6, 33.3%).

Conclusions: The findings of this study, for the first time in real life practice, showed that the switch to a second anti-TNF- α agent allows obtaining MH in almost a third of patients with UC, particularly in those intolerant to the first anti-TNF- α . Further studies in larger cohort of patients are needed to confirm these data.

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A study to determine factors affecting clinical decision making in outpatients with inflammatory bowel disease

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Background: Evaluation of patient-reported symptoms forms the mainstay of disease activity assessment in patients with inflammatory bowel disease (IBD). Despite this, the correlation between symptom reporting and the presence of mucosal inflammation is poor, particularly in Crohn's disease (CD). [1] We conducted a cross-sectional study to determine factors affecting clinical decision making in IBD. **Methods:** Validated questionnaires were used to assess clinical disease activity, self-reported flare, the presence of irritable bowel syndrome (IBS) symptoms and anxiety, depression and somatisation in a cohort of 274 patients with IBD. Patients who had undergone investigations in the preceding 90 days were excluded. Clinicians were blinded to faecal calprotectin (FC), with a cut off of 250 μ g/g used to define active mucosal inflammation. Logistic regression analysis was performed to determine the association between these factors and clinical decision making (investigation requesting or escalation of medical treatment). Results were reported as odds ratios (OR) with 95% confidence intervals (CI).

Results: 18 (50%) of 36 CD patients, and 10 (27.7%) of 36 ulcerative colitis (UC) patients referred for investigations had evidence of mucosal inflammation defined by FC. The proportion of patients with mucosal inflammation who were neither investigated nor received escalation of medical treatment was 33.7% in CD and 39.4% in UC. The results of logistic regression analyses for factors associated with investigation requesting and escalation of medical treatment are displayed in Tables 1 and 2.

Table 1. Relationship between clinician investigation requesting and disease characteristics in CD and UC after logistic regression

	CD and investigation requesting OR (95% CI)	UC and investigation requesting OR (95% CI)
Rome III IBS criteria fulfilled	0.74 (0.25–2.15)	1.07 (0.30–3.81)
Self-reported flare	5.93 (1.93–18.21)	7.29 (2.00–26.54)
Total HBI ≥ 5	1.43 (0.43–4.80)	N/A
Total SCCAI ≥ 5	N/A	1.23 (0.37–4.15)
FC ≥ 250 μ g/g	2.09 (0.77–5.71)	0.19 (0.05–0.64)
Anxiety (per 1-point change on HADS anxiety score)	0.91 (0.78–1.07)	0.81 (0.66–0.98)
Depression (per 1-point change on HADS depression score)	0.98 (0.83–1.17)	1.19 (0.96–1.47)
Somatisation (per 1-point change on PHQ-15 score)	1.02 (0.86–1.20)	1.10 (0.95–1.26)

Conclusions: Bar self-reported flare, factors influencing clinical decision making are uncertain in CD. Clinicians treat, rather than inves-

Table 2. Relationship between clinician decision to escalate treatment and disease characteristics in CD and UC after logistic regression

	CD and escalation OR (95% CI)	UC and escalation OR (95% CI)
Rome III IBS criteria fulfilled	0.87 (0.21–3.69)	1.24 (0.31–5.03)
Self-reported flare	5.62 (1.24–25.5)	2.39 (0.64–8.87)
Total HBI \geq 5	4.73 (0.89–25.06)	N/A
Total SCCAI \geq 5	N/A	10.36 (2.47–43.5)
FC \geq 250 μ g/g	2.02 (0.52–7.94)	4.26 (1.28–14.2)
Anxiety (per 1-point change on HADS anxiety score)	0.95 (0.77–1.17)	1.04 (0.88–1.25)
Depression (per 1-point change on HADS depression score)	1.07 (0.84–1.36)	0.91 (0.73–1.14)
Somatization (per 1-point change on PHQ-15 score)	0.94 (0.73–1.20)	1.01 (0.85–1.21)

tigate active UC, presumably because of the superior correlation between symptoms and inflammation in these patients. [1] At the time of investigation requesting, 50% of CD and 72.3% of UC patients had no evidence of mucosal inflammation, suggesting that these investigations could have been avoided. One third of patients with FC \geq 250 μ g/g received no intervention and were, potentially, managed inappropriately. The introduction of routine point-of-care FC testing may reduce unnecessary investigations and improve the appropriateness of resource allocation, particularly in CD.

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P656**Is there a role for additional oral mesalamine therapy in the treatment of ulcerative proctitis with skip inflammation?**

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Background: Ulcerative proctitis (UP) is limited in the rectum. Therefore, local mesalamine is a mainstay of maintenance therapy. In some UP patients, skip inflammation such as patchy or segmental inflammation is noted in the right-sided colon. However, its clinical significance is currently unclear. Considering the local action of mesalamine suppository or enema, the clinical efficacy of additional oral mesalamine therapy remains questionable. The aim of this study was to evaluate the clinical features and course of UP with skip inflammation according to the additional use of oral mesalamine.

Methods: Data of 388 patients (median age 39 years) with an initial diagnosis of UP at Daehang Hospital, Seoul from January 2005 to October 2016 were reviewed. Each UP patient with skip inflammation was matched with controls (UP patients without skip inflammation) at 1:2. To reduce biases, controls were matched with cases for age, gender, and initial disease activity. Study outcomes were extent progression and acute exacerbation (condition requiring corticosteroid). Patient demographics, endoscopic findings, clinical course, and medication history were also analyzed.

Results: During the follow-up period (median, 69.5 months; range, 12–153 months), the overall extent progression rates of the control group (n=192) versus the skip-inflammation group (n=96) were 13.5% vs. 9.9% at 5 years and 24.0% vs. 32.9% at 10 years (log rank p=0.71). In the skip-inflammation group, the extent progression rates at 5 and 10 years were not significantly different either between

the combination mesalamine group and the local mesalamine group (7.2% vs. 14.6% for 5 years and 33.4% vs. 26.6% for 10 years, log rank p=0.96).

The overall exacerbation rates of the control group versus the skip-inflammation group were 13.0% vs. 10.2% at 5 years and 17.2% vs. 26.8% at 10 years (log rank p=0.68). In the skip-inflammation group, the exacerbation rates were not significantly different between the combination mesalamine group and the local mesalamine group either (12.8% vs. 6.1% at 5 years and 26.6% vs. 23.6% at 10 years, log rank p=0.88).

Conclusions: In UP patients with skip inflammation, combination mesalamine maintenance therapy tends to be preferred over single local mesalamine therapy. However, additional oral mesalamine does not significantly affect the clinical course of ulcerative proctitis with skip inflammation.

P657**The predictors and clinical outcomes of follow up loss of clinics in patients with inflammatory bowel disease**

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Background: The non-adherence was known as one of the risk factors of worsening symptoms of Inflammatory bowel disease (IBD). According to the previous studies, the non-adherence rate in IBD was reported 25–45%. We aimed to analyze the frequency and predictors of follow up loss of clinics and assess the clinical outcomes of the patients who did not visit the outpatient clinics for a long time.

Methods: The medical record of 784 patients with IBD who were followed up between January 2010 and December 2015 were reviewed retrospectively. Among them, 285 patients who was diagnosed IBD at our hospital and followed up at least 12 months without history of other serious comorbidity were included for the analysis. Follow up loss was defined that patients didn't visit clinics at least 6 months.

Results: Of total 285 patients, 162 patients were diagnosed as ulcerative colitis and the other, 124 were Crohn's disease. Mean follow up duration was 58.3 \pm 34 months. Among them, 42 (15%; 27 in UC, 15 in CD) patients were lost to follow up. The sex ratio was more in male than female (28 vs 14). Their average age was 41.2 \pm 14.4 years. Their mean duration until follow up loss was 18 \pm 14.3 months. The severity score at follow up loss, Mayo score was 1.96 and CDAI score was 111.4. On multivariate regression analysis, distance to far clinics (odds ratio (OR): 2.107, p<0.001) and lower C reactive protein (OR: 0.582, p=0.01) were significantly associated with follow up loss patients. Among the 42 follow up loss patients, 36 (85.7%) patients revisited the clinics. Mean follow up loss duration of revisited patients was 18.19 months. Patients with UC were in remission state in 42.8% and in case of CD was 33.3%. However, totally 61.1% of the patients revisited due to disease relapse. Step up treatment was needed in 13 of (39.4%) patients. Steroid was re-introduced in all 13 patients and among them, azathioprine and anti TNF agent were prescribed in 2 and 1 patients, respectively. Finally the 10 of 36 (27%) patients needed surgical treatment and the risk was higher in CD (OR: 4.353, p=0.12).

Conclusions: Predictors for follow up loss were lower C reactive protein and distance to far clinics. In the result, 22 of 36 (61.1%) pa-

tients revisited due to disease flare up. The physician need to make an effort for their IBD patients to keep visiting the clinics.

P658

The Inflammatory Bowel Disease Disability Index (IBD-DI) in ulcerative colitis is related to disease activity, need of immunosuppressive therapy and quality of life

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Background: IBDs are disabling conditions that negatively affect physical, psychological, familial and social dimensions of life. Thus, specific tools have been used to assess the impact of disease and its treatment options on relevant end-points such as health-related quality of life (HRQL), measured by the IBD-Questionnaire (IBD-Q). Recently, the IBD-Disability Index (IBD-DI) has been developed to evaluate the entire spectrum of limitations in functioning in patients (pt) with IBD. This index is inspired to the ICF. The aim of the present study was to assess the relationship between the IBD-DI, clinical characteristics and HRQoL in a cohort of Sicilian pt with ulcerative colitis (UC).

Methods: IBD-Q and IBD-DI questionnaires were administered to consecutive UC adults outpatients from July to November 2016. The IBD-DI consists of 28 items that evaluate the 4 domains of body functions, activity and participation, body structures and environmental factors. A higher score indicating a greater level of disability. IBD-Q consists of 32 questions grouped into 4 dimensions: bowel, systemic, social, emotional. Scores range from 1 to 7 with higher scores indicating better QoL. Disease activity was assessed by partial Mayo score. The mean differences of DI score in relation to dichotomic clinical variables were performed by Student's t test. By linear regression analysis we assessed also the relationship between DI and IBD-Q. Differences were reported as statistically significant if the pvalue was <0.05.

Results: 49 UC patients (69% males, median age 47 years) were enrolled; 24% were smokers. 75% had inactive or mild disease, 12 (25%) moderate disease. None of the recruited pt had severe disease. Concomitant medications at the time of the interview were conventional therapy in 32 pt (65%) or immunosuppressants in 12 pt (24%). 4 pt took no medications and 1 patients was on topical therapy. The mean IBD-DI score was 25.49 ± 19.83 ; 59% of pa-

tients had low $DI \leq 25$ while 14% had high $DI (>50)$. No correlations were found between IBD-DI and gender, disease duration, disease extension (Montreal Classification) and extraintestinal manifestations. IBD-DI was related to clinical disease activity ($p=0.006$) and immunosuppressive therapy ($p=0.060$). By linear regression analysis, IBD-DI was significantly associated with IBD-Q ($R^2 0.693$; $p<0.001$). Interestingly, 8% ($n=4$) of patients with inactive or mild disease had severe disability (>50) and 6% ($n=3$) with active disease had low disability (<25).

Conclusions: Our preliminary results show that the IBD-DI is a reliable tool to measure functional status and disability in UC; it correlates with disease activity, need of immunosuppressive therapy and HR-QoL. This novel index should be adopted as a primary endpoint in disease modification trials.

P659

Therapeutic drug monitoring of anti-TNF α drugs in a UK tertiary IBD unit

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Background: Therapeutic drug monitoring (TDM) of anti-TNF α in IBD is cost effective and may improve clinical outcomes [1,2]. Practice is evolving as TDM is increasingly adopted. Anti-TNF α dosing based on clinical response leads to over or under-treatment and increases anti-drug antibody (ADA) formation [1].

The aim of this study was to assess clinician behaviour and decision-making during the time prior to the adoption of a recognised clinical algorithm for TDM, in a tertiary referral IBD unit in the U.K.

Methods: Patients were recruited retrospectively from a tertiary referral IBD centre in the UK. All patients who had TDM and ADA measured within a 2-year period (2013–2015) were included. Disease type, treatment, clinical indication, outcome and clinical decision were all recorded and compared against a peer-reviewed algorithm [3].

Results: 124 test results were analysed in 115 patients with Crohn's disease and 9 patients with UC. 87 patients were on infliximab and 37 patients on adalimumab; 64 were on combination therapy and 61 patients on monotherapy. Of monotherapy patients, 38 were on infliximab and 23 on adalimumab.

Clinical indication for TDM is shown in Fig. 1; secondary loss of response was the most common (59.7%). TDM outcome is shown in Fig. 2; 55.8% of patients on infliximab were in therapeutic range with undetectable ADA; 47.2% of patients on adalimumab were in therapeutic range with undetectable ADA.

ADAs were more common in patients on infliximab (17% on monotherapy, 6.8% combination) compared to adalimumab (8.7% monotherapy, 0% combination).

When physician response to TDM was compared to an algorithm, 11 responses differed to those suggested by the algorithm.

Conclusions:

- In line with other studies, the majority of patients with secondary loss of response had therapeutic TDM and no ADA. Antibodies to infliximab were found to be more common than antibodies to adalimumab and, in line with other studies, combination therapy reduced the risk of antibody development [4].

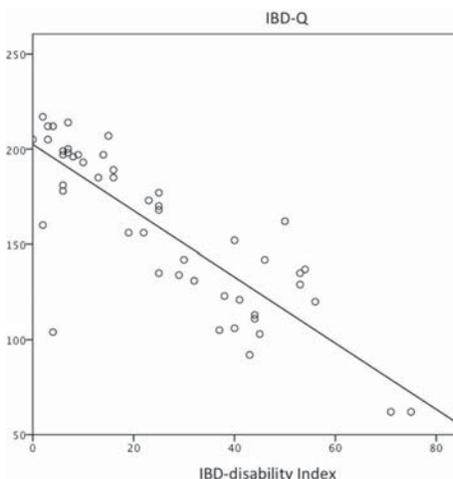
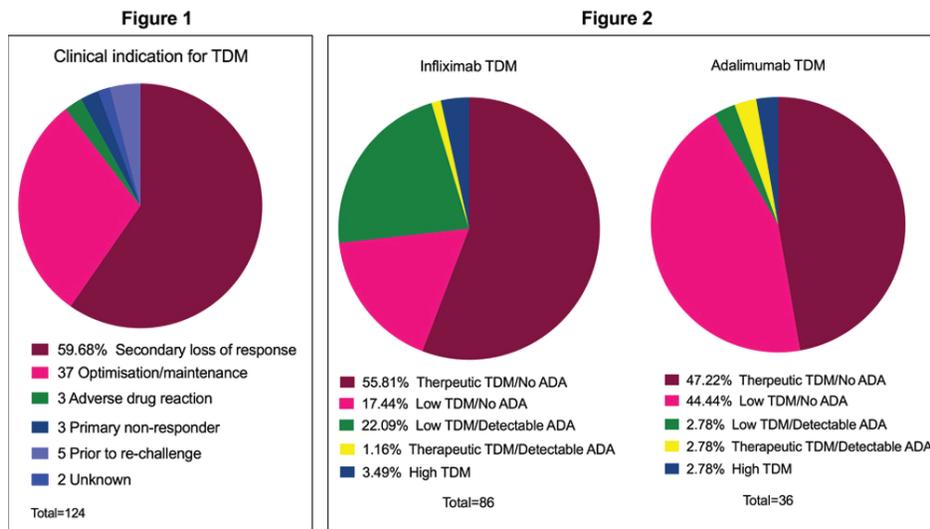


Figure 1



Abstract P659 – Figure 1. The clinical indication for TDM. **Figure 2.** The outcome of TDM for infliximab and adalimumab.

- When an algorithm was retrospectively applied to physician decision, discrepancies were found in only a few patients. This compares favourably with previous studies in which per-protocol management was lower [2].
- This is an evolving field and TDM use is likely to change. TDM for patients re-starting anti-TNF α is now thought to be unhelpful and in future more tests will be performed in possible primary non-response.

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P660

Prevalence and clinical course of cytomegalovirus colitis in Asian patients with acute exacerbation of ulcerative colitis

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Background: In Inflammatory bowel disease (IBD), reactivation of human cytomegalovirus colitis (CMV) infection can occur as a result of chronic immunosuppression and local inflammation in the bowel wall [1]. CMV reactivation is common in patients with severe colitis, with a reported prevalence of 4.5–16.6% [2], and occurs more frequently in ulcerative colitis (UC) than Crohn's disease (CD), possibly due to their different cytokine profile. CMV colonic disease can exacerbate UC disease activity, and has been associated with decrease response to corticosteroids/ immunosuppressive therapy [3],

higher colectomy rates [4] and longer hospitalisation stay. However, it remains controversial if anti-viral therapy alters the course of UC; there is also a lack of data on the prevalence of CMV colonic disease in Asian IBD patients. We aim to determine the prevalence of CMV colonic disease and clinical course in Asian patients with acute exacerbation of UC in Singapore, a multiracial country consisting predominantly of Chinese, Malays and Indians.

Methods: Electronic records of 125 patients with ulcerative colitis (UC) who were hospitalised for acute exacerbation from 2002–October 2016 were retrospectively reviewed. Biodata, clinical presentation and treatment information was extracted. The diagnosis of CMV colonic disease was based on histological identification of CMV inclusion bodies and/or positive immune-histochemistry (IHC). The severity of UC was graded according to Truelove and Witt's criteria.

Results: There were 125 (65% Male; 56% Chinese; 23% Indian, 12% Malay, 9% others) UC patients with 205 admissions to hospital. Of these, 39 patients had 78 admissions for acute exacerbation of disease activity (6% Mild, 27% Moderate, 68% Severe, 2% Fulminant). Four patients (5.1%) were diagnosed with CMV colonic disease, including 1 patient with newly diagnosed UC; of these, 3 were steroid-refractory and 2 were on long-term azathioprine, 2 had deep colonic ulcers at endoscopy and CMV DNA (colon biopsy) ranged 5400–290000 copies/mg. All patients received anti-viral therapy: 2 responded well and achieved steroid-free remission; 2 failed to respond (including 1 who failed infliximab rescue therapy) and subsequently underwent total colectomy. CMV tissue DNA load, presence of deep colonic ulcers did not predict response to treatment or clinical outcome.

Conclusions: The prevalence of CMV colonic disease was 5% in Asian UC patients with acute exacerbation. Anti-viral therapy conferred benefit in only some patients who subsequently achieve steroid-free remission. Larger studies are needed to determine prognostic factors and identify subgroups that will benefit from anti-viral therapy.

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P661

Comparable clinical efficacy, safety and immunogenicity of infliximab biosimilar (CT-P13) after transition from reference infliximab (Remicade®) in children with established inflammatory bowel disease: a multi-centre prospective observational study

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Background: CT-P13 is the first approved biosimilar infliximab (IFX) for all indications of the reference product (Remicade®). Similar-but-not-identical nature of CT-P13 compare to Remicade®, the concept of extrapolating data from one therapeutic indication to another, very limited clinical data on its use in inflammatory bowel disease (IBD) may be puzzling to physicians. In the present study we aimed to gain data on the efficacy, safety and immunogenicity of transition from Remicade to CT-P13 in a real-life IBD paediatric patients.

Methods: In this prospective, multi-centre study, all paediatric IBD patients treated with Remicade at two academic centres in Italy and Poland were electively transitioned to CT-P13. Registration was performed with a start time 2 months before transition, and for the each patient data on the efficacy, safety and immunogenicity were evaluated at the transition to CT-P13, at the second and fourth CT-P13 infusion with the follow up lasted for up to week 24–36. The

primary end-point was the change in clinical disease activity and adverse reaction following transition. The secondary end-points included changes in inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation (ESR), faecal calprotectin (FCP), infliximab trough level (TL) and development of anti-drug antibodies (ADAs).

Results: In total, 45 IBD children, 38 Crohn's disease (CD) and 7 ulcerative colitis (UC) were transitioned at the mean time elapsed between the beginning of Remicade therapy of 23.6±15.5 months for CD and 12.0±15.5 months for UC. At the time of the transition 33/38 CD and 4/7 UC patients presented with clinical remission. We did not observe any change in clinical disease activity, CRP, ESR, FCP, TL-IFX for both CD and UC. Of three patients having CT-P13 discontinued, only for one case the reason was an adverse reaction with high ADAs, presented even before the transition. One patients developed new detectable ADAs, while one patient with detectable ADAs before transition presented with undetectable level thereafter. **Conclusions:** Our data indicate that clinical efficacy, safety and immunogenicity profile were highly comparable before and after the transition from Remicade® to CT-P13 in paediatric IBD patients.

P662

Tofacitinib for induction of remission in ulcerative colitis: systematic review and meta-analysis

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Background: We performed a systematic review and meta-analysis to assess efficacy, safety and impact on patient-reported outcomes of tofacitinib for the induction of remission in patients with active moderate to severe ulcerative colitis (UC).

Methods: Medline, Embase, CENTRAL, and grey literature sources were systematically searched up to October 2016. We included randomized controlled trials in adults with moderate to severe UC that compared tofacitinib to other active comparator or placebo. Efficacy outcomes were remission, response, mucosal healing and endoscopic remission (Mayo endoscopic subscore of 0). PRO endpoints included IBDQ response (a ≥16-point increase from baseline) and IBDQ remission (total score ≥170). Safety was assessed with incidence of serious adverse events and incidence of infections. We conducted subgroup analyses based on prior anti-TNF therapy.

Results: We included three randomized, double-blind, placebo-controlled trials (1355 patients). Tofacitinib treatment led to remission, response, and mucosal healing regardless of prior anti-TNF exposure. Greater effects were observed in anti-TNF treated patients. Tofacitinib resulted in higher IBDQ response and remission rates

Abstract P662 – Table 1. Results for efficacy, safety and patient-reported outcomes for Tofacitinib compared to placebo

Outcomes	Anti-TNF naïve patients		Anti-TNF treated patients		All patients	
	No. studies/No. patients	OR [95% CI]	No. studies/No. patients	OR [95% CI]	No. studies/No. patients	OR [95% CI]
Clinical remission	2/521	2.20 [1.18, 4.10]	2/618	12.15 [2.38, 62.07]	3/1313	3.48 [2.12, 5.71]
Clinical response	3/610	2.67 [1.80, 3.95]	3/658	3.76 [2.45, 5.76]	3/1313	2.77 [2.09, 3.67]
Mucosal healing	2/521	2.06 [1.25, 3.40]	2/618	4.53 [2.15, 9.56]	2/1139	2.70 [1.81, 4.03]
Endoscopic remission	–	–	–	–	3/1333	5.71 [2.31, 14.11]
IBDQ response	–	–	–	–	3/1333	2.07 [1.59, 2.70]
IBDQ remission	–	–	–	–	3/1333	2.73 [2.01, 3.71]
Incidence of serious adverse events	–	–	–	–	3/1355	0.81 [0.43, 1.54]
Incidence of infections	–	–	–	–	3/1333	1.39 [0.97, 1.99]

compared to placebo. No difference was found concerning serious side effects. Although it was not statistically significant, there was a trend toward increased incidence of infections in tofacitinib-treated patients (Table 1).

Conclusions: Tofacitinib seems effective in inducing both clinical and endoscopic remission in UC, and improves quality of life. It appears to be safe, but concerns regarding risk of infections need further research.

P663

Switching from Remicade® to biosimilar CT-P13 in inflammatory bowel disease patients: one year follow-up of a prospective observational cohort study

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Background: The infliximab biosimilar CT-P13 is EMA and FDA approved, based on data extrapolated from phase III studies in rheumatoid arthritis and ankylosing spondylitis patients. Anti-tumor necrosis factor (TNF) naive IBD patients frequently start CT-P13 in current daily practice but the switch from Remicade® to CT-P13 is less common due to limited data on long-term clinical outcomes. Therefore, we aimed to prospectively investigate long-term efficacy, safety, pharmacokinetic profile and immunogenicity following an elective switch from Remicade® to CT-P13 in IBD patients.

Methods: We performed a single-centre prospective observational cohort study. All Remicade®-treated IBD patients were actively switched to CT-P13 regardless of disease activity. Primary endpoint was change in disease activity scores at week 52 compared to week 0 as measured by Harvey-Bradshaw Index (HBI) for Crohn's disease (CD) and Simple Clinical Colitis Activity Index (SCCAI) for ulcerative colitis (UC) and IBD unclassified (IBD-U). C-reactive protein (CRP), fecal calprotectin (FCP), infliximab trough levels and antidrug antibodies to infliximab (ADA) were measured at week 0, 16 and 52. Adverse events and reasons for discontinuation were documented during follow-up.

Results: Eighty-three patients were included, 57 CD, 24 UC, 2 IBD-U (28 male, median age 36, range 18–79) and 68 patients completed 1-year follow-up. Median change in disease activity was 0 (HBI, range –9 to +15, n=49) for CD and 0 (SCCAI, range –4 to +4, n=19) for UC/IBD-U (Figure 1). FCP and CRP levels did not significantly change during follow-up. CT-P13 dosing was adjusted in 20/68 (29%) of the patients and the proportion of trough levels within the “therapeutic range” 3.0–7.0 ng/ml was 40% at baseline and 48% at week 52. In total 7 patients demonstrated detectable

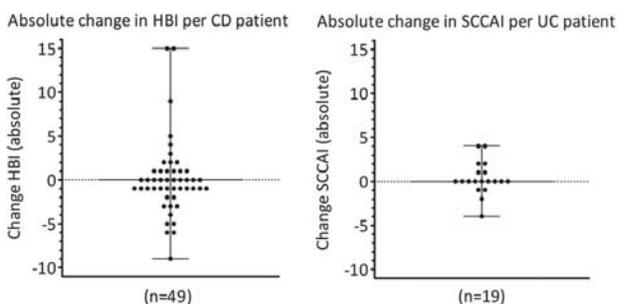


Figure 1. Change in disease activity scores during follow-up.

ADA during follow-up, 5/7 ADA titers were already detectable at baseline. Fifteen out of 83 patients (18%) discontinued CT-P13 during follow-up for reasons of clinical remission (n=3), loss of response (n=5) including 3/5 demonstrating detectable ADA, arthralgia (n=3), skin rash and itching (n=2) and migration to another hospital (n=2). **Conclusions:** Eighty-two percent of the patients continued CT-P13 through 52 weeks after switching from Remicade®. Disease activity scores and inflammatory markers remained unchanged during follow-up and no CT-P13-related serious adverse events occurred. These 1-year data suggest that switching to CT-P13 in Remicade®-treated IBD patients is feasible.

P664

The transitioning healthcare economy of IBD: changes in resource allocation over time

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Background: There is limited longitudinal IBD healthcare cost data in the post-biologic era.

Aims: To calculate the direct healthcare costs in the first 4 years following diagnosis using two well characterized cohorts of recently diagnosed IBD patients from a population based and hospital based cohort in order to determine:

- 1) The total direct healthcare cost of IBD in the first 4 years.
- 2) The proportional change in IBD health care costs over time.
- 3) The change in mean IBD healthcare costs per patient over time.
- 4) If there is any difference in cost of care between a hospital and population-based IBD cohort.

Methods: From June 2007 to September 2016, newly diagnosed IBD cases were recruited from a tertiary referral center to form a hospital-based cohort, or a regional center to form a population-based cohort. Healthcare resource utilization and clinical data for each patient was collected. Total costs were calculated for investigations, specialist visits, medications, and hospitalization each 12 months from diagnosis to a maximum of 48 months.

Results: 353 IBD patients were recruited (171 Hospital, 182 Population). There were no significant differences in disease phenotype at diagnosis between each cohort.

1) Total direct cost: The total cost of care for the first 4 years was A\$10,847,094. CD accounted for 70% of total cost. Medication expenditure accounted for 61% of total. Biologic medication cost accounted for 80% of total medication cost. Inpatient admissions accounted for 27% of total cost.

2) Change in health care costs over time: In the CD cohort, inpatient admissions accounted for 45% in the first 12 months compared with only 9% in months 36–48. Medication costs accounted for 40% in the first 12 months, but increased to 80% in months 36–48. In UC, inpatient medical admissions and surgical admissions accounted for 32% in the first 12 months compared with 21% in months 36–48. Medication costs accounted for 47% in the first 12 months, but increased to 68% in months 36–48.

3) The mean annual cost reduction from the 1st to the 4th year in CD was \$4,011 per patient. The mean medication cost increased by \$3,083 over this time. The mean cost reduction in the UC cohort was \$4,022. There was no significant change in mean medication cost. All of the other healthcare costs reduced over time.

4) There was no significant difference in median cost of care for the first 4 years between the hospital-based cohort versus the population-based cohort in CD or UC.

Conclusions: The cost of care in IBD is driven by medication and

inpatient admission costs. Over time, medical and surgical admission costs fall while the cost of medication increases. The cost of care is highest in the first year and reduces over time.

P665

Unchanged infliximab serum concentrations after switching from the reference infliximab to the biosimilar CT-P13 in patients with quiescent Crohn's disease: a prospective study

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Background: The biosimilar infliximab (IFX) can reduce healthcare costs when patients are switched from the reference to the biosimilar IFX; however this switch has raised concerns about potential immunogenicity. The objective of the SECURE study was to demonstrate that the IFX serum concentrations of the biosimilar IFX were non-inferior to the IFX concentrations of the reference 16 weeks after switch in subjects with rheumatoid arthritis, ulcerative colitis and Crohn's disease (CD) in stable remission for >30 weeks. This abstract presents the preliminary results of CD patients only.

Methods: In this prospective, open-label, interventional, non-inferiority, multicentre, phase IV trial, adult CD patients in clinical remission >30 weeks (Harvey Bradshaw Index; HBI ≤4) were switched from the reference IFX to the biosimilar IFX at stable doses. Patients were followed for 16 weeks after switch (2 infusions at 8 week interval). The primary endpoint was the serum IFX trough level concentration measured by a bridging enzyme-linked immunosorbent assay (ELISA) 16 weeks after switch (non-inferiority margin of 15%). Secondary endpoints included antibodies to IFX (ATI), clinical disease activity (HBI score), C-reactive protein (CRP), fecal calprotectin and quality of life (EQ-5D score) 16 weeks after switch compared to reference IFX.

Results: In total 61 CD patients were enrolled in 9 centers and 44 patients were included in the per protocol analysis (PP); 17 patients were excluded due to violation of eligibility criteria (4), not compliant with the study protocol (5), early termination of the study (3) and missing IFX serum samples (5). Mean age of the patients was 42±16 years (50% male) and mean duration on IFX treatment 4.9±3.8 years. The LS mean serum IFX concentration (90% CI) was 2.97 (2.78–3.18) for the reference IFX and 3.25 (3.04–3.48) 16 weeks after switch, with an IFX ratio of 109.6% (99.7%–120.6%) demonstrating non-inferiority of the biosimilar IFX to the reference IFX. One patient developed ATI's after 2 infusions. At the end of the study 38 (86%) patients were still in remission (HBI ≤4). The CRP, fecal calprotectin and EQ-5D were not significantly different for the biosimilar at week 16 compared to the reference IFX. In the enrolled population (61 patients) 2 SAEs (3.2%) were reported (both perianal abscess). The adverse event profile was not changed compared to the reference IFX.

Conclusions: This prospective, interventional study demonstrated that the IFX serum concentration of the biosimilar IFX was non-inferior to the IFX concentration of reference IFX 16 weeks after switching in patients with CD. Efficacy and tolerability were also similar.

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Short-term outcomes of adalimumab for patients with Crohn's disease and associated prognostic factors: a multicentre retrospective cohort study

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Background: There are few studies on the short-term efficacy of adalimumab treatment for patients with Crohn's disease (CD). Here, we report the results of the Short-term Outcomes of Adalimumab for Patients with Crohn's disease and Associated Prognostic Factors: A Multicentre Retrospective Cohort Study in Japan (SAPPORO).

Methods: The SAPPORO study was conducted at 9 institutions. Data were retrospectively collected from CD patients who received adalimumab from October 2010 to September 2015. Patients had to have a Harvey–Bradshaw index (HBI) of ≥5 points at the first adalimumab administration. The HBI score and C-reactive protein (CRP) level were investigated at baseline and at 2, 4, 8 and 12 weeks following adalimumab administration. Remission was defined as an HBI score of ≤4. Rate of remission and remission with a normal CRP level were assessed at 2, 4, 8 and 12 weeks. The prognostic factors associated with the rate of remission with a normal CRP level at 4 and 12 weeks were evaluated using univariate and multivariate logistic regression analysis.

Results: Of the 160 patients included in this study (median age, 29.3 years), 56 were female. The HBI scores significantly decreased sequentially from baseline to 2, 4, 8 and 12 weeks as follows: 8.0, 4.0, 3.3, 3.4 and 3.5, respectively. The CRP levels also significantly decreased sequentially as follows: 2.43, 0.71, 0.95, 0.91 and 1.37 mg/dL, respectively. Rates of remission at 2, 4, 8 and 12 weeks were 61%, 73%, 71% and 69%, respectively, while rates of remission with a normal CRP level were 36%, 51%, 49% and 49%, respectively. In the univariate analyses, previous infliximab (IFX) use, penetrating disease, a disease duration of ≥4.3 years, previous bowel resection, being ≥29.3 years old and CRP levels of ≥1.55 mg/dL were significant prognostic factors for a lower rate of remission with a normal CRP level at 4 and 12 weeks. In addition, a body mass index (BMI) of ≥18.5 and HBI of ≥7 were significant prognostic factors for a lower remission rate with a normal CRP level at 12 weeks. In the multivariate logistic regression analysis, previous IFX use and CRP levels of ≥1.55 mg/dL were identified as independent predictors of a lower rate of remission with a normal CRP level at 4 and 12 weeks. Furthermore, a BMI of ≥18.5 was identified as an independent predictor for a lower rate of remission with a normal CRP level at 12 weeks.

Conclusions: The short-term efficacy of adalimumab treatment for CD patients was demonstrated by the second week. Approximately 50% of the patients achieved remission with a normal CRP level at 4 weeks. Previous IFX use, higher CRP levels and a higher BMI appear to be associated with poor short-term outcomes of adalimumab treatment.

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Safety of anti-TNF treatment in liver transplant recipients – a meta-analysis

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Background: Primary Sclerosing Cholangitis (PSC) patients with refractory inflammatory bowel disease (IBD) after liver transplantation (LT) pose a dilemma for treating physicians, as little is known about the risk of serious infection when combining anti-TNF therapy with immunosuppression for prevention of rejection.

Our aim was to investigate the infection risk in this patient group by systematic review and meta-analysis of the available data.

Methods: A literature search was conducted for full papers and conference proceedings through September 2015 regarding liver transplant recipients and anti-TNF therapy. All studies were appraised using the adapted Newcastle-Ottawa Scale (NOS), which contains 9 criteria for cohort studies and is adapted to 6 criteria for case series and case reports. Two reviewers (MWvM and PWJM) independently extracted study and control-patient data (age, duration of follow up, number of all infections, number of serious infections, time since transplant). As additional control population, PSC-IBD patients from the LUMC LT cohort were used. Poisson regression was used to compare serious infections (according to ICH-definition)

per patient year follow up between the anti-TNF and control group, correcting for mean time since transplant.

Results: Initially, 465 articles and abstracts were identified, of which 8 were included. These 8 studies contained 53 post-LT patients on anti-TNF therapy and 23 post-LT control patients not on anti-TNF therapy. None of the studies scored less than 75% of the NOS quality criteria. From the LUMC LT cohort, 41 PSC-patients with PSC-IBD but without anti-TNF therapy were included as control population. Serious infection rates differed from 0 to 0.38 serious infections per patient year in the anti-TNF therapy group, and 0.04 to 0.24 in the control group.

The overall infection rate for TNF-exposed patients was 0.12, compared to 0.15 in the control patients, resulting in a rate ratio of 0.80 (95% CI: 0.17–3.97, p=0.80). Age at time of transplant was not associated with the rate ratio for serious infections, whereas the time since transplantation was. Although correcting for time since transplant causes the infection rates in the anti-TNF-group to be higher than in the control group (0.13 vs 0.12 serious infections per patient year) the rate ratio remained non-significant (1.1, p=0.82).

Conclusions: No significant increase in the serious infection rate was observed in LT-recipients with PSC-IBD during exposure to anti-TNF therapy. However, the wide confidence intervals of these results show that more data is needed to provide a definitive conclusion on the safety of anti-TNF therapy in these patients.

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Post-marketing experience of vedolizumab in inflammatory bowel disease: analysis of pneumonia and other respiratory tract infections

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Background: The annual incidence of pneumonia has been reported as 13.8/1000 in patients with IBD versus 7.6/1000 in healthy subjects (IRR 1.82; 95% CI: 1.75–1.88) [1]. Vedolizumab (VDZ) is a hu-

Abstract P668 – Table 1. Patient demographics and clinical characteristics

	URTIs (n=300 patients)	LRTIs (n=106 patients)
Female sex, n (%)	173 (57.7)*	66 (62.3) [†]
Age, mean (SD), years	43.0 (14.7)	46.5 (16.5)
Current/former smoker, n (%)	5 (1.7) [‡]	6 (5.7) [§]
Prior/concomitant anti-TNF α therapy, n (%)	59 (19.7)	53 (50.0)
Prior/concomitant IMM use, n (%)	59 (19.7)	26 (24.5)
No prior/concomitant medications reported at all, n (%)	61 (20.3)	32 (30.2)
Surgery \leq 30 days prior to event onset reported, n (%)	1 (0.3)	2 (1.9)
VDZ treatment status after event, n (%) [¶]		
Continued	229 (76.3)	61 (57.5)
Discontinued	25 (8.3)	14 (13.2)
Interrupted	2 (0.7)	7 (6.6)
NR	43 (14.3)	17 (16.0)

*Sex was not reported in 21 patients

[†]Sex was not reported in one patient

[‡]Smoking status was not reported in 280 patients

[§]Smoking status was not reported in 96 patients

[¶]1 and 6 patients reporting URTIs and LRTIs, respectively, died after the event; treatment was discontinued in one patient prior to LRTI event onset. Treatment status after the event therefore does not apply in these patients

IMM, immunomodulator; LRTI, lower respiratory tract infection; NR, not reported; TNF α , tumour necrosis factor-alpha; URTI, upper respiratory tract infection; VDZ, vedolizumab

manised monoclonal antibody that binds to $\alpha_4\beta_7$ integrin, selectively blocking gut-specific lymphocyte trafficking. Gut selectivity may reduce the infection risk compared with anti-tumour necrosis factor- α [anti-TNF α] agents, which cause systemic immunosuppression. Here we describe pneumonia and other respiratory tract infections reported after initiation of VDZ therapy in the post-marketing (PM) setting.

Methods: PM VDZ safety data from the Global Safety Database (May 2014–May 2016) were reviewed to identify reports of lower respiratory tract infections (LRTIs) and upper respiratory tract infections (URTIs) using the following MedDRA v19.0 High Level Terms: “LRT and lung infections”, “LRTIs not elsewhere classified (NEC)”, “URTIs”, and “URTIs (NEC)”.

Results: During almost 50,000 (~46,978) patient-years of VDZ therapy, 40 serious and 68 non-serious LRTI events were reported in 106 patients; 54 events were pneumonia (n=34 serious; n=20 non-serious; ~1 event/1000 patient-years of therapy). Regarding potential risk factors for pneumonia, 2 patients had undergone surgery ≤ 30 days prior to the event; 2 were current/former smokers (smoking history and prior surgery information not provided in 51/54 and 16/54 patients, respectively). Other LRTI events were: bronchitis (n=1 serious; n=26 non-serious); LRTIs (not otherwise specified; n=2 serious; n=20 non-serious); lung infection (n=2 serious; n=2 non-serious); lung abscess (n=1 serious; n=0 non-serious). Most LRTIs occurred ≥ 2 months after first VDZ infusion (n=32/108 events; not reported [NR] n=64/108 events). There were 4 serious and 313 non-serious URTIs in 300 patients, with nasopharyngitis the most frequently reported (n=201/317 events). Most URTIs occurred ≥ 2 months after first VDZ infusion (n=77/317 events; NR n=182/317 events). Patient demographics/clinical characteristics are shown (Table 1).

Conclusions: From almost 50,000 patient-years of VDZ therapy, RTIs (including pneumonia) were infrequent and most patients continued VDZ. These data represent experience of VDZ in a “real-world” setting and complement existing data from clinical trials. Limitations associated with PM safety reporting (incomplete data, voluntary reporting and difficulty establishing a causal relationship between drug and event) must be considered when interpreting these results.

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P669

Adalimumab long-term effectiveness in adalimumab-naïve patients with Crohn’s disease: final data from PYRAMID registry

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Background: PYRAMID was an international multi-center non-interventional postmarketing registry assessing long-term safety and effectiveness of Humira® (adalimumab [ADA]) as used in routine clinical practice. Patients with and without prior ADA experience were allowed to enroll. This analysis evaluates the long-term effectiveness of ADA in ADA-naïve, i.e., patients who had not received ADA before the registry enrollment, adult patients with moderate to severe Crohn’s disease (CD) who were treated according to the local product label.

Methods: All patients entering the registry were followed for up to 6 years. Effectiveness of ADA was measured using Physician’s Global Assessment (PGA; [a composite of Harvey Bradshaw Index and rectal bleeding score]), Short Inflammatory Bowel Disease Questionnaire (SIBDQ), and 4 components of the Work Productivity and Activity Impairment questionnaire (WPAI), including absenteeism, presenteeism, overall work impairment, and activity impairment.

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Table. Change from enrollment (baseline) in effectiveness measure scores in ADA-naïve patients with CD (N=2657)

Effectiveness measure	Enrollment, mean (SD)	Change from enrollment, mean (SD)					
		1 year	2 years	3 years	4 years	5 years	6 years
PGA	7.1 (5.6) n=2542	-2.6 (5.4) n=1742	-2.7 (5.6) n=1469	-3.2 (5.3) n=1348	-3.1 (5.3) n=1255	-3.2 (5.6) n=1117	-3.2 (6.0) n=1056
SIBDQ*	43.9 (13.6) n=1840	7.3 (13.0) n=967	6.4 (14.2) n=728	7.2 (13.9) n=618	7.8 (13.6) n=541	7.8 (13.6) n=472	7.6 (13.5) n=424
WPAI Absenteeism**	17.1 (30.7) n=1081	-7.2 (31.1) n=473	-5.8 (29.9) n=333	-9.7 (32.9) n=275	-7.3 (35.3) n=241	-6.1 (32.7) n=214	-6.9 (28.4) n=172
WPAI Presenteeism**	34.6 (30.2) n=1130	-11.6 (31.6) n=513	-10.8 (33.6) n=383	-14.0 (31.9) n=308	-11.3 (35.8) n=267	-11.8 (31.2) n=239	-11.7 (31.7) n=201
WPAI Overall Work Impairment**	41.7 (34.3) n=1079	-14.0 (35.4) n=469	-12.6 (38.3) n=330	-17.3 (36.9) n=269	-13.9 (38.8) n=240	-12.8 (35.1) n=212	-14.6 (37.2) n=170
WPAI Activity Impairment**	44.0 (31.4) n=1802	-15.0 (31.8) n=943	-14.7 (33.7) n=718	-14.7 (33.7) n=593	-15.0 (33.3) n=522	-15.1 (31.5) n=458	-15.4 (30.6) n=407

*Total SIBDQ score ranges from 1 (poor health-related quality of life) to 70 (optimum health-related quality of life). A 9-point change in total SIBDQ score correlates with a 100-point change in Crohn’s Disease Activity Index score (Irvine EJ, Zhou Q, Thompson AK *Am J Gastroenterol* 91:1571-8, 1996). ** A 7-percentage point change in WPAI score represents the minimum clinically important difference. (Reilly MC, et al. *Gut* 2007. 56Suppl3 A159).

Effectiveness measures, captured in all patients who received at least 1 dose of ADA in the registry and had at least 1 post-enrollment measurement, were summarized descriptively by the number of observations that were not missing at each registry visit; data were used as observed.

Results: Among 5025 patients evaluated in the registry, 2657 patients (52.9%) were ADA-naïve. Of them, 1531 patients (57.6%) were female; mean age 37.7 years at enrollment. Mean±SD ADA exposure for the ADA-naïve subgroup during the registry was 1179.6±837.3 days. A total of 1413 patients (53.2%) had prior exposure to anti-TNF biologics; 1039 (39.1%) and 914 patients (34.4%) used immunomodulators and corticosteroids, respectively, at enrollment. Mean change from enrollment (baseline) in effectiveness measures for patients with CD is shown in the table. Mean PGA and SIBDQ scores as well as WPAI domain scores improved in ADA-naïve patients from enrollment to as early as 1 year and sustained for up to 6 years (table). No new safety signals were identified.

Conclusions: At 1 year after entering the international postmarketing registry of ADA use in routine clinical practice, clinically meaningful improvements in disease activity, work productivity, and activity impairment were achieved in ADA-naïve patients with moderately to severely active CD. These improvements were maintained for up to 6 years of the registry.

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Evaluating the management of Vitamin D in Crohn's disease patients in a secondary care population

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Background: Evidence is accumulating for an important role of vitamin D in aetiopathogenesis and outcomes in Crohn's disease (CD) [1]. Vitamin D monitoring and supplementation is now recommended for the general population in the UK; however, there is no recent European guidance on this in CD [2]. We undertook an audit to assess awareness of vitamin D monitoring in our regional CD outpatients.

Methods: We randomly selected 146 patients from the South Birmingham University CD cohort, covering a total population of around 750,000. Using clinical and informatics databases, we retrospectively collected data concerning patient demographics, concomitant steroids and smoking status. We determined whether vitamin D level had been measured within past 2 years. In those vitamin D deficient patients, we assessed whether parameters of bone metabolism (calcium, phosphate and parathyroid hormone) had been measured and if vitamin D supplementation had been provided or recommended.

Results: The mean age of our sample was 41 years and 85/146 (58%) were female. Around 20% (29/146) patients were current smokers and 71% (103/146) had some/variable degree of diagnosed small bowel CD. Vitamin D levels were checked in 46% (68/146) patients, of which 47% (32/68) patients had vitamin D deficiency (<50 nmol/L) and 21/32 patients had severe vitamin D deficiency (<30 nmol/L). Among these deficient patients, there were no clear gender or ethnic differences, but current smokers were more common (37% (12/32)). 63% (20/32) of the deficient patients had some/variable degree of small bowel disease. All had normal calcium: none had parathyroid hormone checked whilst only 22% (7/32) patients had

phosphate checked (all normal). Four patients (13%) were taking concomitant steroids. Supplementary treatment or request to GP to prescribe vitamin D supplement was undertaken in 56% (18/32) of vitamin D deficient patients.

Conclusions: In this single-center random UK sample, vitamin D levels were checked in less than half of the sampled population. Of those checked, around half were vitamin D deficient, and around one third were severely deficient, with smokers. Whilst about half of them did receive required supplements following their tests, many did not, highlighting that increased awareness of the role of vitamin D in CD is required.

References:

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Early suppression of the serological macrophage activity biomarker VICM, and not suppression of CRP, predicts the response to infliximab in Crohn's disease patients

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Background: Anti-tumour necrosis factor-alpha treatments, e.g. infliximab, are an important treatment option for inflammatory bowel disease. However, up to 40% of patients do not respond to infliximab upon evaluation after several infusions. Currently, there are no biomarkers with adequate sensitivity to separate responders from non-responders at an early stage. We hypothesised that macrophage activity may be a measure of early efficacy. We investigated if an early change in serum VICM levels (citrullinated and MMP-degraded vimentin), a biomarker of activated macrophages, would be associated with prediction of a positive clinical benefit defined as responders to infliximab treatment in Crohn's disease (CD) patients.

Methods: Serum VICM levels was measured by ELISA in the induction phase of infliximab treatment (5mg/kg) at baseline, week 2, week 6 and week 14 in 60 CD patients. Disease activity for CD was assessed by applying the Harvey Bradshaw index (HBI, >4=active disease) and the Physician's Global Assessment (PGA, >0: active disease). The median disease duration was 9.3 years. 44 (73%) patients responded, whereas 16 (27%) patients did not respond to infliximab (median follow-up 3.9 years). Clinical response was defined as having >1 decrease in PGA at week 14 or being in remission at last follow-up. Non-response was defined as <2 PGA decrease and failure to induce clinical remission (in PGA and HBI) at last follow-up.

Results: VICM predictive for response to treatment at week 2 (OR=8.5, (CI: 2.059–31.5), p<0.01; AUC=0.65, p<0.05). Responders had significantly decreased VICM levels at week 2 (p<0.001, >30% decrease from baseline), week 6 (p<0.001, >20% decrease from baseline), and week 14 (p<0.001, >20% decrease from baseline) compared to baseline (Fig. 1A). VICM levels in non-responders

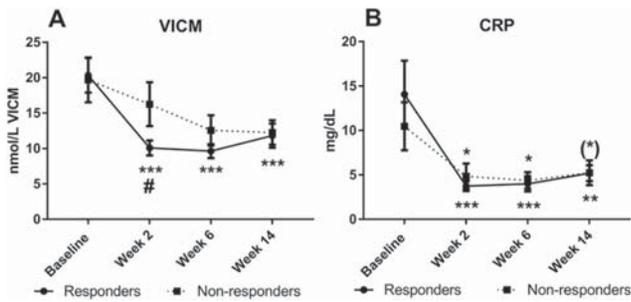


Figure 1. A) VICM and B) CRP in response to infliximab. *Indicates significance, $p < 0.05$, $***p < 0.001$. #Indicate significant difference between responders and non-responders ($p < 0.01$). Marker levels are presented as mean and standard error of the mean.

were not significantly different compared to baseline. VICM serum levels at week 2 were significantly different in responders compared to non-responders ($p < 0.01$) (Fig. 1A). CRP was significantly suppressed in both responders and non-responders at all time points, but showed no significant difference between responders and non-responders (Fig. 1B).

Conclusions: Macrophage activity, quantified by VICM, predicted early response to infliximab in CD patients, with an OR of 8.5. This provides value to patients, by selecting those patients with an early and superior response to infliximab. VICM was time dependently suppressed, suggesting that macrophage activity was significantly attenuated by infliximab treatment.

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Surgical and anti-TNFs combined therapy prevents Crohn's perianal fistula recurrence: a systematic review and meta-analysis

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Background: The management of perianal Crohn's disease (CD) fistula represents a significant challenge. We aimed to conduct a meta-analysis to evaluating the efficacy and safety of combined surgical and anti-TNFs treatment compared with either single therapy in fistulising perianal CD.

Methods: MEDLINE, EMBASE and the Cochrane database were searched. The primary outcome was the number of patients who developed fistula closure as defined by the primary studies.

Results: Eight studies (3 prospective studies and 5 retrospective studies) involving 688 patients were included. The rate of fistula closure of the combination therapy (78.5%, 197/251) was not significant higher compared with the surgical therapy alone (65.2%, 215/330) (OR 2.21, 95% CI 0.83–5.90, $p = 0.11$). Similarly, neither the rate of complete closure nor the rate of partial closure was significantly different between the two groups. Significant lower proportion of patients in the combination group developed fistula recurrence (20.8%, 11/53) compared with the single surgical group (76.1%, 35/46) (OR 0.13, 95% CI 0.03–0.58; $p = 0.007$). No significant difference observed between the combination therapy and anti-TNF therapy alone in the rate of fistula closure. However, the combination therapy was associated with a 76% risk reduction of fistula recurrence (OR 0.24, 95% CI 0.06–0.93, $p = 0.04$, $n = 57$). The adverse events were mostly related to anti-TNFs infusion.

Conclusions: Combined surgical and anti-TNFs therapy did not significantly improve the fistula closure than the surgery or anti-TNFs

therapy alone. However, it is superior to either therapy in preventing fistula recurrence of fistulising perianal CD without causing more adverse events.

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Intra-abdominal collections in Crohn's disease: outcomes following anti-TNF therapy

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Background: Anti-tumour necrosis factor (TNF) agents have demonstrated efficacy in achieving remission, reducing hospitalisations and enhancing quality of life for patients with Crohn's disease. There are a number of studies addressing the risk of infection and post-operative complications of anti-TNF therapy. However, few studies have examined the outcome of intra-abdominal collections that develop before or during anti-TNF therapy. Our aim was to examine the clinical course of patients who developed intra-abdominal collections immediately before or during anti-TNF therapy.

Methods: We reviewed retrospectively the medical records of all CD patients attending Canberra Hospital between 2004 and 2015 who developed intra-abdominal collections and were treated with anti-TNF therapy. An intra-abdominal collection was defined as an abscess, collection or phlegmon seen on medical imaging with raised inflammatory markers. Perianal collections were excluded.

Results: A total of 13 CD patients developed intra-abdominal collections before or during anti-TNF therapy. The mean age was 32.8 years (SD =12.9) and 62% were females. Patients commenced anti-TNF therapy an average of 6.5 years (SD =7.2) from diagnosis of CD.

62% (8/13) received antibiotics and did not require surgery. Of these, two had evidence of micro-perforation that was managed with antibiotics; anti-TNF therapy was commenced subsequently with an effective outcome. Another two who had been on anti-TNF therapy, an average of 16 months, had radiological-guided drainage of an abscess. Of the other four patients who were treated successfully using antibiotics, two had commenced anti-TNF therapy an average of two months prior to developing intra-abdominal collections and another two were commenced on anti-TNF therapy two weeks after developing intra-abdominal collections.

Five patients (38%) underwent surgery. One each had a colo-enteric and a colo-cutaneous fistula, one had evidence of a perforation that needed urgent operative management, another had radiological drainage without success and one patient had initiation of anti-TNF therapy under antibiotic cover, but did not respond adequately and underwent surgery.

Conclusions: CD patients with intra-abdominal collections may be safely and effectively managed with a combination of antibiotics, percutaneous drainage and anti-TNF therapy. Surgery may not be necessary in the majority of cases. Further studies are needed to confirm these findings.

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Potential utility of therapeutic drug monitoring of adalimumab in predicting short-term mucosal healing and histologic remission in paediatric Crohn's disease patients

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Background: There is limited data regarding mucosal healing (MH) and therapeutic drug levels in paediatric Crohn's disease (CD) patients under adalimumab (ADL) treatment. We aimed to investigate the association between ADL trough levels (TLs) and MH, and between ADL TLs and histologic remission (HR) at 4 months from ADL treatment in the paediatric population of CD.

Methods: This study was a preliminary analysis of an ongoing prospective cohort in paediatric CD patients receiving ADL at the Department of Pediatrics, Samsung Medical Center. Moderate-to-severe luminal CD patients who were naïve to biologics and receiving ADL before 19 years-old were included. Ileocolonoscopy and biopsies as well as clinical activity assessment, laboratory exams, including tests for ADL TLs and antibody to adalimumab (ATA) were performed at 4 months from adalimumab initiation. MH was defined as a Simple Endoscopic Score for Crohn's disease (SES-CD) of 0. Histologic remission (HR) was defined as the complete absence of microscopic inflammation on biopsy specimens obtained from sites of previous and current ulcerations. Adalimumab TLs were compared according to MH status at 4 months.

Results:

Table 1. Baseline characteristics of the subjects (n=17)

Characteristics	
Male, n (%)	13 (76%)
Diagnosis age, year	14.4 (10.8–18.6)
Disease duration to adalimumab, month	1.9 (0.2–47)
Adalimumab within 3 month of diagnosis, n (%)	15 (88%)
Age at adalimumab initiation, year	14.8 (10.9–18.6)
PCDAI prior to adalimumab initiation	35 (30–50)
CRP prior to adalimumab initiation, mg/dL	1.98 (0.15–7.52)
SES-CD prior to adalimumab initiation	19 (6–31)
Concomitant azathioprine, n (%)	14 (82%)

Continuous variables are expressed in median (range).

Seventeen subjects were included in this study. At 4 months from ADL initiation, 14 (82.4%) were under clinical remission, 8 (47.1%) had achieved MH, and 4 patients (23.5%) had achieved HR. Dose intensification by interval shortening to every week was done in 1 patient (5.9%). ADL TLs were significantly higher in patients who achieved MH compared to those who did not (13.0 ± 6.5 $\mu\text{g/mL}$ vs. 6.2 ± 2.6 $\mu\text{g/mL}$, $p=0.023$), and also significantly higher in patients who achieved HR compared to those who did not (17.9 ± 5.3 $\mu\text{g/mL}$ vs. 6.8 ± 2.5 $\mu\text{g/mL}$, $p=0.02$). ATA was detected in 1 patient (5.9%). According to receiver operator characteristic (ROC) curve analysis, the optimal cut-point for predicting MH was 8.76 $\mu\text{g/mL}$.

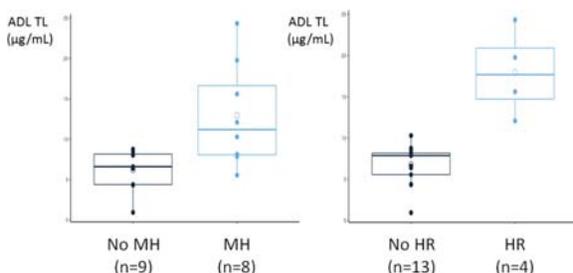


Figure 1. Adalimumab trough levels according to mucosal healing, histologic remission at 4 months.

Conclusions: Serum ADL TLs at 4 months were significantly higher

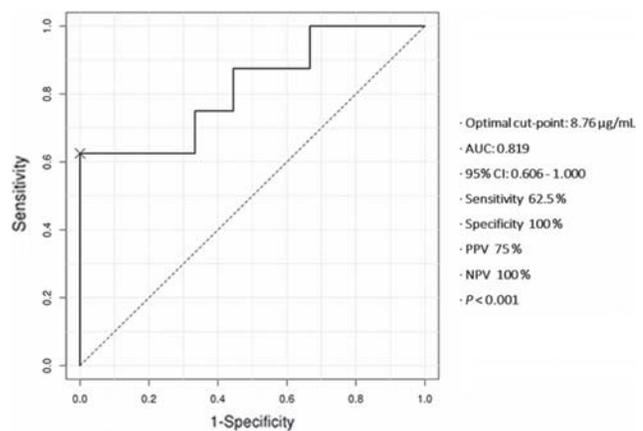


Figure 2. ROC curve of adalimumab trough levels in predicting mucosal healing at 4 months.

in paediatric CD patients under MH or HR, compared to those who failed to achieve each outcome. Future relevant large-scale studies may guide in predicting short-term MH and HR in the era of treat-to-target.

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Infliximab biosimilar CT-P13 therapy is effective in maintaining clinical remission in Crohn's disease and ulcerative colitis – 54 week data

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Background: CT-P13, the first biosimilar monoclonal antibody to infliximab (IFX) has previously been confirmed to be efficacious in inducing remission in inflammatory bowel disease (IBD) patients. The aim of this study was to evaluate the long-term efficacy and safety of CT-P13 therapy in Crohn's disease (CD) and ulcerative colitis (UC) in our tertiary center.

Methods: Patients diagnosed with CD and UC, who were administered CT-P13 from June 2014 at the 1st Department of Medicine, University of Szeged, were prospectively enrolled. Clinical outcome was estimated at fixed appointments throughout the 54-week treatment period. Rates of clinical remission, response and non-response at week 14, rates of continuous clinical response (CCR), remission and loss of response at week 54 and proportion of patients remaining on CT-P13 therapy at the end of the first year were examined. CT-P13 trough levels at week 2, 6 and 14, antibody positivity at week 2, 6 and 14, CRP level at week 2, 6, 14 and 30, fecal calprotectin at week 2, 6 and 46, concomitant steroid and azathioprine therapy at the time of induction therapy and at weeks 14 and 54, previous use of anti-TNF drug, need of dose intensification and mucosal healing in UC as possible predictive factors for disease outcome at week 54 were statistically evaluated.

Results: Fifty-seven CD and 57 UC patients were included in the study of which 46 CD and 46 UC patients completed the induction therapy and 36 CD and 33 UC patients completed the 54-week treatment period. Clinical response was achieved in 44 CD patients (95.6%) and in 45 UC patients (97.8%) at week 14. Of the 36 and 33 patients who completed the 54-week treatment period, CCR were

shown in 25 CD (69.4%) and 19 UC (57.6%) patients. The overall rate of loss of response was 30.4% in CD and 34.8% in UC at week 54. High CRP level at week 30 and low CT-P13 trough level at week 14 predicted to loss of response in CD. None of the examined parameters were predictive to the therapeutic outcome in UC. No difference was observed regarding the clinical outcome at week 54 between anti-TNF naïve patients and patients previously treated with an anti-TNF agent.

Conclusions: This study confirmed the long-term efficacy and safety of CT-P13 therapy IBD. However, lower response rate was shown at week 54 in UC than in CD. High CRP and low CT-P13 trough levels were predictive to treatment outcome in CD but not in UC.

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Comparison of real-world outcomes of adalimumab and infliximab for patients with ulcerative colitis in the United States

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Background: Adalimumab (ADA) and infliximab (INF) are approved for treating patients with ulcerative colitis (UC) who have failed conventional therapy. Research comparing the effectiveness of these therapies following induction is limited. We compared the real-world effectiveness of initiating ADA versus INF among patients in the early weeks of treatment.

Methods: 170 randomly selected physicians in the U.S. retrospectively abstracted clinical and healthcare resource utilization information from the charts of adults with UC initiating ADA or INF therapy between 1 Oct 2012 and 30 Apr 2014. Patients were anti-TNF naïve, did not have a Crohn's disease diagnosis and had ≥ 6 months of follow-up data available. Disease and symptom control were assessed by measuring the probabilities of remission, normal physician global assessment (PGA), normal stool frequency, and absence of rectal bleeding at 8, 12, 16, 20, and 24 weeks after initiating ADA or INF. Probabilities were estimated using Kaplan–Meier curves and compared between treatments using log-rank tests. Patient demographics and the time to first physician- or patient-initiated office

Table 1

	Follow-up week ¹	Adalimumab ²	Infliximab ²	P-value (Log-rank) ³
Probability of achieving remission	8 weeks	10.7%	8.2%	0.2240
	12 weeks	21.2%	18.3%	0.3180
	16 weeks	30.3%	28.2%	0.4947
	20 weeks	41.0%	38.3%	0.4253
	24 weeks	45.3%	44.3%	0.6721
Probability of no rectal bleeding	8 weeks	11.3%	10.0%	0.5415
	12 weeks	19.8%	18.5%	0.6203
	16 weeks	28.9%	27.4%	0.6225
	20 weeks	40.8%	39.4%	0.6556
	24 weeks	45.2%	45.1%	0.8767
Probability of normal stool count	8 weeks	7.0%	6.1%	0.6437
	12 weeks	12.8%	13.2%	0.8863
	16 weeks	20.3%	19.8%	0.8695
	20 weeks	27.8%	28.1%	0.9342
	24 weeks	32.6%	33.0%	0.9107
Probability of Normal PGA score	8 weeks	4.7%	4.3%	0.7682
	12 weeks	11.3%	10.7%	0.8097
	16 weeks	17.7%	17.4%	0.9417
	20 weeks	25.3%	25.3%	0.9935
	24 weeks	30.6%	29.6%	0.8136

¹Weeks after index date; ²Probability of achieving parameter to each of the assessment points after the index date; ³The log-rank tests for the homogeneity of the results from the index date to each of the assessment points after the index date. PGA, physician's global assessment.

Table 2

	Office visit within	Adalimumab (N=380)	Infliximab (N=424)	P-value
Time to first office visit, n (%)	8 weeks	159 (41.8%)	171 (40.3%)	0.6635
	12 weeks	217 (57.1%)	238 (56.1%)	0.7810
	16 weeks	254 (66.8%)	284 (67.0%)	0.9666
	20 weeks	276 (72.6%)	311 (73.3%)	0.8190
	24 weeks	287 (75.5%)	318 (75.0%)	0.8629

visit since starting treatment were compared using Wilcoxon rank sum tests (continuous data) and chi-squared tests (categorical data).

Results: Of 804 eligible patients, 380 initiated ADA and 424 initiated INF. Both groups were similar demographically, except for race/ethnicity. More ADA patients were white (ADA 78.9% vs INF 71.5%, $p=0.0144$) and fewer were black (ADA 8.7% vs INF 16.3%, $p=0.0012$). There were no differences between ADA and INF patients with regards to the probabilities of disease and symptom control at any time point between 8 and 24 weeks after initiating therapy (Table 1). The number of patients with a first office visit after starting treatment by each follow-up point was similar between groups (Table 2).

Conclusions: ADA and INF were similarly effective in UC patients in real-world clinical practice as early as 8 weeks after initiating treatment. These data are consistent with those from clinical trials and network meta-analyses.

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Impact of patient reported outcomes, coping strategies and psychosocial factors on medication adherence in inflammatory bowel disease

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Background: Medication adherence is pivotal to the optimal management of inflammatory bowel disease (IBD) patients and this could be influenced by various patient related factors independent of disease course. This study aims to evaluate the impact of patient reported outcomes, coping strategies and psychosocial factors on adherence.

Methods: We conducted a cross-sectional study on patients with Crohn's disease (CD) or ulcerative colitis (UC) at McGill IBD centre between September 2015 and March 2016. Patients were assessed for quality of life, disability and productivity using validated short IBD questionnaire (SIBDQ), IBD disability index (IBDDI) and work productivity assessment index (WPAI) respectively. Psychological assessment was performed using hospital anxiety and depression score (HADS). Brief COPE questionnaire were used for assessing coping strategies. Disease activity was determined by Harvey Bradshaw index (HBI >4) and partial Mayo score (PMS >2). Medication adherence was evaluated using the medication adherence questionnaire (poor adherence defined as MAQ >2) and the treating physician also independently provided their perception of individual patient adherence. Results were examined using descriptive and regression analysis.

Results: 207 (144 CD/63 UC) patients, with median age of 39 (IQR 26) and 42.5% male, were included. 24.2% of patients had clinically active disease. 23.2% of patients were on immunomodulators and 52.7% on biologic therapy. Around one third of patients identified moderate to severe impairment on disability (31.3%), quality of life (33.3%) and productivity (29.1%); along with some degree of anxiety (32.9%) and depression (23.3%). Poor adherence

was reported by 29.5% of patients and it is inadequately identified by treating physicians ($r=0.19$, $p=0.009$). Patients with poor quality of life, anxiety, depression and maladaptive coping behaviours were less likely to be adherent to therapy on univariate analysis (Table 1). Conversely adherence is associated with older age, biologic use, and marital status. Disease activity, duration, disability, education, employment and insurance status were not significantly associated with adherence. Age, marital status, biologic use and maladaptive behaviour remain significant on multi-variate analysis.

Table 1. Medication adherence: Logistic regression analysis

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Poor quality of life (SIBDQ <47)	0.42 (0.22–0.81), $p=0.009$	$p=NS$
Anxiety	0.91 (0.84–0.98), $p=0.014$	$p=NS$
Depression	0.88 (0.81–0.96), $p=0.005$	$p=NS$
Maladaptive behavior	0.84 (0.72–0.97), $p=0.021$	0.59 (0.41–0.86), $p=0.006$
Age	1.06 (1.03–1.08), $p<0.001$	1.04 (1.01–1.08) $P=0.013$
Biologic use	2.0 (1.07–3.75), $p<0.001$	4.95 (2.17–11.27), $p<0.001$
Marital status	3.28 (1.68–6.42), $p=0.001$	2.617 (1.02–6.70), $p=0.045$

Conclusions: Selected patient characteristics and reported outcomes including age, biologic use, marital status and maladaptive behaviour may help to identify those patients at risk of medication non-adherence.

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Did toxicity profile of azathioprine changed within the last 10 years: comparative 17 years data from a single tertiary IBD center

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Background: We aimed to evaluate the toxicity profile of the AZA. We obtained the information from our 17 years old IBD registry. We also wished to compare the parameters of these current information with our a decade old previously registered IBD data.

Methods: We reviewed the charts of our IBD outpatient clinic from 1999 to 2016.

Results: 2200 patients (pts) were evaluated retrospectively, among them 601 (27%) were treated with AZA (264 F 45% and 321 M 55%) with a mean duration of treatment 41.8 ± 40.7 months (mo) (range: 0.25–244 mo median: 30 mo). Diagnosis was CD in 67%, UC in 29%, ID colitis in 4%. AZA toxicity was observed in 25% and AZA was discontinued in 22%. The causes of drug withdrawal are shown in the table 1. In 65% of the pts who had developed adverse events, the duration of AZA use was less than 12 mo. A total of 65 pts have had leukopenia, in 31 (5%) of these pts AZA dosage was reduced, in 25 pts (4%) therapy could had been continued with dose reduction. In 40 pts AZA therapy was stopped due to leukopenia, 2 pts were hospitalized with febrile neutropenia for both GSF was needed. Five pts had developed drug rash which required drug withdrawal. One of them was diagnosed as AZA related Sweet Syn-

drome. Two pts have had severe myalgia. There were 5 pts who had malignancy during the follow-up period (vulvar ca, AML, gastric ca, breast ca, renal cell ca). The past AZA toxicity rates of leukopenia, GI intolerance, pancreatitis and hepatotoxicity in 2007 were respectively: 8%, 6%, 1.3%, 1.9% in 151 pts with a mean duration of AZA use of 23.8 mo. When compared with the past, toxicity rates are similar. AZA toxicity which necessitates drug discontinuation were twice more common in our recent IBD pts than the pts in our historical cohort. As a not fairly well described entity GI intolerance seems to happen just after taking AZA with similar GI symptoms to pancreatitis without any increase in amylase and very quick disappearance of symptoms in case of cession of AZA.

Conclusions: As most of the side effects occurred within a year period, and the long term AZA use didn't change the prevalence of the adverse events, AZA use seems to be safer and the toxicity is lower when the use is longer than a year without toxicity. Although the current cohort is bigger and the duration of AZA use is nearly twice longer than the historical cohort the rate of AZA toxicity did not increase by the time. Increase in AZA withdrawal nearly two fold within a decade may need attention but may still have some influence from the biologic era necessities.

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Infliximab biosimilar CT-P13 in inflammatory bowel disease patients that require intensification treatment

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Background: CT-P13 was the first Infliximab biosimilar approved in Europe. Several studies confirmed the efficacy, safety, and interchangeability of CT-P13 in patients with immune mediated inflammatory disorders, but there are limited reports on clinical outcomes in patients with inflammatory bowel disease (IBD) requiring dose escalation.

Methods: IBD patients that required dose escalation during treatment with Remicade, or were previously under escalated dosing, were switched to biosimilar CT-P13. Escalation was defined as increased dose ≥ 7.5 mg/kg/8 weeks and/or a shortening of the interval ≤ 6 weeks.

Disease activity was evaluated with the Crohn's Disease Activity Index (CDAI) for Crohn's Disease (CD) and full Mayo Score (including endoscopy) for Ulcerative Colitis (UC). Clinical and biological variables were analyzed before the first infusion of CT-P13 and after 24 weeks of treatment.

Results: Thirty patients received escalated CT-P13 dose (18 CD and 12 UC), 53% men, median age 42 years (IQR 22–71). 9/30 patients (30%) were previously intensified with Remicade and switched to CT-P13 maintaining the same dose and 21/30 patients (70%) were switched at the time of dose escalation.

Median time with Remicade treatment before switching to CT-P13

Abstract P678 – Table 1. The toxicity and withdrawal rates of azathioprine

Side effects	Withdrawal rate N (%)	Age at the time of toxicity	Mean time to toxicity mean \pm SD	Concomitant 5-ASA %	Concomitant CS %	Concomitant anti-TNF %
Leukopenia	40/601 (6.8%)	47.4 \pm 14.2	12.9 \pm 15.1 (1–62) months	70	50	25
Pancreatitis	26/601 (4.3%)	36.3 \pm 11.8	3.8 \pm 8.1 months	46.2	34.5	7.7
Hepatotoxicity	17/601 (2.8%)	36.5 \pm 14.1	7 \pm 6.5 months	58.8	58.8	29.4
Gastrointestinal intolerance	34/601 (5.6%)	39 \pm 11.5	1.1 \pm 0.4 (0–2) weeks	52.9	35.3	20.6

was 44 months (IQR 4–110). At 24 weeks of follow-up 80% were in clinical remission: 15/18 (83%) of CD patients had CDAI <150 and 9/12 (75%) of UC patients had Mayo score ≤ 2 points. No adverse events were observed in this group of patients treated with CT-P13. 26/30 patients (87%) had Infliximab serum levels <3.0 before intensification and 5/30 (17%) after intensification. No patient developed antibodies against Infliximab, during CT-P13 treatment. No significant changes were observed in clinical and biological parameters after switching to CT-P13 in patients previously intensified with Remicade in whom the dose of Infliximab was maintained stable (see Table 1).

Table 1. Clinical and biological variables in 9 patients previously intensified with Remicade before and after switching to CT-P13

	Before switch	After switch	P
CDAI	63.60 \pm 26.0	37.00 \pm 30.7	0.179
Mayo	1.25 \pm 0.9	0.25 \pm 0.5	0.92
PCR (mg/L)	5.5 \pm 5.3	3.5 \pm 3.8	0.70
Hemoglobin (g/dl)	13.1 \pm 1.6	13.7 \pm 1.3	0.101
IFX levels (μ g/ml)	4.0 \pm 4.7	6.6 \pm 2.5	0.205

Conclusions: This study provides evidence of the efficacy and safety of CT-P13 in IBD patients that require intensification of anti-TNF treatment, and would incur in the highest cost.

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Quality of sex life in patients with inflammatory bowel disease: the gastroenterologists' perspective

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Background: Management of Inflammatory Bowel Disease (IBD) patients focuses on inflammation control and quality of life improvement. Sexuality is a major determinant of quality of life but few data exist concerning the approach of this aspect by gastroenterologists. The present study aimed to describe the approach of gastroenterologists towards the sexual function of IBD patients.

Methods: An anonymous questionnaire was distributed to gastroenterologists taking part to a continuing medical education event, followed by an email reminder 2 months later. The objective of this form was to assess the proportion of gastroenterologists addressing this issue with patients and to determine reasons for not doing so.

Results: Sixty-nine gastroenterologists participated to the survey: 84% reported never or rarely addressing sexuality with IBD patients, while 16% addressed this topic often or always. To the question "Do you think that gastroenterologists should address the subject of sex life with IBD patients?", 93% answered "yes". The first reason mentioned to explain the reluctance to discuss the topic was the absence of a known solution for treating sexual dysfunction (45% of answers); 29% of physicians didn't want to embarrass patients and 19% were themselves embarrassed; 9% blamed lack of time. Neither age nor gender of the gastroenterologist was associated with a different attitude. The ratio of physicians asking about sexuality was significantly higher among proctologists than gastroenterologists (55% and 9%, respectively; $p > 0.001$).

Conclusions: Although a majority of gastroenterologists considers that sexuality is a topic to address with IBD patients, only 16% actually do so. Limited knowledge of solutions for sexual dysfunction management is the first reason explaining this gap. Gastroenterologists' training on sexual dysfunction management could help to better meet patients' expectations.

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Assessing internet based information used to aid patient decision making in surgery for perianal Crohn's fistula

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Background: Decision making in surgery for patients with perianal Crohn's fistula (pCD) is complex. There is often more than one treatment choice, which may be modified by patient treatment preferences. Patients are increasingly using the internet to find out more information about different surgical options. The purpose of this study was to assess the online information and patient decision aids relating to surgery for pCD.

Methods: A systematic review of patient decision aids was carried out in accordance with PRISMA guidance and registered with the PROSPERO database (CRD42016046689). The Google search engine and the Decision Aids Library Inventory (DALI) were searched using a predefined search strategy. Sources that were patient focussed and provided information about pCD surgery were included in the analysis. Academic literature, and sources not in English were excluded. Source descriptors including URL, title and purpose, country of origin and upload source were noted. The quality of source content to aid patient decision making was assessed using the International Patient Decision Aids Standards (IPDAS) and DISCERN criteria. The IPDAS and DISCERN scores reflect the usefulness of a source in aiding patient decision making; the higher the score, the better. The readability of the source content was assessed using the Flesch-Kincaid score.

Results: The initial search yielded 210 sources. We excluded 125 sources at screening and a further 56 at full-text review, leaving 20 sources for analysis. The majority of sources originated from the UK (n=11), the remainder being from the USA (n=8) and Canada (n=1). The most common upload source was hospital/speciality association (n=7). The mean IPDAS and DISCERN score was 6.4 \pm 1.957 out of 12 (range=3–10) and 2.9 \pm 0.718 out of 5 (range=2–4) respectively. The mean reading ease was 46.5 \pm 1.566 (U.S. college standard). Nine sources mentioned more than three surgical options to treat pCD. Perianal Crohn's disease was the main focus of seven sources, with the remainder encompassing both pCD and cryptoglandular fistula disease.

Conclusions: The online sources providing information for surgery in pCD are few and their quality poor, as reflected in a low IPDAS and DISCERN score. This is due to a lack of key information and a high readability score, making the sources unhelpful and difficult to understand for patients when making a treatment choice. Health care professionals should recognise that online information for surgical management in pCD may be misleading. There is a responsibility of individual professionals and their societies to produce a patient friendly decision aid to assist patients when making their surgical treatment choices for pCD.

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Risk factors and clinical outcome in IBD patients with melanoma

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Background: Patients with inflammatory bowel disease (IBD) are at increased risk to develop malignant melanoma and this risk may increase with the use of anti-TNF therapy. Impaired survival of immunosuppressed melanoma patients is reported in transplant and rheumatology patients

This study aims to 1) identify risk factors for melanoma development in IBD patients, 2) compare clinical characteristics of melanoma in IBD patients to the general population and 3) assess the influence of immunosuppressive medication use on survival.

Methods: We retrospectively searched the Dutch Pathology Database to identify all Dutch IBD patients with cutaneous melanoma between January 1991 and December 2011.

We then performed two case-control studies. To identify risk factors for melanoma development in IBD, we compared IBD patients with melanoma to the general IBD population. To compare outcome and survival after melanoma diagnosis, we compared cases with non-IBD melanoma patients.

Results: We included 304 IBD patients with melanoma, 1800 IBD controls, and 8177 melanoma controls. IBD cases had more extensive IBD (ulcerative colitis: pancolitis: cases 44.5% versus IBD controls without melanoma 28.1%; $p < 0.01$; Crohn's disease: ileal and colonic disease: cases 57.9% versus controls 48.9%; $p = 0.02$).

Despite a lower N-stage in IBD patients (N1+ 8.3% versus 18.2%; $p < 0.01$) with comparable T and M stages, survival was similar between groups, regardless of immunosuppressive or anti-TNF therapy.

Conclusions: This study showed that IBD extent is a risk factor for melanoma development. Despite the lower N-stage in IBD patients, we could not confirm impaired survival after melanoma in IBD patients, regardless of anti-TNF and/or thiopurine use.

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Leishmania infantum asymptomatic infection in inflammatory bowel disease patients under anti-TNF- α treatment

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Background: Clinical manifestations of leishmaniasis vary depending on parasite virulence and host immune response. While immuno-

competent individuals have an effective Leishmania-specific response that makes the infection asymptomatic or at least subclinical in most cases, immunosuppressed patients are at risk of developing the disease. TNF- α mediated response is crucial for the control of several opportunistic infections caused by intracellular microorganisms such as Leishmania. Some cases of cutaneous as well as visceral leishmaniasis have been described in patients under anti-TNF therapy. We have reported a case of an ulcerative colitis patient treated with infliximab in our Unit who developed cutaneous leishmaniasis.

The aim of this study was to detect asymptomatic infection in patients with inflammatory bowel disease (IBD) receiving anti-TNF- α therapy from Catalonia area (Spain), where *L. infantum* is endemic and can cause cutaneous and visceral disease.

Methods: 192 patients with Crohn disease (n=126) or ulcerative colitis (n=46) receiving anti-TNF treatment were recruited consecutively from May 2016 to October 2016 at the Crohn's and Colitis attention Unit (Hospital Vall d'Hebron). Anti-Leishmania antibodies were tested by ELISA and Western Blotting (WB) and Leishmania DNA was detected in peripheral blood mononuclear cells (PBMCs) by real time qPCR. Epidemiological and clinical data were also recorded in a clinical interview.

Results: One hundred and ninety-two patients were included, 126 with Crohn's disease (CD) and 46 with Ulcerative Colitis (UC). Ninety six patients were receiving infliximab, 89 Adalimumab and 7 Golimumab. There was no previous history of leishmaniasis recorded in any patient. Fourteen patients (7.3%, 95% CI 4.3–11.9%) were positive for leishmaniasis, 7 of them treated with IFX and 7 with ADA. Eleven patients had CD and 3 UC.

Serology for leishmaniasis was positive in 12 patients, determined by ELISA in ten patients (5.2%) and in six patients by WB (3.1%). All patients with positive serology had a negative qPCR.

Leishmania DNA was detected by qPCR in 2 patients, indicating active infection. None of the patients had clinical symptoms suggestive of leishmaniasis.

Conclusions: Prevalence of asymptomatic carriers of Leishmania in IBD patients receiving anti-TNF is relevant in our area. This population is, therefore, at high risk of developing clinical leishmaniasis. Screening for presence of Leishmania in this group of patients could be recommended before initiating therapy.

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A first clinical trial of a novel narrow spectrum kinase inhibitor TOP1288 in patients with ulcerative colitis

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Background: TOP1288 a novel narrow spectrum kinase inhibitor (NSKI), selectively targets key kinases fundamental to inflammatory cell signalling in innate and adaptive immune responses: p38-alpha MAP kinase, Src family kinases (Src and Lck) and Syk. Through synergistic effects on these kinases TOP1288 is a potent inhibitor of the inflammatory cascade and offers therapeutic potential in ulcerative colitis and Crohn's disease with minimal systemic absorption which could provide a significant safety advantage over current therapies. In healthy subjects TOP1288 (evaluated up to 400mg total daily rectal dose for 4 days) is well tolerated, with measurable drug levels in

colonic biopsies in a pharmacologically relevant range but with minimal systemic exposure. Positive signals for target engagement and biological effects were seen. The present phase 1b study was designed to evaluate TOP1288's safety, tolerability, PK and PD in ulcerative colitis patients.

Methods: Subjects (n=6) aged 18–55 years with moderate ulcerative colitis (total Mayo Clinic Score 5–10; sigmoidoscopy subscore ≥ 1) experiencing rectal bleeding and receiving oral 5-ASA (<2.4g/day) were randomized double blind to TOP1288 200mg or placebo rectal solution once daily for 4 days. Subjects were resident in a phase 1 accredited clinical trials' unit for assessments. Safety parameters were assessed and serial blood samples collected to measure TOP1288 plasma concentrations. Subjects had sigmoidoscopy at baseline and approx. 24 hours after final dose to obtain recto-sigmoid biopsies to measure TOP1288 concentration and selected inflammatory biomarkers.

Results: TOP1288 was well tolerated with no clinically significant adverse events. Plasma exposure occurred in a minority of subjects (below quantification limit in 3/5 TOP1288 subjects by Day 4) and measurable drug concentrations were very low (<0.134 ng/mL). Colon tissue exposure approx. 24 hours after final dose occurred in most (4/5) subjects (0.2–1.2 ng TOP1288/mg protein). TOP1288 inhibited IL-8 and IL-6 release from unstimulated whole colonic biopsies: IL-8 was reduced from 110647 pg/mL pre-dose to 62429 pg/mL post-dose (placebo 84971 pg/mL pre-dose; 90079 pg/mL post-dose) and IL-6 from 8247 pg/mL pre-dose to 4341 pg/mL post-dose (placebo 7423 pg/mL pre-dose; 7400 pg/mL post-dose).

Conclusions: In this first study in ulcerative colitis the NSKI TOP1288 was well tolerated with measurable drug levels in colonic biopsies in a pharmacologically relevant range, but with minimal systemic exposure. Positive signs for target engagement and biological effects were demonstrated suggesting a normalization of dysregulated cytokine pathways.

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Switching from originator-infliximab to biosimilar-infliximab has no influence on health-related quality of life and clinical disease activity among patients with inflammatory bowel disease

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Background: Biosimilar-infliximab (CT-P13) was approved for all indications as an originator-infliximab although the clinical efficacy was only demonstrated in rheumatoid arthritis and ankylosing spondylitis. The objective of this study was to evaluate the clinical efficacy and effectiveness of biosimilar-infliximab in the maintenance treatment of inflammatory bowel diseases (IBDs).

Methods: We conducted an observational, prospective single-center study of the IBD patients receiving infliximab (IFX) maintenance treatment. All IBD patients on IFX maintenance treatment were systematically switched from originator-IFX to biosimilar-IFX. The health-related quality of life (HRQoL) measures used in this survey were a disease-specific Inflammatory Bowel Disease Questionnaire (IBDQ) and a generic 15D instrument. Patient reported outcomes were collected at three IFX administration visits at clinic: 8 weeks before the switching (the last originator-IFX infusion), at the time of switching (the first biosimilar-IFX infusion) and 16 weeks after the

switching (the third biosimilar-IFX infusion). Clinical disease activity (Harvey-Bradshaw Index (HBI) or partial Mayo score) was collected from patients' records. The primary endpoints of the study were the changes in HRQoL and clinical disease activity before and after the switching.

Results: In the study, 56 patients (30 male and 26 female) were included: 24 patients diagnosed with Crohn's disease, 29 with ulcerative colitis and 3 as IBD unclassified. The patients' ages varied from 20 to 74 (mean 35.82, SD 11.51). Seven patients were smoker, 13 patients were former smoker and 36 patients never smoked. The duration of the treatment with originator-IFX ranged from 3 months to 11 years (mean 3.3 years, SD 2.91). The median IBDQ score was 189 (SD 29.006) 8 weeks before the switching, 186 (SD 31.789) at the time of switching, and 192 (SD 29.340) 16 weeks after the switching. Respective median 15D scores were 0.915 (SD 0.067), 0.909 (SD 0.072), and 0.913 (SD 0.080). Before the last originator-IFX infusion the mean HBI was 1.80 (SD 3.34) and the mean partial Mayo score 0.95 (SD 1.69), whereas the mean HBI was 1.93 (SD 3.71) and the mean partial Mayo score 0.60 (SD 1.05) before the third biosimilar-IFX infusion. No statistically significant difference was observed between IBDQ (p=0.300), 15D (p=0.700), HBI (p=0.317), and the partial Mayo scores (p=0.481) before and after the switching. No serious adverse events were observed during the follow-up.

Conclusions: These early data suggested that in maintenance treatment of IBDs biosimilar-IFX was, in light of IBDQ, 15D, HBI, and the partial Mayo scores, comparable to originator-IFX during the first 16 weeks after the switching.

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Application of dried blood spots for pharmacokinetic profiling of golimumab-treated patients with ulcerative colitis

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Background: Preventing loss of response to golimumab, an anti-tumour necrosis factor (TNF) biologic, is a challenge for clinicians treating patients with ulcerative colitis (UC). Although drug serum concentrations and anti-drug antibody serum concentrations have suggested an association between golimumab exposure and clinical outcome, detailed information on absorption, distribution and elimination of the drug in a real-life cohort of patients is lacking. Dry blood spot (DBS) sampling involves a finger prick to apply whole blood to a sampling paper after which drug is extracted. We wanted to study if golimumab efficacy can be increased by exploring its full pharmacokinetic (PK) profile in UC patients by intensive sampling via DBS.

Methods: First, DBS were obtained through spotting of 45 μ L of golimumab (0.2–20 μ g/mL) or anti-golimumab antibody (20–200 ng/mL) spiked in whole citrated blood, to a filter paper. After punching, DBS were extracted and DBS extracts were analysed on both the MA-GOM171D8/MA-GOM159B8-HRP ELISA and the MA-GOM159B8 bridging ELISA. Extraction efficacy, accuracy, imprecision, sensitivity and robustness were determined as well as the impact of anti-golimumab antibodies on the detection of golimumab (and vice versa). Second, DBS were obtained by spotting blood obtained through a finger prick of eight golimumab-treated patients with UC of whom serum was taken simultaneously by venepuncture, allowing

the calculation of a real-life conversion factor between golimumab serum concentration and DBS extract.

Results: The selected extraction condition yielded an average extraction efficiency of 54% and 53% for golimumab and anti-golimumab determination, respectively. Overall-assay accuracy and imprecision were between 80–120% and <15%, respectively, for each concentration analysed. Storing the sampling papers at room temperature for one month or the extracts at -20°C for three months did not impair DBS recovery. The presence of golimumab hampered the detection of anti-golimumab and vice versa. A real-life conversion factor of 3.8±0.3 (n=6) from DBS to serum was calculated. The blood volume per spot did not influence the results if it had at least a diameter of six mm, which was not the case in two out of eight patients and is the main drawback of this method.

Conclusions: The described DBS method is robust and can be used as a patient friendly and inexpensive method to perform rich sampling in patients treated with biologic agents. Proper patient education on how to sample is essential and will result in an accurate determination of exposure to golimumab in patients with UC. The method will be applied in a prospective cohort of ten patients with UC by collecting 20–40 DBS per patient over time.

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Fate of the rectum in anorectal Crohn's disease

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Background: The long term risk of permanent stoma in patients with anorectal Crohn disease is high. About 34% of patients with Crohn's disease have perianal disease. Little is known about the results of restorative surgery after enterostomy for Crohn's colitis with severe anorectal involvement.

The aim of this study is to assess the effectiveness of restorative surgery.

Methods: We retrospectively analysed a cohort of Crohn's disease patients affected by severe anorectal involvement underwent surgery from 1986 to 2016, who received an enterostomy at first surgery. We have excluded patients affected with extensive colitis and severe anorectal involvement who received total procto-colectomy. Only patients having primary surgery with an "intent to restore approach" were included in order to analyse factors (smoking, age more or less than 30 years, familiarity, type of primary surgery) affecting the probability for restoring the intestinal function.

Results: Among 24 patients undergone enterostomy with an "intent to restore approach", the median follow-up was 16 years. Only rectal involvement was found in 3 patients (12.5%), perianal disease in 21 patients (87.5%). Patients underwent different types of surgery: 3 subtotal colectomies with rectal stapling (12.5%), 8 total colectomies with rectal stapling (33.3%), 10 rectal anterior resections with colorectal anastomosis with protective ileostomy or colostomy (41.7%), 1 ileocolic resection with ileo-colostomy (4%), 2 temporary ileostomies for severe perianal disease (8.3%). Eleven patients (45.8%) were restored, while 13 patients had permanent stoma (54.2%). The type of surgical procedure did not affect the risk of permanent stoma. Smoking habits resulted to improve the risk for permanent stoma (p=0.04, CI 95%=-1.6;1.9). Other variables showed to have a trend towards but not a statistical significance.

Conclusions: Approximately one of two patients that had received an enterostomy at the time of surgery for Crohn's colitis with severe anorectal involvement can be restored. As a consequence, half of the patients observed, received definitive enterostomy. Smoking habits

was associated with an increasing risk of permanent stoma, but other variables could be involved.

Epidemiology

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Crohn's disease patients with a concordant family history are diagnosed earlier and are at increased risk for complicated disease

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Background: Family history is the strongest risk factor for developing Crohn's disease (CD) or ulcerative colitis (UC). However, whether familial Inflammatory Bowel Disease (IBD) differs from sporadic IBD in its natural history has not been well defined. We investigated whether the proximity of relationship with the affected relative and concordance for type of IBD modifies the effect of family history on the phenotype and severity of IBD.

Methods: This study included patients with a confirmed diagnosis of IBD enrolled in a prospective patient registry at a tertiary referral hospital from January 2005 to August 2016. Family history of CD or UC was assessed by a questionnaire ascertaining presence of disease in a 1st degree (parent, child, sibling), 2nd degree (grandparent, uncle, aunt), or a distant relative (familial IBD). IBD occurring in the absence of such a history was termed sporadic IBD. Our primary outcomes were disease phenotype according to the Montreal classification and severity measured by need for immunomodulator, biologic, or surgical therapy. Adjusted regression models were used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI).

Results: Our study included 2,136 patients with IBD (1,197 CD, 939 UC) with a mean age of 41 years; just over half were women (52%). Just under one-third (32%) of cases were familial IBD (17% 1st degree relative, 21% 2nd degree relative) while the remainder were sporadic IBD. Familial IBD was diagnosed at an earlier age than sporadic IBD, both in CD (26 vs. 28 years, p=0.0006) and UC (29 vs. 32 years, p=0.01). This effect was more striking in those where the family history was concordant for type of IBD (p=0.0005) than when it was discordant (p=0.06). Among CD patients, a positive family history for CD was associated with an increased risk for complicated disease (B2/B3 phenotype or perianal involvement) in the presence of an affected family member (OR 1.48, 95% CI 1.07–2.03). However, this effect was significant only if the affected member was a 1st degree relative (OR 1.82, 95% CI 1.19–2.78) (Table 1).

Table 1. Likelihood of complicated Crohn's disease, by family history

Affected relative	Odds ratio (95% CI)
Any family history (1 st , 2 nd , or distant)	1.48 (1.07 – 2.03)
1 st degree relative with CD	1.82 (1.19 – 2.78)
2 nd degree relative with CD	1.17 (0.79 – 1.72)
Any relative with UC (Discordant)	0.66 (0.42 – 1.02)

Among 1st degree relatives, the association with complicated CD was more striking in the presence of CD in a sibling (p=0.008). A family history was not associated with need for immunosuppressive therapy or surgery in either CD or UC.

Conclusions: A family history of CD in 1st degree relatives was as-

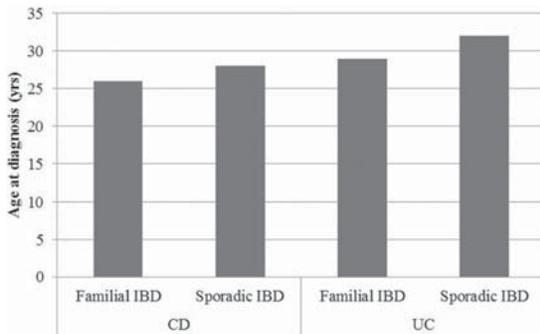


Figure 1

sociated with complicated CD. Family history discordant for type of IBD or in more distant relatives did not influence disease phenotype or natural history in the affected patient.

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Biologics utilization in children with inflammatory bowel diseases is higher and earlier than in adults: a report from the epi-IIRN group

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Background: The diagnosis of Inflammatory bowel diseases (IBD) during childhood is associated with a more aggressive and extensive phenotype compared with adults, necessitating early introduction of effective therapy. We aimed to study differences in biologic therapy in pediatric and adult IBD patients in the Israeli population.

Methods: IBD cases were identified within the databases of three national health maintenance organizations (HMOs), covering 48% of the Israeli population. Identification as well as differentiation into Crohn's disease (CD) or ulcerative colitis (UC) patients was performed using previously validated algorithms, with the effective date of 31.12.2015. Biologic therapy was determined by pharmacy purchases as recorded by the HMOs; expenses are covered by the national public health care system, ensuring complete unbiased records.

Results: Of 19,780 IBD patients identified, 3,445 (17%) commenced on biologics by 31.12.2015. Children (≤ 18 years) were twice as likely to be treated with biologics ($n=326/1005$, 32%) vs. adults ($n=3119/18,775$, 16%; $p<0.001$). The difference was more pronounced in UC than CD (CD- 41%/25%, UC- 17%/6%, for pediatrics and adults, respectively). Amongst patients diagnosed between 2005–2015, time in months from diagnosis to initiation of biologics was shorter for children (CD- median: 43 [IQR: 16–80], UC- 48 [19–85]), as compared to adults (CD- 54 [25–90], UC- 66 [37–101]; $p<0.001$ for both CD and UC, Figs. 1 and 2).

Conclusions: Biologic utilization in pediatric IBD is significantly higher and earlier than in adults. The possible explanations include

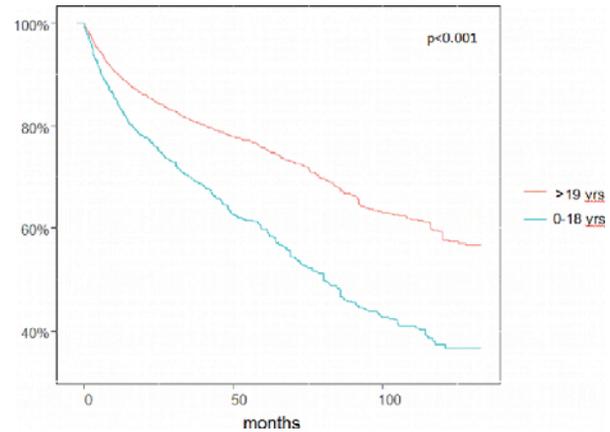


Figure 1. Kaplan-Meier curves for time from diagnosis to start of biological therapy in CD patients.

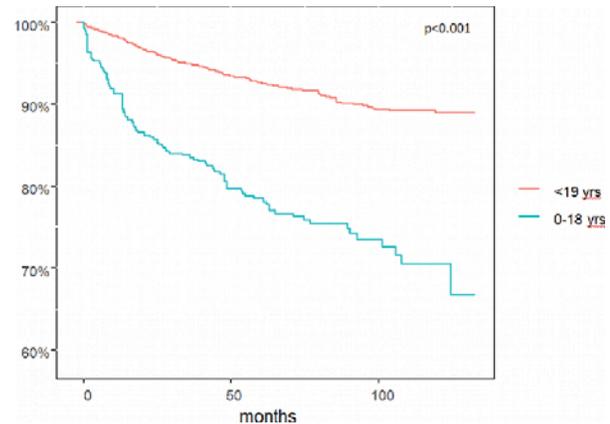


Figure 2. Kaplan-Meier curves for time from diagnosis to start of biological therapy in UC patients.

a more aggressive and extensive disease, differing clinical practices and the role of biologics for the treatment of growth impairment. This study was supported by a grant from the Leona M. and Harry B. Helmsley Charitable Trust.

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Ambient air quality does not affect disease course in inflammatory bowel disease – a population based risk factor analysis using geographic information systems

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Background: Epidemiologic and mechanistic studies found smoking to be associated with the disease course of Crohn's disease (CD) and ulcerative colitis (UC). Ambient air pollution is also a source for air-

borne toxins, and an emerging problem worldwide. The role of air quality on the course of inflammatory bowel disease (IBD) has not been studied yet. We aimed to study associations between ambient air quality and disease course in CD and UC patients from the Dutch population based IBDSL cohort.

Methods: IBDSL patients diagnosed between 2001 and 2010 with a stable home address (≥ 3 years before and after diagnosis) were included. Geographic coordinates of addresses were linked to calendar year specific maps on (in)direct air quality data, including (1) air pollutants, and parameters related to (2) land use, (3) urbanity and (4) traffic. Demographic-, clinical- and smoking data were retrieved. A severe disease course was defined as having IBD surgery, hospitalization (≥ 2), progression, steroid use (≥ 2 courses), biological use (all CD and UC), or presence of a fistula or stricture (CD), within 2 years after diagnosis. Parameters with a $p < 0.10$ in univariable logistic regression analyses were included in a multivariable analysis together with possible confounders. Sensitivity analyses were performed for (a) 5 years follow up, (b) separate components of the disease course definition, and (c) non-smokers at diagnosis.

Results: In CD, 174 of 338 patients had severe disease within 2 years. Lower NO₂ levels, longer distance to first major road, to highway, and lower age at diagnosis were associated to severe disease in the univariable-, but not in the multivariable analyses. In UC, 112 of 576 patients had severe disease. Less industry (500 and 2500m buffer zones), more nature (2500m), male gender, and higher age at diagnosis were associated to severe disease in the univariable analyses. Less industry (500m), more nature (2500m), and higher age at diagnosis remained so in the multivariable analyses (all $p = 0.01$). Although more patients smoked in the severe CD group, smoking was not associated to severe disease course in CD or UC. Odds ratios are shown in the figure. Sensitivity analyses did not reveal new associations.

Conclusions: In this population based study, neither ambient air quality nor smoking was associated with severe disease course in CD or UC, except for less industry and more nature in UC. Regional exposure differences were small. We conclude that ambient air quality is not a strong contributing factor in IBD's disease course in The Netherlands.

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UV exposure and skin type are more important than thiopurine exposure for non-melanoma skin cancer risk in IBD

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Background: Several retrospective studies have found an increased risk of non-melanoma skin cancer (NMSC) in patients with inflammatory bowel disease (IBD) on thiopurines (TP). Other demographic and behavioural risk factors are well established for skin cancer development in the general population, however, these have not been controlled for in the IBD studies. Our study compared the influence of IBD patients' demographic and behavioural characteristics with that of thiopurine therapy on their NMSC prevalence.

Methods: IBD patients were recruited from 4 specialist centres in Australia (Brisbane latitude 27°25'S, Perth latitude 31°57'S and Adelaide latitude 34°52'S) and New Zealand (Christchurch latitude 43°33'S). Patients completed a comprehensive validated questionnaire. Data pertaining to age, ethnicity, skin colour, freckling, methods of sun-protection and number of sunburns in childhood, dose and duration of TP therapy, as well as corresponding metabolite levels were collated. Skin cancer prevalence was documented via self-reporting. Multiple logistic regression was performed.

Results: 691 patients with IBD were included in this cross-sectional

Abstract P690 – Table 1. Results of the univariable and multivariable analyses in CD and UC

	Mild CD mean (SD)	Severe CD mean (SD)	Uni OR/95CI/p	Multi p	Mild UC mean (SD)	Severe UC mean (SD)	Uni OR/95CI/p	Multi p
Pollutants (in µg/m³)								
NO ₂	26.6 (2.4)	26.2 (2.6)	0.93/0.85-1.01/0.08	0.34	25.8 (3.0)	25.7 (3.0)	0.98 (0.92-1.05)/0.64	-
O ₃	37.3 (2.5)	37.6 (2.7)	1.05/0.97-1.14/0.21	-	37.5 (2.7)	37.7 (2.6)	1.04 (0.96-1.12)/0.35	-
PM ₁₀	28.0 (2.4)	28.0 (2.5)	1.00/0.92-1.09/0.99	-	28.0 (2.5)	28.1 (2.3)	1.01 (0.93-1.10)/0.79	-
Landuse (in %)*								
Residential								
-500m	65.6 (26.3)	66.5 (28.4)	1.14 (0.52-2.48)/0.75	-	64.8 (27.1)	67.0 (27.4)	1.35 (0.62-2.93)/0.45	-
-2500m	33.1 (15.5)	32.2 (16.3)	0.70 (0.18-2.68)/0.60	-	31.9 (16.3)	30.4 (17.9)	0.58 (0.17-2.01)/0.39	-
Industrial								
-500m	3.7 (9.1)	3.7 (10.5)	0.95 (0.11-8.39)/0.96	-	4.0 (10.2)	1.1 (4.1)	0.01 (0.00-0.15)/0.01	0.01
-2500m	8.1 (7.3)	7.6 (7.0)	0.36 (0.02-7.18)/0.50	-	8.2 (7.1)	6.5 (6.4)	0.03 (0.00-0.68)/0.01	-
Agricultura								
-500m	25.5 (26.5)	24.6 (28.8)	0.89 (0.41-1.92)/0.77	-	24.8 (26.9)	24.3 (27.6)	0.93 (0.43-2.01)/0.85	-
-2500m	45.9 (20.8)	46.9 (22.0)	1.24 (0.46-3.36)/0.67	-	46.7 (22.5)	47.8 (23.9)	1.24 (0.50-3.05)/0.64	-
Natural								
-500m	1.6 (5.1)	1.7 (6.2)	1.35 (0.03-59.7)/0.88	-	2.3 (8.0)	3.5 (11.6)	4.03 (0.52-31.0)/0.18	-
-2500m	5.5 (5.9)	6.3 (6.2)	7.23 (0.20-257)/0.28	-	6.1 (6.7)	8.3 (8.3)	44.78 (3.12-643)/0.01	0.01
Urbanity (in density)**								
Population	2.9 (1.8)	2.8 (1.8)	0.96 (0.85 - 1.09)/0.54	-	2.8 (1.8)	2.8 (1.8)	1.02 (0.91-1.15)/0.71	-
Address	1.2 (0.7)	1.1 (0.4)	0.86 (0.62 - 1.19)/0.37	-	1.2 (0.6)	1.2 (0.7)	1.11 (0.81-1.51)/0.52	-
Traffic (in km)								
Cum. road length*								
-200m	3.5 (1.3)	3.6 (1.1)	1.01 (0.84-1.21)/0.93	-	3.4 (1.1)	3.4 (1.3)	0.99 (0.83-1.18)/0.89	-
-500m	18.6 (6.2)	18.4 (6.0)	0.99 (0.96-1.03)/0.76	-	18.2 (6.0)	18.1 (6.2)	1.00 (0.97-1.03)/0.90	-
Dist. to first major road	0.8 (0.5)	1.0 (0.9)	1.44 (1.06-1.96)/0.02	0.14	0.9 (0.7)	1.0 (0.8)	1.19 (0.92-1.54)/0.18	-
Dist. to first highway	2.5 (2.1)	3.0 (2.1)	1.13 (1.02-1.25)/0.02	0.11	2.9 (2.1)	3.3 (2.3)	1.07 (0.98-1.18)/0.12	-
Confounders (in %)								
Male	44.5	41.4	0.88 (0.57-1.35)/0.56	0.70	51.1	59.8	1.43 (0.94-2.17)/0.10	0.22
Diagnosed in first lustrum	39.6	40.2	1.03 (0.66-1.59)/0.91	0.58	39.0	45.5	1.31 (0.86-1.98)/0.21	0.22
Age at diagnosis (in yr)	45.6 (14.8)	42.8 (15.0)	0.99 (0.97-1.00)/0.08	0.08	51.7 (14.9)	54.6 (15.7)	1.01 (1.00-1.03)/0.07	0.01
Smoking at diagn.(binary)	44.9	47.8	1.13 (0.71-1.78)/0.61	0.51	-	-	-	-
Smoking at diagn.								
-current	-	-	-	-	12.7	15.6	1.35 (0.71-2.56)/0.36	0.34
-quit<3yr	-	-	-	-	13.0	16.7	1.41 (0.76-2.64)/0.28	0.33
-other	-	-	-	-	74.4	67.7	REF	REF
Appendect. before diagn.	-	-	-	-	2.6	3.6	1.40 (0.44-4.41)/0.57	0.61

* within a buffer around residential address/ ** Population density, in 10³ inhabitants per km², and Address density in 10³ addresses per km²

study with 62 (9%) patients reporting NMSC development. The median age was 49 years old and 56% patients were women. The majority of patients (81%) stated exposure to a thiopurine medication. The rate of thiopurine exposure was similar in patients who developed skin cancer and those without skin cancer (92 vs. 89%, $p=0.3$). There was no significant association between NMSC and TP dose or 6-thioguanine nucleotides (6-TGN) levels. Subtropical Brisbane has the highest UV exposure index compared to the other three sites. In multivariate models, 4 factors were independently and significantly associated with NMSC; age per 1 year increase (OR 1.05; 95% CI 1.03–1.07), residing in Brisbane vs. Christchurch (OR 3.3; 95% CI 1.6–6.8), never staying in the shade vs. staying in the shade $\geq 50\%$ of the time (OR 3.8; 95% CI 1.4–10.5) and having a skin type that never tanned vs. other skin types (OR 6.9; 95% CI 2.9–16.0). Thiopurine duration >3 years vs thiopurine duration <3 months (OR 1.5, $p=0.26$) and never using sunscreen (OR 1.03, $p=0.95$) did not reach statistical significance.

Conclusions: Our study demonstrated the significant impact of traditional risk factors on skin cancer development in an IBD population, but failed to find an association between TP dose, or metabolite levels, and NMSC. This suggests that traditional risk factors play a substantial role in NMSC development irrespective of TP exposure. Future studies investigating the role of TPs in skin cancer development need to control for traditional risk factors.

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Inflammatory bowel diseases in Faroese-born Danish residents and their offspring. Further evidence of the dominant role of environmental factors in IBD development

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Background: The Faroe Islands have the world's highest recorded incidence of inflammatory bowel disease (IBD) [1]. The Faroe Islands form part of the Danish realm and many Faroese immigrate to Denmark, where the IBD incidence is considerably lower. We studied the IBD incidence in first-, second-, and third-generation immigrants from the Faroe Islands to Denmark to assess the extent to which the immigrants adopt the lower IBD incidence of their new home country.

Methods: Data on Faroese-born Danish residents and their children were retrieved from the Danish Central Population Register for

1980–2014. Incident IBD cases for immigrants and the Danish background population were identified from the Danish National Patient Register. Standardised Incidence Ratios (SIRs) were used to compare the IBD risk in immigrants with that of Danish residents. 95% confidence intervals (CI) were calculated using the square-root transform. **Results:** First-generation Faroese immigrants had a higher IBD incidence than Danes, SIR 1.25 (95% CI, 0.97;1.59) for men and 1.28 (95% CI, 1.05;1.53) for women. This excess risk derived from ulcerative colitis (UC), SIR 1.44 (95% CI, 1.10;1.87) for men and 1.36 (95% CI, 1.09;1.68) for women. No excess risk was found for Crohn's disease (CD). The excess UC risk disappeared over one generation in men and over two generations in women.

Conclusions: Although some impact of genetic dilution cannot be excluded, our findings indicate the importance of the gene-environment interplay in the development of UC, as the excess risk of UC in Faroese immigrants to Denmark disappeared over one to two generations.

References:

- [1] Burisch J, Pedersen N, Čuković-Čavka S, et al. (2014), East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. *Gut* 2014 Apr;63(4):588–97.

P693

Patients with inflammatory bowel disease who are on immunosuppressive therapy perform regular gynecologic screening for uterine cervical cancer?

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Background: There is an increased risk of high-grade uterine cervical dysplasia and cervical cancer among patients with inflammatory bowel disease (IBD) who are on immunosuppressive medications compared with the general population. Other risk factors have also been identified such as smoking, prolonged use of oral contraceptives and many pregnancies to term. ECCO guidelines recommend regular gynecologic screening for uterine cervical cancer in women with IBD, especially if they were treated with immunosuppressant. Young women with immunosuppressive treatment should obtain a Papanicolaou test twice in the first year after diagnosis and annually thereafter if the results are normal. Our aim was to evaluate the performance of the regular gynecologic screening for uterine cervical cancer among patients with IBD who are on immunosuppressive therapy.

Methods: We performed a cross-sectional study in 101 patients with IBD who are on immunosuppressive therapy. An interviewer-administered questionnaire was used to collect information on demo-

Abstract P692 – Table 1. Standardised Incidence Ratios (SIRs) of CD, UC and IBD for male and female first, second, and third-generation immigrants from the Faroe Islands to Denmark

	CD		UC		IBD	
	Men	Women	Men	Women	Men	Women
First	0.81 (0.45;1.34)	1.00 (0.70;1.40)	1.44 (1.10;1.87)	1.36 (1.09;1.68)	1.25 (0.97;1.59)	1.28 (1.05;1.53)
Second	0.81 (0.47;1.30)	0.92 (0.60;1.36)	1.01 (0.71;1.40)	1.29 (0.97;1.69)	0.96 (0.71;1.26)	1.18 (0.92;1.48)
Second: One parent	1.00 (0.60;1.53)	0.80 (0.47;1.26)	1.03 (0.70;1.45)	1.21 (0.87;1.64)	1.01 (0.74;1.35)	1.09 (0.82;1.41)
Second: Two parents	NA	1.60 (0.63;3.32)	0.94 (0.30;2.22)	1.71 (0.85;3.07)	0.65 (0.21;1.54)	1.65 (0.94;2.69)
Third	1.12 (0.53;2.10)	1.83 (1.08;2.90)	0.87 (0.39;1.66)	1.18 (0.62;2.02)	0.97 (0.55;1.57)	1.46 (0.95;2.14)

NA 95% CI cannot be calculated using the square-root transform

graphics, immunosuppressive therapy, risk factors and last screening for uterine cervical cancer.

Results: In total, 101 patients with IBD (69 Crohn's disease, 32 ulcerative colitis), and immunosuppressive therapy (58% anti-TNF, 37% thiopurins, 3 MTX and 2% CTC) were included in the study. Up to 28% of patients underwent combined immunosuppressive therapy. 47.5% of patients were smokers and 15% therapy with oral contraceptives. 55.5% of patients had at least two risk factors and 7% had three or more factors. Only 28% of patients had screening for uterine cervical cancer in the last year, 36% for 2–5 years and 36% more than 5 years. Some degree of dysplasia was observed in 10% of patients with screening uterine cervical cancer in the last year. Only 17% of patients with two or more risk factors had performed screening for uterine cervical cancer in the last year. No patient knew that immunosuppressive therapy is a risk factor for uterine cervical cancer.

Conclusions: Most IBD patients with immunosuppressive therapy are not successfully screening for cervical cancer. The low rate of correct follow-up in patients with two or more risk factors is really alarming. Although the incidence of dysplasia is low, patients with IBD should be informed about cervical cancer risk factors and the benefit of early detection of dysplasia.

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Disease course during the first five years following diagnosis in a prospective European population-based inception cohort – the ECCO-EpiCom cohort

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Background: The EpiCom-cohort is a European prospective population-based cohort of unselected, uniformly diagnosed patients with inflammatory bowel disease (IBD) diagnosed in 2010 in centres from Western and Eastern European countries. The cohort aims at describing differences in occurrence, treatment strategies, disease course and prognosis within Europe.

Methods: Patients were followed each 3rd month for the first year after diagnosis and then according to the treating physician for the 2–5th year of follow-up. Clinical data on surgery, hospitalizations and medical treatment incl. biological therapy were captured prospectively throughout the follow-up period and entered in a validated web-based database. The aim of the study was to investigate differences in disease outcome and the use of biologicals between Eastern and Western Europe during the first 5 years of follow-up. Associations between outcomes and covariates were analysed by Cox regression analyses.

Results: A total of 1,148 patients aged 15 years or older from 26 centres in 13 Western and 7 Eastern European countries were followed prospectively of whom 623 (54%) had ulcerative colitis (UC), 425 (37%) had Crohn's disease (CD), and 100 (9%) had IBD unclassified (IBDU). At 5-years follow up a total of 123 (11%) patients had undergone 1st surgery (resections or colectomy), 190 (17%) had received biological therapy and 289 (25%) were hospitalized. Crude annual rates for CD and UC patients regarding surgery, biological treatment and hospitalization are shown in Table 1. Significantly more patients in Western Europe received biological therapy ($p < 0.05$), while surgery and hospitalization rates did not differ between the regions at 1, 3 and 5-year follow-up ($p > 0.05$). Cox regression analysis showed that in CD only stricturing or penetrating disease carried the highest risk for surgery and hospitalization while

Abstract P694 – Table 1. Crude rates for surgery, biological therapy and hospitalization after 1 and 3 years follow-up in the EpiCom-cohort

	Biological therapy			Surgery			Hospitalization		
	1 year	3 years	5 years	1 year	3 years	5 years	1 year	3 years	5 years
CD – Eastern Europe	4 (5%)	7 (9%)	12 (15%)	12 (15%)	16 (20%)	17 (22%)	22 (28%)	26 (33%)	28 (35%)
CD – Western Europe	71 (21%)	96 (28%)	108 (31%)	37 (11%)	55 (16%)	72 (21%)	75 (22%)	102 (29%)	122 (35%)
UC – Eastern Europe	1 (1%)	6 (6%)	10 (9%)	1 (1%)	1 (1%)	2 (2%)	6 (6%)	14 (13%)	19 (18%)
UC – Western Europe	22 (4%)	45 (9%)	60 (12%)	15 (3%)	24 (5%)	32 (6%)	70 (14%)	104 (20%)	120 (23%)

younger age was associated with the risk for receiving biological therapy. In UC only females and patients with extensive disease carried the highest risk for hospitalization while younger age was associated with the risk for receiving biological therapy.

Conclusions: In an era of early and aggressive immunological therapy, surgery and hospitalization rates for CD and UC patients were similar in Eastern and Western Europe and comparable to population-based cohorts from the past decade and pre-biological era. This similar disease course was in spite of more early and aggressive treatment with biologicals, with significantly more CD and UC patients in Western Europe receiving biologicals.

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The risk of proximal disease extension in patients with limited ulcerative colitis in a prospective European population-based inception cohort – the ECCO-EpiCom cohort

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Background: Ulcerative colitis (UC) is a progressive and dynamic disease and many patients will experience an extension of inflammation from their initial disease location. Disease extent is the most important factor determining disease prognosis over the long-term. As only few population-based studies have investigated the disease extension and subsequent risk of surgery in UC, we sought to investigate this in the European population-based EpiCom-cohort.

Methods: The EpiCom-cohort is a population-based cohort of unselected patients with inflammatory bowel disease diagnosed in 2010 in Eastern and Western European centres. Patients were followed prospectively for five years and clinical data were captured throughout the follow-up period and entered in a validated web-based database. Disease extension was defined in patients with limited UC at diagnosis (proctitis, E1 or left-sided, E2) as a progression from the initial extent defined by endoscopy or surgery. The risk of colectomy was assessed in all incident patients. Associations between progression or colectomy and multiple covariates (age, gender, initial disease extent, diagnostic delay, smoking status, increase in extent, geographic region) were analysed by Cox regression analyses using the proportional hazard assumption.

Results: A total of 614 incident UC patients were included in the study, of which 390 (64%) had E1 or E2 at diagnosis. Extent at diagnosis and during follow-up is shown in Table 1. During the follow-up period, 68 (18%) patients with E1/E2 progressed to E3, and 20 (5%) patients with E1 progressed to E2. No clinical predictors of extension to either E2 or E3 were identified. During follow-up, a total of 35 (6%) patients had a colectomy. Of patients with E1/E2 as initial extent a total of 18 (5%) patients had a colectomy. Progression from E1/E2 to E3 or from E1 to E2 was a significant risk factor for colectomy (HR 7.4 CI95%: 2.7–20.2). No difference in the results was found between Eastern and Western European patients.

Table 1. Disease extent in ulcerative colitis patients at diagnosis and follow-up

At diagnosis	At follow-up			Total (diagnosis)
	E1 (proctitis)	E2 (left-sided)	E3 (extensive)	
E1 (proctitis)	96 (25%)	20 (5%)	18 (4%)	134 (34%)
E2 (left-sided)	–	206 (53%)	50 (13%)	256 (66%)
Total (follow-up)	96 (25%)	226 (58%)	68 (17%)	390 (100%)

Conclusions: In this European population-based inception cohort of unselected UC patients one out of four patients with proctitis or left-sided colitis at diagnosis experienced a progression in disease extent after five years of follow-up. The risk of colectomy was increased in patients who progressed to either left-sided or extensive colitis. No clinical predictors for disease extension could be identified, thus highlighting the need for new histological or serological markers in order to identify patients at risk for disease progression.

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Ambient air quality as risk factor for microscopic colitis – a Geographic Information System study

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Background: Microscopic colitis is a chronic inflammatory disorder of the colon with watery diarrhea as main symptom. The pathophysiology is not completely understood. Smoking has found to be an incontestable risk factor for MC. Furthermore, the older age of onset suggests a contributive role for environmental factors. Considering the compositional overlap between cigarette smoke and polluted air, and the negative impact of air pollution on mortality, hospitalizations and various chronic disorders, we aimed to assess the association between ambient air quality and the risk of MC in a large cohort of MC patients from South Limburg, the Netherlands.

Methods: A case-control study was performed. MC cases, diagnosed between 2000 and 2012 within South Limburg, were retrieved from the national pathology registry and matched to non-MC controls from the general population, based on age (± 2 years) and gender. The index date of the cases was defined as the date of diagnosis, controls were assigned the same index date as their matched case. All included subjects had a stable residential address for ≥ 3 years at index date. (In)direct markers for residential ambient air quality, including: air pollution compounds, land use, road length, distance to major roads, and demography were determined using a Geographic Information System (GIS). Univariate and multivariable analyses were performed and corrected for age, gender and smoking status.

Results: In total, 345 MC cases (78.6% female) and 583 (matched) controls (77.2% female) were included. Biopsy specimens were revised to confirm the diagnosis in 318 (92.2%) of the cases. In total, 123 (35.6%) CC, 188 (54.6%) LC and 34 (9.8%) MCi cases were included. Univariate, percentage of urban green ($< 500\text{m}$), distance to the nearest highway, and average benzene concentration were associated with MC ($p < 0.10$). The latter remained significant in the multivariable model (OR 4.41, 95%-CI 1.23–15.78). A higher age (OR 1.02; 95%-CI 1.01–1.04) and current smoking (OR 4.39, 95%-CI 3.07–6.28) were also significantly associated with MC. A sensitivity analyses, only including biopsy proven CC and LC cases, showed the same results.

Conclusions: This is the first study that systematically assessed the relationship between ambient air quality and MC, but did not reveal significant associations. Despite the equal exposure to air pollution observed in cases and controls, a contributory role for ambient air pollution in MC pathophysiology could not completely excluded. A genetic susceptibility in MC cases to react upon the same levels of exposure compared to non-MC controls, might still be present. Comparable studies in different populations are warranted in order to validate the current findings.

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Association of inflammatory bowel disease and celiac disease. Experience in a hospital of the autonomous community of Madrid (Spain)

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Background: There are multiple and controversial data about the relationship between Celiac Disease (CeD) and Inflammatory Bowel Disease (IBD).

We pretend to study the prevalence of CeD in patients diagnosed *de novo* of IBD in the area of Infanta Sofía University Hospital (a secondary center which serves more than 303,000 inhabitants in 53 municipalities in the northern area of the Autonomous Community of Madrid) between 2008 and 2012.

Methods: CeD screening was performed in newly diagnosed IBD patients by the determination of blood levels of IgA and IgA tissue transglutaminase antibodies (anti-tTG) (in case of IgA deficiency, IgA levels with high sensitivity techniques or levels of IgG anti-tTG were determined). In those patients with positive anti-tTG, an endoscopic duodenal biopsy and a genetic test of CeD susceptibility (HQ DQ2/DQ8 heterodimers) were performed.

None of the patients had received steroids or immunosuppressive or biological drugs in the three months prior to endoscopy. Celiac disease was diagnosed in patients with positive anti-tTG, a compatible duodenal biopsy, and good response to a gluten-free diet.

The prevalence of celiac disease in our group was compared with the expected prevalence in the general population according to published adult series of national studies.

Results: CeD screening was performed in 163 patients with *de novo* IBD: 65 with Crohn's disease (CD), 92 with Ulcerative Colitis (UC) and 6 with Unclassified Colitis (UnC). Six patients have positive anti-tTG (3.7%), 2 patients with CD (1 with colonic CD and 1 with ileocolonic CD) and 4 patients with UC (2 with ulcerative proctitis and 2 with extensive colitis), with no statistically significant differences between groups ($p=0.999$). 5/6 patients with positive anti-tTG were female and 1 patient was male; 5/6 were Caucasian, 1/6 was Hispanic. 5/6 patients with positive anti-tTG have positive CeD genetic test (2 with CD, 3 with UC). Duodenal biopsy was normal in 2 patients, and 4/6 presented histological results compatible with CeD (3 patients with UC and 1 with CD).

In all patients with CeD and IBD, IgA was in a normal range, anti-tTG were positive, and all of them had positive CeD genetic markers, and none of them had family history of CeD.

The prevalence of CeD in our group of patients with IBD is 2.45% (4/163 patients), 3 with UC and 1 with CD.

Conclusions: In our group of patients with *de novo* IBD, the prevalence of CeD is higher than the prevalence in the general adult population in Spain (expected prevalence about 1:370–1:389) and higher than the prevalence in our region (1:222–1:370 between adults). Therefore, it seems advisable to perform CeD screening in newly diagnosed IBD patients, especially in patients with UC or with CD with colon involvement.

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The risk of developing subsequent immune mediated inflammatory diseases: a retrospective matched cohort study

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Background: Patients with an existing immune mediated inflamma-

Abstract P698 – Table 1

Primary IMID	Sample size		Incidence of any subsequent IMID (per 1,000 person years)		% with ≥ 1 subsequent IMID		Hazard ratio of subsequent IMID									
	Case	Control	Case	Control	Case	Control	Any	AS	CE	HS	LU	PA	PS	RA	UV	IBD
AS	6,352	4,059,296	105.2	3.3	26.0	1.0	31.4		11.2	3.3	23.7	50.8	8.6	63.2	54.9	16.0
CE	19,217	11,520,448	28.2	3.6	7.9	1.0	7.8	4.0		4.0	8.7	2.8	5.4	6.0	5.3	17.6
HS	14,136	8,447,796	17.6	3.2	5.2	0.9	5.4	4.4	3.2		4.1	2.7	6.7	4.6	5.3	5.6
LU	29,690	19,812,412	71.9	3.7	19.8	1.1	18.9	15.5	11.5	7.5		7.8	5.1	41.8	9.7	7.0
PsA	8,406	5,380,715	234.1	3.6	47.2	1.1	62.2	71.4	5.3	10.5	14.1		163.2	91.5	10.0	7.3
PsO	115,141	74,228,131	33.4	2.6	10.2	0.8	13.0	5.8	5.5	8.5	4.7	197.3		7.9	4.5	4.1
RA	103,036	68,808,782	46.3	2.7	13.1	0.8	16.8	78.5	10.3	8.1	55.3	46.9	7.2		8.2	7.6
UV	34,422	22,166,447	32.7	3.4	9.7	1.0	9.6	89.3	4.8	6.9	8.6	5.5	4.2	11.1		8.7
IBD	68,535	42,371,769	23.1	3.1	7.2	1.0	7.5	13.4	15.1	8.0	5.6	2.3	5.0	7.4	10.2	

Notes: Hazard ratios are from Cox proportional hazards models. Hazard ratios >1 indicate higher risk for case patients relative to controls. All hazard ratios are significant at $P<0.002$.
AS=ankylosing spondylitis; CE=celiac disease; HS=hidradenitis suppurativa; IBD=inflammatory bowel disease (Crohn's disease or ulcerative colitis); LU=lupus; PsA=psoriatic arthritis; PsO; psoriasis; UV=uveitis.

tory disease (IMID) may be more likely to develop other IMIDs based on limited research. We sought to compare the risk of developing subsequent IMIDs among patients with and without an existing IMID.

Methods: IMID risk was estimated in a large US insurance claims database (MarketScan Commercial Claims and Encounters, 1/2006–9/2015) for patients with each of 9 initial IMIDs (ankylosing spondylitis [AS], celiac disease [CE], hidradenitis suppurativa [HS], inflammatory bowel disease [IBD]; lupus [LU], psoriatic arthritis [PsA], psoriasis [PsO], rheumatoid arthritis [RA], uveitis [UV]). Up to 1,000 controls were matched with replacement by age, sex, state of residence and insurance type to case patients aged 18–64 who had an initial, incident IMID. Initial IMIDs were identified with ICD-9 diagnosis codes on ≥ 2 medical service claims ≥ 30 days apart. A case patient's earliest IMID claim was designated as the index date for the case and all matched controls. The 8 secondary IMIDs were identified by their first claim after the index date. All subjects had to have ≥ 365 days of continuous health plan enrollment before and after their index date. Risk of developing a secondary IMID (each of 8 and any of the 8) was analyzed by initial IMID with stratified Cox proportional hazards models and clustered standard errors to account for case-control match group.

Results: Among 398,935 cases, mean age was 46 years and 63% were female. Mean number of matched controls per case was 644. Across the 9 initial IMID cohorts, range of median follow-up was 918–1,023 days for cases and 883–971 days for controls. Overall, any secondary IMID occurrence was significantly higher for cases (range: 5.2–47.2%) than for controls (range: 0.8–1.1%). Relative to matched controls, patients with an initial IMID had significantly higher risk of developing any of the other 8 secondary IMIDs ($p \leq 0.002$) (Table 1).

Patients with IBD as the primary condition had 7.5 times higher risk of developing a subsequent IMID compared with controls.

Conclusions: The incidence risk for developing a subsequent IMID was significantly higher for patients newly diagnosed with an initial IMID than matched controls without the same initial IMID. Considering the risk of developing a subsequent immune-mediated comorbidity while establishing treatment goals may help maximize patients' long-term health-related quality-of-life.

P699

Impact of adalimumab's patient support program on clinical outcomes in inflammatory bowel diseases: results from the COMPANION study

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Background: Adalimumab (ADL) is an anti-TNF biologic therapy indicated for the treatment of inflammatory bowel diseases (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC). Patients receiving ADL in Canada are eligible to enroll in the AbbVie Care patient support program (PSP) which provides them with personalized services including ongoing care coach calls (CCC). In a previous study, IBD patients enrolled in AbbVie Care receiving CCC demonstrated significantly greater persistence and adherence to ADL than patients that did not receive CCC (no-CCC). The objective of this study is to compare the likelihood of achieving clinical remission in a cohort of IBD patients treated with ADL enrolled in the ADL PSP between those who received CCC versus those who did not receive CCC.

Methods: A longitudinal analysis using de-identified aggregate-level data collected through the AbbVie Care PSP was performed. Patients were indexed on the date of their first injection of ADL between January 2010 and October 2015. The ADL PSP database included patient measurements of the Harvey-Bradshaw Index (HBI), a measure of disease severity. To be eligible, patients had to have a baseline HBI measurement 90 days before to 30 days after their index date and have had a follow up HBI measurement 6 to 18 months later. HBI remission ($HBI \leq 4$) at the time of the follow up HBI assessment was compared in patients having received CCC and patients without CCC (no CCC). Robust Poisson regression was used to estimate the adjusted relative risk (RR) of HBI remission. Analyses were adjusted for patient age group, sex, region, prior biologic use, days

lapsed between HBI assessments, and baseline disease severity category.

Results: A total of 1469 IBD patients met eligibility criteria and 916 (62%) of these had received CCC. Of the 1469 patients, 1046 (71%) were in HBI remission at the second assessment, 682 (74%) in the CCC group and 364 (66%) in the group not receiving CCC. In the multivariable regression analysis, there was a 12% increased likelihood of achieving HBI remission in the CCC group relative to the group without CCC (RR=1.12, 95% confidence interval: 1.04, 1.20; p-value =0.002).

Conclusions: IBD patients receiving tailored services through the ADL PSP in the form of care coach calls have an increased likelihood of achieving HBI remission within 6 to 18 months. These results may help refine interventions aiming at improving clinical outcomes in IBD patients.

P700

Epidemiology of genital lymphoedema as the initial presentation of paediatric Crohn's disease

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Background: Genital lymphoedema is caused by inflammation and granuloma formation in the lymphatic system and is recognised as a presentation of cutaneous metastatic Crohn's disease (CD). It can precede luminal presentation by months to years, particularly in younger patients; many children with cutaneous CD have genital involvement. Despite several case reports, there is a scarcity of epidemiological studies demonstrating the incidence of genital lymphoedema in a paediatric population with Crohn's disease. We aimed to identify the incidence of genital lymphoedema as the initial presentation of paediatric CD within a population-based cohort.

Methods: Using a prospective regional database demographics and phenotypic data of all incident and prevalent paediatric inflammatory bowel disease (PIBD) patients in South-East Scotland between 01.08.97 and 31.12.11 were reviewed. Case notes of all CD patients were reviewed and those with genital involvement identified. Using all CD as the denominator, the incidence of genital lymphoedema as the initial presentation of CD in all patients (incident and prevalent) in this cohort was calculated.

Results: A total of 204 incident and prevalent cases of CD diagnosed less than 17 years of age were recorded in SES during the study period. 5 patients (2.5%) were identified as having genital involvement prior to, or at the time of, CD diagnosis. These patients were aged 4–15 years at presentation (median 9 years); 3 were male. One patient was diagnosed with CD despite normal endoscopic examination after developing perianal abscesses and fissures one year after histologically proven granulomatous genital oedema. Of the other 4 patients, only one presented with concomitant gastrointestinal and genital disease. The other patients were diagnosed with CD on endoscopy 8 months, 1 year and 3 years after initial presentation with genital oedema. 4 patients with genital oedema had concurrent perianal disease and one had oral disease.

Conclusions: To our knowledge, this is the first paediatric population-based study of genital lymphoedema as an initial presentation of CD. In this cohort, 2.5% of paediatric CD within a regional PIBD cohort at diagnosis had prior or concurrent genital lymphoedema due to CD. This significant proportion highlights the importance of considering CD as one of the many differential di-

agnoses of genital oedema, particularly in the presence of perianal disease or other gastrointestinal symptoms.

P701

Late-onset Crohn's disease is associated with high risk of intestinal perforation and low risk of perianal fistula as compared with early-onset Crohn's disease: the CONNECT cohort

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Background: The late-onset Crohn's disease has several different clinical characteristics from the early-onset Crohn's disease. This study was aimed to compare abdominal and perianal complications between early-onset and late-onset Crohn's disease.

Methods: The Crohn's Disease Clinical Network and Cohort (CONNECT) retrospective cohort was used in this study. Between 1982 and 2010, patients with confirmed Crohn's disease were enrolled. The early-onset Crohn's disease was defined as age at the diagnosis ≥ 20 and $30 <$ (549 patients), and the late-onset as ≥ 40 and < 70 (185 patients). The multivariable logistic regression analyses were performed with adjustment of sex, smoking, location (L), and behavior (B) or Crohn's disease.

Results: The patients with late-onset Crohn's disease underwent higher rate of abdominal surgery and lower rate of perianal surgery than those with the early-onset Crohn's disease (33.0% vs. 25.0% and 3.8% vs. 22.6%, $p < 0.0001$). The patients with late-onset Crohn's disease had lower rate of perianal fistula than those with the early-onset Crohn's disease (14.8% vs. 41.7%, $p < 0.0001$). In the multivariable analysis, the patients with late-onset Crohn's disease had odds ratio of 3.090 ($n=312$, 95% confidence interval [CI]: 1.228–7.772, $p=0.017$) for intestinal perforation, and odds ratio of 0.122 ($n=313$, 95% CI: 0.053–0.285, $p < 0.0001$) for perianal fistula.

Table 1. Association between late-onset Crohn's disease and complications

Dependent variable	Number	Odds ratio (95% CI)*	p value
Intestinal perforation	312	3.090 (1.228–7.772)	0.017
Intrabdominal abscess	313	0.703 (0.261–1.890)	0.485
Intestinal stricture	311	0.956 (0.464–1.968)	0.903
Perianal fistula	313	0.122 (0.053–0.285)	< 0.0001

Conclusions: The late-onset Crohn's disease is associated with high risk of abdominal surgery and intestinal perforation, but low risk of perianal fistula as compared with the early-onset Crohn's disease.

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P702

F-calprotectin use in inflammatory bowel disease is characterized by improved diagnostic accuracy, less patient harm and decreased costs, compared with conventional serological markers and colonoscopy. A cost-effectiveness study in Italy

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Background: Gastrointestinal disorders may exhibit overlapping symptoms making diagnosis difficult in primary and specialty care. Inflammatory bowel disease (IBD), prevalence <0.5% in the general population, is characterized by chronic inflammation of the gastrointestinal tract, non-specific elevation of inflammatory markers such as ESR and CRP and may present with extra-intestinal manifestations. Irritable bowel syndrome (IBS) is a functional disorder without gastrointestinal inflammation and with an estimated prevalence of 10–20%.

Endoscopy is the gold standard for detecting IBD vs. IBS, but due to the low prevalence of IBD, is negative in the majority of cases. Furthermore, it is invasive, expensive, and uncomfortable for the patient and not without risks. Moreover, inadequate bowel preparation prior to colonoscopy is known to increase the burden of disease from both the clinical and the economic perspective: shorter intervals between repeated procedures, higher missed rates, patient inconvenience, and increased risk of complications are reported in the scientific literature.

F-Calprotectin (FC) is a fecal marker of intestinal inflammation; IBD patients exhibit FC levels higher than the general population; IBS patients have FC levels higher than controls, but lower than IBD patients. Therefore, FC can be used as a pre-endoscopic test to differentiate between IBD and IBS.

This study evaluates the cost-effectiveness (CE) of FC compared to CRP+ESR, and to colonoscopy to rule out IBD in Italy.

Methods: A Markov model was developed for each diagnostic strategy, simulating 1000 patients presenting to primary care with unspecific gastrointestinal symptoms. In the model, 1.6% of the colonoscopies brought about complications (Rabasinghe, 2016), resulting in Emergency Room visits/surgery. Inadequate colon preparation (23%-Kilgore, 2011) and repeated colonoscopies (30.3%-Hendry, 2006) were included in the calculations.

Outcomes include cost savings, cost per corrected IBD diagnosed, colonoscopy reduction.

Results: FC is CE when compared to CRP+ESR, and to colonoscopy.

Table 1. Clinical and economic results of the simulation model

	F-Calprotectin	CRP+ESR	Colonoscopy
Total costs (EUR)	66 088	68 796	111 807
Average cost/patient (EUR)	66.1	68.8	111.8
N colonoscopies avoided	736	722	
Colonoscopy – costs avoided (EUR)	75 257	74 233	
N correctly diagnosed IBS	683	657	–
N correctly diagnosed IBD	98	35	–
Colonoscopy – complication costs (EUR)	2 667	3 071	8 548
Colonoscopy – inadequate colon preparation costs (EUR)	2 171	2 490	6 928

It results in more correctly IBD diagnoses at a lower price; it reduces the unnecessary endoscopies, increasing the number of correctly diagnosed IBD (63) and IBS (26) patients.

Conclusions: Results show that the as pre-endoscopic tool FC is associated with fewer colonoscopies and correctly identifies more disease

while decreasing costs compared to the alternatives. FC demonstrates superior value both from patient and payer perspective, while simultaneously increasing diagnostic efficacy.

P703

Risk of disease progression in patients with Crohn's disease after 7 years of follow-up in a Danish population-based inception cohort

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Background: Crohn's disease (CD) is a progressive disease that over time can lead to the development of complications such as strictures or internal penetrating disease that will ultimately lead to surgery. Only few population-based studies have investigated the risk factors for disease progression in CD including the effect of smoking. We therefore sought to identify the risk factors associated with complicated CD in a Danish population-based inception cohort from the biological era.

Methods: All incident patients diagnosed with CD or UC in a well-defined Copenhagen area 1.1.2003–31.12.2004 were registered and followed prospectively until 31.12.2011. Clinical data including medical and surgical treatment and disease phenotype according to the Montreal classification were registered. Disease progression in CD was defined as the first occurrence of a bowel stricture (B2) or internal penetrating disease (B3), defined by endoscopy, cross-sectional imaging or surgery, or the need for non-perianal surgery. Possible associations between disease progression and multiple covariates (age, gender, disease location, type of medical treatment, diagnostic delay and smoking status) were analysed by Cox regression analyses using the proportional hazard assumption.

Results: The cohort consisted of 213 incident CD patients that were followed prospectively. Of those, a total of 165 (77%) patients had non-penetrating, non-stricturing disease behaviour (B1) at diagnosis and were included in the analysis. Of those with B1, 44 (27%) patients experienced progression of disease during the seven year follow-up: 21 (48%) B2, 5 (11%) B3, and 18 (41%) had surgery. Patients with ileal disease location (L1 or L3) had increased risk of disease progression (HR =2.1 CI95%: 1.1–4.0) as was also seen in patients who did not receive medical treatment during follow-up compared to those who did (HR =9.0 CI95%: 3.3–25.0). Other covariates including active smoking at the time of diagnosis were not associated with the risk for a disease progression.

Conclusions: In this population-based inception cohort of unselected CD patients one out of four patients with B1 behaviour at diagnosis experienced disease progression during follow-up. Clinical variables associated with the risk of progression were ileal disease location and not receiving medical treatment for CD. Smoking was not associated with the risk of disease progression in CD.

P704 The impact of travel distance on disease outcomes in inflammatory bowel disease

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Background: The management of inflammatory bowel diseases (IBD, Crohn's disease (CD), ulcerative colitis (UC)) is increasingly complex and optimal treatment often requires specialized healthcare. Prior studies showed that high volume institutions or specialist gastroenterologist care was associated with superior outcomes in patients with IBD. One factor that could limit regular access to specialist care may be distance from such facilities. The effect of distance from area of residence to a referral IBD hospital on the need for surgery and biologic therapy in patients with CD or UC has not been examined previously.

Methods: This study included patients enrolled in a prospective patient registry at a tertiary referral hospital from January 2005 to August 2016. Distance to our healthcare center was determined for each patient by using their zip code of residence. This was then modeled in quartiles with higher quartiles increasingly further away from the hospital. Patients were excluded from our analysis if they lived more than 100 miles from our hospital. Disease outcomes were defined as the need for immunomodulator therapy, biological therapy and the need for surgery. Regression models were used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI).

Results: Our study included 2,136 patients with IBD (1,197 CD, 939 UC) with a mean age of 41 years; just over half were women (52%). The mean distance from zip code of residence to our hospital was 2.5 (± 1.4), 8.8 miles (± 2.6), 22.0 miles (± 5.0), and 50.8 miles (± 16.5) in the 1st, 2nd, 3rd, and 4th quartiles respectively. Among all IBD patients, patients in the most distant quartile had a statistically significant and meaningful increase in need for immunomodulator use (OR 1.69, 95% CI 1.29–2.22), biological therapy (OR 2.19, 95% CI 1.69–2.85) and surgery (OR 2.44, 95% CI 1.80–3.32) (Figure).

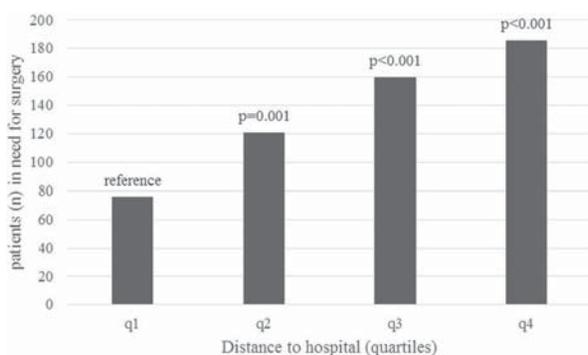


Figure 1. Relationship between distance from hospital and risk of surgery in inflammatory bowel diseases.

Differences remained significant within each type of IBD. To minimize referral bias, restricting our cohort to those who lived within 50 miles (OR for surgery Q4 vs. Q1 1.82, 95% CI 1.20–2.79) or 25 miles from hospital respectively did not change our findings.

Conclusions: Greater distance to a specialized healthcare center was associated with an increased risk of poor outcomes including need for surgery in inflammatory bowel diseases. There is an important need to ensure access to and dissemination of components of specialized IBD care across populations to ensure best patient outcomes.

P705 Peripheral arterial disease is associated with an increased risk of elderly-onset inflammatory bowel disease

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Background: The less aggressive natural history and lower genetic predisposition in elderly-onset inflammatory bowel disease (EO-IBD) suggest a unique disease pathophysiology in the elderly. Given the theoretical role of intestinal microvascular ischemia in IBD pathogenesis, we aimed to assess if peripheral arterial disease increases the risk of EO-IBD.

Methods: We conducted a case-control study using a national medical claims and pharmacy database from Source Healthcare Analytics LLC, containing data from January 2008 to December 2012. Incident cases of EO-IBD were defined as: 1) ≥ 60 years old, 2) ≥ 3 ICD-9 codes for either Crohn's Disease (CD) or Ulcerative Colitis (UC) in 2012, and 3) no IBD-related prescriptions or IBD ICD-9 codes for patients between 2008 and 2011. EO-IBD patients with a history of ischemic colitis were excluded. Controls had no IBD-related medications, IBD ICD-9 codes, IBD-associated autoimmune disease or ischemic colitis. Controls were matched to cases by age group, gender, race and geographic location. Patients were determined to have peripheral arterial disease (PAD) if they had one or more of the following ICD-9 codes on or before the first IBD code: 440.2–440.4, 443.89, 443.9. Conditional logistic regression was performed to assess the association of PAD with EO-IBD. All models were adjusted for age, vascular risk factors and diseases (diabetes, hypertension, hyperlipidemia, obesity, coronary artery disease, cerebrovascular disease) and medications previously associated with new-onset IBD (statins, antibiotics and hormone therapy).

Results: In the analysis, 3846 EO-IBD cases (CD =1479, UC =2097, IBD-U =270) and 19,222 controls were included. Baseline characteristics and the distribution of vascular comorbidities between cases and controls are shown in Table 1.

Table 1. Baseline characteristics and vascular comorbidities

Characteristic	Cases (N=3846)	Controls (N=19,222)
Male	1557 (40.5)	7590 (39.5)
Age (mean \pm SD, yr)	71.7 \pm 7.9	71.1 \pm 7.7
Peripheral arterial disease	555 (14.4)	1551 (8.1)
Diabetes mellitus	1139 (29.6)	4585 (23.9)
Hypertension	2681 (69.7)	10,940 (56.9)
Hyperlipidemia	2341 (60.9)	10,428 (54.3)
Obesity	405 (10.5)	1366 (7.1)
Coronary artery disease	1210 (31.5)	4038 (21.0)
Cerebrovascular disease	292 (7.6)	766 (4.0)

Categorical values are reported as n (%).

After controlling for vascular and medication confounders, PAD was significantly associated with an increased risk of EO-IBD (OR 1.52, 95% CI 1.36–1.71, $p < 0.001$). The risk was greater in elderly-onset UC patients (OR 1.61, 95% CI 1.39–1.87, $p < 0.001$) compared to elderly-onset CD patients (OR 1.37, 95% CI 1.13–1.68, $p = 0.002$). To address the potential misclassification of ischemic colitis as IBD, a subgroup analysis of ulcerative pancolitis patients was performed which also suggested an association between PAD and EO-IBD (OR 1.38, 95% CI 0.94–2.01, $p = 0.10$).

Conclusions: PAD was associated with an increased risk of EO-IBD suggesting that vascular factors may contribute to EO-IBD pathogenesis.

P706

Characterization of *de novo* inflammatory bowel disease (IBD) diagnosed in immigrants migrating from low to high prevalence areas of IBD: a case-control study

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Background: Immigrants moving from low to high prevalence areas of inflammatory bowel disease (IBD) increase disease incidence. Data regarding the IBD phenotype compared to local patients of high prevalence are scarce. Background differences in those factors implicated in IBD pathogenesis (genome, microbiome, immunome and exposome) may result in different clinical features. The aims of the present study were to evaluate IBD phenotypic features as well as therapeutic requirements in *de novo* IBD immigrant population patients with respect to a local control group.

Methods: We identified *de novo* IBD immigrant patients from Africa and Latin-America (minimum of 12 months of residence in Spain and with at least 6 months of follow-up) from the respective local database of three tertiary referral centres of IBD. Each immigrant case was matched by gender, type of IBD and year and age at IBD diagnosis (± 5 years) with a native Spanish IBD patient (controls). Data regarding type of IBD, location/extent, behaviour and therapeutics and surgery requirements, as well as demographic and epidemiological variables were recorded.

Results: We included 88 cases and 88 controls. Median time from immigration to IBD diagnosis in cases was 103 months (IQR 72–154) with median age at IBD diagnosis of 31 years (IQR 25–37). Among African patients (N=28) with ulcerative colitis, 9% of cases developed steroid-dependence (51% controls, $p=0.013$), whilst none required biological therapy (for 23% among controls, $p=0.025$); regarding Crohn's Disease (CD), up to 50% of Africans required surgery for 17% of controls ($p=0.041$). Among Latin-American patients (N=60) with CD, up to 23% of cases developed steroid-refractoriness (for none of the controls, $p=0.034$). No other significant differences regarding disease phenotype and demographic and epidemiological features were found neither in UC nor CD between cases and controls.

Conclusions: Although *de novo* IBD cases in our country seem to have a similar phenotype as in native IBD controls, African patients who develop UC have lower rates of steroid-dependence and biologic therapy requirements. Moreover, CD African patients presented a higher need of surgical treatment than local CD patients. Conversely, no significant differences between Latin-American patients and native Spanish patients were identified except for a higher rate of steroid-refractoriness in CD with respect to local CD patients.

P707

Paediatric IBD patients do not meet the daily recommendations of vitamin D and calcium intake: survey based analysis in a tertiary centre

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Background: Achieving optimal levels of vitamin D (VitD) and calcium (Ca) is essential for developing children, especially in patients with inflammatory bowel disease (IBD). VitD and Ca play a major role in bone health and recently VitD has shown to potentiate the effect of anti-inflammatory treatments. However, achieving a sufficient oral intake is difficult in this group taking into account young age, modern eating habits and the nature of IBD itself. The purpose of this study was to evaluate if children with IBD seen in our centre achieve optimal Vit D and Ca intake according to recommendations made by the British Scientific Advisory Committee on Nutrition and the UK Department of Health.

Methods: A prospective dietetic survey was conducted among sequential IBD children seen in clinics over a 12 month period. Ca and VitD intakes were assessed through a 24-hour recall of dietary intake questionnaire. Children who had been placed on restricted diets for allergic disease were excluded as well as children under 4 years. Included patients were classified according to age into 2 groups: 4–10 and 11–18 years. Sources of VitD were divided into dairy, oily fish, fortified cereals and egg. Analysis was performed using absolute values, percentages and means in Microsoft Excel.

Results: Survey was conducted in 151 patients, this represents 68.3% of all IBD patients under follow-up. 94 patients were included for analysis and 57 were excluded. 43/94 (45.7%) were females. Overall, only 26.6% and 21.3% of the surveyed population achieved the current recommended intake for Ca and VitD respectively. In the younger group, only 7/31 (22.6%) met the current VitD recommendations, the same figure repeats with regards Ca intake. In the older group, only 13/63 (20.6%) and 18/63 (28.6%) met the Ca and VitD recommendations respectively. In both groups dairy was the main source of vitamin D (61.3% young ones and 58.7% older ones). Less than 1/3 of the patients have an optimal intake of oily fish and egg (sufficient intake 19%, 9% for children and 30%, 26% for adolescents).

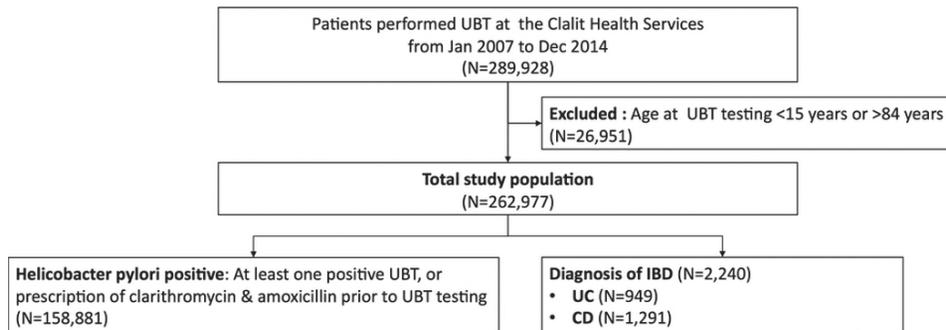
Conclusions: Paediatric IBD patients living in the UK do not meet the minimum requirements of VitD and Ca intake and therefore are at risk of having poor bone health, calcium homeostasis imbalance and VitD deficiency. In the great majority, Ca and VitD sources come from dairy whereas the contribution of oily fish and egg as a VitD source is minimal. We recommend that paediatric IBD patients receive frequent counseling on healthy eating habits and proactive intake monitoring. Routine VitD supplementation recommended by local authorities must be followed as there is an insufficient vitD oral intake among these population.

P708

Helicobacter pylori and IBD are inversely related, suggesting that individuals infected with the bacteria are less susceptible to the disease

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Abstract P708 – Figure 1. Study flow.

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Background: Data regarding the association between *H. pylori* carriage and a decreased risk of inflammatory bowel disease (IBD) are conflicting, as socioeconomic status (SES) is inversely related to both conditions, and could hypothetically confound the results.

We aimed to assess whether this association exists independently of SES.

Methods: We analyzed socioeconomic and medical information of 262,977 adult patients who consecutively performed urea breath tests (UBT) in Clalit Health Services at set intervals from 2007 to 2014.

IBD diagnosis and demographic, prescription and smoking status data and were extracted from HMO electronic database, and synchronized with detailed government-source socioeconomic information.

Results: Out of the 262,977 subjects included, 2,240 (0.9%) had been diagnosed with IBD.

	N	%
Total	262,977	100%
H. pylori status	Negative	104,096 (39.6%)
	Positive	158,881 (60.4%)
Age	Mean ±SD, years old	45.4±18.4
Gender	Male	95,495 (36.3%)
	Female	167,482 (63.7%)
Ethnicity	Jewish	228,786 (87.0%)
	Non-Jewish	34,191 (13.0%)
Smoking status	Non-smoker	180,210 (68.5%)
	Current smoker	67,522 (25.7%)
	Former smoker	15,245 (5.8%)
Socioeconomic Status	Low	52,520 (20.0%)
	Medium	105,119 (40.0%)
	High	84,228 (32.0%)
	Total	241,867 (92.0%)
	Missing data	21,110 (8.0%)
IBD	IBD	2,240 (0.9%)
	UC	949 (0.4%)
	CD	1,291 (0.5%)

IBD: Inflammatory Bowel Disease; CD: Crohn’s disease; UC: Ulcerative Colitis.

The overall rate of *H. pylori* carriage among IBD vs. non-IBD subjects in the low, medium and high SES groups was 60.2% vs. 70.3%, 58.3% vs. 62.0% and 46.6% vs. 51.3%, accordingly; p<0.001 for each group.

In multivariate analysis, *H. pylori* carriage was inversely associated with the diagnosis of IBD (OR 0.80; 95% CI 0.73–0.87; p<0.001).

	No IBD	IBD	p	
Total	260,737	2,240		
H. pylori status	Negative	103,049 (39.5%)	1,047 (46.7%)	p<0.001
	Positive	157,688 (60.5%)	1,193 (53.3%)	
Age, years	Mean ±SD	45.3±18.40	46.8±18.68	p<0.001
Gender	Male	94,564 (36.3%)	931 (41.6%)	p<0.001
	Female	166,173 (63.7%)	1,309 (58.4%)	
Ethnicity	Jewish	226,711 (87.0%)	2,075 (92.6%)	p<0.001
	Non-Jewish	34,026 (13.0%)	165 (7.4%)	
Smoking status	Non-smoker	178,801 (68.6%)	1,409 (62.9%)	p<0.001
	Current smoker	66,876 (25.6%)	646 (28.8%)	
	Former smoker	15,060 (5.80%)	185 (8.3%)	
Socioeconomic Status	Low	52,201 (21.8%)	319 (15.2%)	p<0.001
	Medium	104,260 (43.5%)	859 (40.9%)	
	High	83,307 (34.7%)	921 (43.9%)	

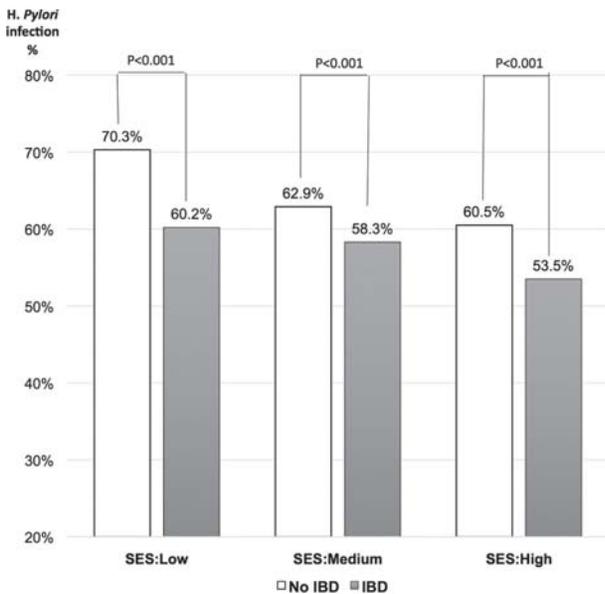
IBD: Inflammatory Bowel Disease

	OR	95% CI	p	
H. pylori status	Negative	1.00		
	Positive	0.80	0.73 0.87	<0.001
Socioeconomic Status	Low	1.00		
	Medium	1.13	0.99 1.30	0.081
	High	1.44	1.25 1.66	<0.001
Smoking status	Non-smoker	1.00		
	Current smoker	1.18	1.07 1.30	0.001
	Former smoker	1.31	1.12 1.54	0.001
Gender	Female	1.00		
	Male	1.22	1.11 1.33	<0.001
Ethnicity	Jewish	1.00		
	Non-Jewish	0.65	0.54 0.78	<0.001
Age	1.01	1.00 1.01	<0.001	

IBD: Inflammatory Bowel Disease; CI: Confidence interval.

This effect was independent of socioeconomic confounders, and evident for all SES.

Conclusions: Among a cohort of more than a quarter-million adult patients who performed a UBT, *H. pylori* carriage is inversely associated with a diagnosis of IBD, independently of socioeconomic confounders. Subjects carrying *H. pylori* may be less susceptible to develop IBD. Further studies are needed to explore the precise cause-and-effect relationship of this association.



Abstract P708 – Figure 2. Inverse association between *H. pylori* and IBD is independent of SES.

P709 inflammatory bowel disease and colorectal cancer: analysis of a single center retrospective chart review

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Background: Colorectal cancer (CRC) is perhaps the most undesirable adverse outcome in inflammatory bowel disease (IBD). The aim of this study is to estimate the rate of CRC in a single center cohort of IBD patients and to identify potential predisposing factors.

Methods: A retrospective review of the endoscopy charts of the period 1996–2016 was conducted. All patients enrolled exhibited both endoscopic and histologic documentation of IBD. Patient and disease (Montreal classification) characteristics, change in location and behaviour of IBD, location of CRC and treatment with immunomodulators and anti-TNF α agents were recorded. As index colonoscopy was defined the one that established IBD diagnosis.

Results: 1131 IBD patients having undergone 3584 colonoscopies have been registered. Males are 630 [55.7%]. Median age at IBD diagnosis is 40 years [IQR: 28, range: 2–89]. Median follow-up period is 45.5 months [IQR: 100.4, range: 0–507.5]. Ulcerative colitis (UC) was diagnosed in 614 [54.3%], Crohn's disease (CD) in 507 [44.8%] and IBD unclassified in 10 [0.9%] patients. IBD location changed in 111 UC [18.07%] and in 58 CD [11.44%] patients. CD behaviour progressed to a worse state in 46 [9.07%] patients. Thirteen patients [1.15%] developed CRC; 3 with CD ileocolitis (all in the right colon) and 10 with UC of whom 8 were classified as having extensive colitis (four rectal, three in the right and one in the left colon) and 2 as having left-sided colitis (both in the left colon). None of these patients had been operated for IBD. A non-passable colonic stenosis was already known before CRC diagnosis in only one patient while no apparent stenosis had been detected in the rest. Two patients with CRC received azathioprine for more than 3 years, whereas one was treated with infliximab.

Conclusions: The rate of CRC is low in our cohort of IBD patients

and compatible with literature data regarding Caucasian populations. No association was observed with specific predisposing factors that were studied.

P710 Vitamin D deficiency is not associated with depression in IBD patients

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Background: Depression has been reported to be more common in inflammatory bowel disease (IBD) than in the reference population. Since vitamin D deficiency has been associated with depression in other inflammatory diseases, the aim of the present study was to investigate possible associations between depressive symptoms and vitamin D deficiency in IBD.

Methods: Participants were recruited from nine hospitals in the southeastern and western regions of Norway to participate in a multicentre study from March 2013 to April 2014. Clinical and epidemiological data were collected by interview, from laboratory tests and medical records. Depression was measured with the Hospital Anxiety and Depression Scale (HADS). Depression was defined as HADS-D subscore >8 and severe depression as subscore >11 . Disease activity was assessed with clinical indices (Harvey Bradshaw index and simple clinical colitis activity index), C-reactive protein and faecal calprotectin. Vitamin D deficiency was defined as a 25-OH-D <50 nmol/l. The possible association between depression and vitamin D deficiency was investigated using Pearson correlation coefficient for continuous variables and with Students T-tests for categorical variables.

Results: In total, 407 patients were available for analyses, 229 (56%) with Crohn's disease (CD) and 178 (44%) with Ulcerative colitis (UC). There were no significant differences between UC and CD patients regarding age or gender, but CD patients had significantly longer disease duration (median 11 vs. 6 years since diagnosis). Almost 50% (199/407) of the patients had vitamin D deficiency. Depression was found in 14% (57/407) and severe depression in 17% (17/407) with even distribution between men and women and between CD and UC. In general, no significant correlation between the HADS-D and vitamin D levels were observed. In addition, no significant differences in mean vitamin D levels among patients over or under cut-off for depression (HADS-D >8 , $p=0.10$; HADS-D >11 , $p=0.26$) were found.

Conclusions: In the current study, no significant associations between Vitamin D deficiency and depression were observed in IBD patients.

P711

Vegetarian or gluten-free diet in patients with IBD – associated with lower psychological well-being and quality of life but no indication of beneficial effects on course of disease

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Background: Many IBD patients report restricting their diet due to perceived positive effects on their symptoms despite a current lack of evidence-based nutritional recommendations in this specific population. To date little is known about dietary habits of IBD patients, especially on the prevalence of vegetarian diet (VD) and gluten-free diet (GFD), while to the best of our knowledge no studies have yet investigated the impact of VD on course of disease in IBD patients.

Methods: We included 1254 patients from the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) with prospective acquisition of clinical data, psychosocial, disease-related and lifestyle factors between 2006 and 2015. Dietary habits (not part of routine enrollment and follow-up questionnaires) were subsequently inquired through a self-report questionnaire.

Results: Overall 4.1% of the IBD patients reported to follow a VD (reported underlying reasons: respect for animals, 42.3%; expected benefit for general health, 17.3%; or IBD in specific, 17.3%) and 4.7% a GFD (majority of patients referred to a perceived beneficial effect on course of their IBD as underlying reason for gluten withdrawal). We did not find any differences in essential baseline disease characteristics, such as age at diagnosis of IBD, disease duration, type of IBD and disease localization in omnivores vs. patients with a VD or GFD. However, in IBD patients following a VD there were significantly more women ($p=0.002$) and patients with a lower body weight (median 63 vs. 71 kg in VD vs. normal diet patients; $p<0.001$). No differences regarding disease activity, overall complications, fistula, hospitalization or surgery rates were observed between patients following VD or GFD vs. their counterparts with regular diet. Nevertheless, we found evidence for higher psychological impairment and lower quality of life measures with a significantly higher Post Traumatic Stress Diagnostic Scale and lower mental component levels of the Short Form 36 Health Survey (SF-36) in patients on VD or GFD as well as significantly higher indexes for anxiety and depression in the Hospital Anxiety and Depression Scale (HADS) in GFD patients.

Conclusions: In contrast to a significant fraction of patients perceiving (or potentially relying on, respectively) beneficial effects, no impact of VD or GFD on course of disease or complication rates was identified as compared to a regular diet. There was however a significant association to higher anxiety and depression as well as lower overall health score levels in VD or GFD patients. The latter may indicate, that psychosocial factors and expectations might be of higher importance in the decision to initiate and maintain a specific diet than as a matter of fact occurring effect on course of IBD

P712

Risk factors for the development of fistulae and stenoses in Crohn's disease patients in the Swiss IBD cohort

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Background: Fistulae and stenoses represent frequent and severe complications in patients with Crohn's disease (CD). For an optimal treatment it would be helpful to identify factors being predictive for the development of CD-associated fistulae and stenoses to guide the clinical management or, ideally, prevent their occurrence. Our study therefore aimed to identify risk factors for fistulae and stenosis formation in CD patients.

Methods: We retrieved data of 1'600 CD patients from the nationwide Swiss IBD cohort study (SIBDCS). The risk of fistulae and stenoses in relation to gender, age at diagnosis, smoking status at diagnosis and ileal involvement at diagnosis were analyzed.

Results: In the multivariate analysis female gender showed a lower risk for developing perianal and any fistula (RR 0.721, 95% CI 0.582–0.893, $p=0.003$ and RR 0.717, 95% CI 0.580–0.888, $p=0.002$, respectively) and older age at diagnosis showed a lower risk for developing perianal fistula (RR 0.661, 95% CI 0.439–0.995, $p=0.047$). Furthermore, ileal involvement was associated with a lower risk for perianal fistula (RR 0.713, 95% CI 0.561–0.906, $p=0.006$), a lower risk for any fistula (RR 0.709, 95% CI 0.558–0.901, $p=0.005$) and a higher risk for stenoses (RR 2.170, 95% CI 1.728–2.725, $p<0.001$).

Conclusions: In the nationwide Swiss IBD cohort younger age at diagnosis and male gender were risk factors developing perianal and non-perianal fistulae. Additionally, ileal involvement revealed to be a potent risk factor (RR 2.170) to develop stenoses.

P713

Possible explanations of the marked differences in the incidence of microscopic colitis between Denmark and Sweden

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Background: Microscopic colitis is a common cause of chronic watery non-bloody diarrhoea. Two major subtypes have been described, collagenous colitis (CC) and lymphocytic colitis (LC). Reported incidence rates differ markedly even between comparable countries and

centres such as between the region Skåne in Sweden and Zealand in Denmark. A thorough comparison of the incidence, awareness, diagnostic strategy, endoscopic activity, histopathological assessment, population characteristics including age distribution, autoimmune diseases, smoking and medicines utilization in the two neighbour regions could help assess possible explanations of the different incidence rates.

Methods: Consecutive patients diagnosed with LC and CC were prospectively identified in the Departments of Pathology in the two regions during the years 2011–15. Putative factors affecting the incidence rates were identified in the literature and compared across the two regions.

Results: The incidence of CC changed from 5.4 to 7.5 in 2011–15 in Skåne and from 15 to 15.3 in 2010–15 in Zealand. The incidence of LC changed from 2.5 to 5.1 and from 9 to 12.4, respectively. At the end of 2015 Skåne had 1.3 million inhabitants and Zealand had 0.8. The family doctor appraisal of MC, the number of large bowel endoscopies, the incidence of coeliac disease, diabetes mellitus, thyroid disease, rheumatoid arthritis and the use of MC risk medication in particular and medication in general was compared across the two regions. An inter-observer variation study on the pathology assessment was performed.

Conclusions: The incidence rates for CC and LC differ substantially between the neighbour regions Zealand and Skåne. These differences may in part be explained by differences relating to awareness, diagnostic work out and risk factors.

P714

Vitamin D deficiency in inflammatory bowel disease: prevalence and relation to disease activity in a cohort of patients of a Mediterranean country

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Background: Vitamin D deficiency is more common in inflammatory bowel disease (IBD) patients than in the general population. It is known that vitamin D seems to play a role in inflammation. However, there is conflicting data about the predictive factors of vitamin D deficiency and its potential relation to disease activity. The aims of this study were to determine the prevalence and predictive factors of vitamin D deficiency and to evaluate a possible relation to disease activity.

Methods: We designed a prospective observational study including a cohort of inpatients and outpatients with IBD diagnosis followed at our department from January to July 2016. We considered The Endocrine Society guidelines for deficiency (<20 ng/mL, being <10 ng/mL a severe one), insufficiency (21–29ng/mL) and adequate (>30 ng/mL) levels of serum 25-hydroxyvitamin D (25-OH-D). Demographic, clinical and laboratorial parameters were collected. Disease activity was measured both clinically – by Harvey-Bradshaw index (HBI) for Crohn's Disease (CD) and Truelove and Witts score (TLWs) for ulcerative colitis (UC) – and analytically – by hemoglobin (Hb), C-reactive protein (CRP), sedimentation rate (SR) and fecal calprotectin (FC). Statistical analysis was performed using SPSS v.20.

Results: We included 152 patients (52% men; 47.2±17.3 years) of which 70% with CD, 29% with UC and 1% with unclassified disease. Of the total, 37% were on immunosuppression and 17% on biologics, and 11.8% were inpatients. Mean 25-OH-D levels were 17.1±8 ng/mL (CD: 16.7±8 ng/mL vs. UC: 17.6±7 ng/mL, p=0.1)

with a prevalence of inadequate levels in 90.8% of the total (deficiency: 68.4%; insufficiency: 22.4%). We found a significant negative correlation between 25-OH-D levels and age ($r=-0.2$, $p=0.04$), CRP levels ($r=-0.22$, $p=0.004$) and HBI ($r=-0.32$, $p=0.001$). Patients with severe deficiency also showed a higher CRP (0.6 vs. 1.4 mg/dL, $p=0.03$), SR (22 vs. 31mm/h, $p=0.03$) and HBI (2 vs. 5, $p<0.001$) and lower Hb (13.6 vs. 12.7 g/dL, $p=0.02$). We didn't find a relation between vitamin D deficiency and gender, type, extent or duration of disease, surgery, hospitalization and other measures of disease activity as SR, Hb (these two except for severe deficiency), FC or TLWs.

Conclusions: There is a high prevalence of inadequate levels of vitamin D in IBD patients, particularly deficiency (68.4%). In our cohort, patients with lower levels of vitamin D tended to be older and have markers of disease activity (CRP and HBI), especially the ones with severe deficiency (besides those two, also SR and Hb), but not others (FC and TLWs).

P715

Trends in emergency department visits and hospitalization rates for inflammatory bowel disease: results from a single-center in 2004, 2009 and 2014

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Background: The use of biologics in inflammatory bowel disease (IBD) has increased recently. However, studies on whether the proportion of emergency department (ED) visits has decreased are scarce. The aim of this study was to investigate the trends in IBD-related ED visits and hospitalization rates.

Methods: Medical records of IBD-related visits in ambulatory department and ED at Seoul National University Bundang Hospital in 2004, 2009 and 2014 were reviewed. Demographics and clinical characteristics were compared among IBD patients who visited ED. Multiple-variable regression analysis was used to identify possible covariates as significant risk factors for hospitalization in IBD patients who visited ED.

Results: The proportion of IBD patients who visited ED was 6.67% in 2004, 9.44% in 2009 and 6.24% in 2014. The proportions were not significantly different in these three years ($p=0.138$). The mean age of them was 34.5±14.0 years and 70.8% of them were men. Median duration of disease was 44.2 months (interquartile range [IQR] 11.5 to 73.3). The most common chief complaints were abdominal pain (67.6%) in Crohn's disease (CD) patients and hematochezia (39.4%) in ulcerative colitis (UC) patients. The hospitalization rate from ED was 48.5% in CD patients and 50% in UC patients. Median duration of hospitalization was 14.2 days (IQR 4.3 to 16.5). Multiple-variable regression analysis showed that significant risk factors associated with hospitalization were disease duration less than 6 years (RR=3.116, $p=0.028$), leukocytosis (WBC >10.0×10³) (RR=2.608, $p=0.031$) and elevated C-reactive protein (CRP >1.0 mg/dL) (RR=2.751, $p=0.021$). Time interval between the last ambulatory department and the ED visit was not associated with hospitalization.

Conclusions: The absolute number of IBD-related ED visits increased from 2004 to 2014; but there was no significant change in proportion of ED visits and hospitalization rates during these time period. Disease duration less than 6 years, leukocytosis, elevated CRP were associated with hospitalization among IBD patients who visited ED.

P716**Beta-blocker use is associated with a higher relapse risk of inflammatory bowel disease – a Dutch retrospective cohort study**

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Background: Inflammatory bowel disease (IBD) is a multifactorial disease and as such, many factors may influence the disease course – like the concomitant use of medication. One such drug group is beta-blockers, a medication group primarily prescribed for the treatment of cardiovascular disease, which is used by approximately 10% of the Dutch population. Beta-blockers block the β -adrenergic receptors. β -adrenergic receptor activation has potent anti-inflammatory effects on the myeloid compartment of the immune system.

In this pilot study, we addressed whether an association exists between the use of beta-blockers and the course of IBD, as defined by the risk of a disease relapse in patients with IBD.

Methods: In this retrospective cohort study design, we used a population-based IBD cohort of 1461 patients. We identified relapses using medication prescriptions as a proxy. We calculated the number of relapses per 100 person-years and compared this between IBD patients using beta-blockers and IBD patients not using beta-blockers. We used Cox proportional hazards models with shared frailty to compare the risk of a relapse between both groups.

Results: 250 IBD patients had available prescriptions and were included in the study, 30 patients (12%) used a beta-blocker. In the beta-blocker group, there were 21 relapses per 100 person-years (95% confidence interval (CI): 14.0–28.6) versus 29 relapses per 100 person-years (95% CI: 26.2–32.4) in the group of patients that did not use a beta-blocker. However, when we used the Cox proportional hazard model with shared frailty and adjusted for age and gender we observed a 54% higher risk of a relapse in the group of IBD patients that used a beta-blocker versus the IBD patients that did not use a beta-blocker (adjusted hazard ratio: 1.54, 95% CI: 1.05–2.25; $p=0.03$).

Conclusions: The results of our study suggest that beta-blocker use is associated with an increased risk of disease relapses in patients with IBD. Indeed, concomitant medication use seems to be one of the factors that can influence the course of IBD and this should be acknowledged while making decisions about treatment of IBD and follow-up. These results warrant confirmation in a larger cohort.

P717**Higher ulcerative colitis/Crohn's disease ratio in a central region of Argentina**

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Background: The prevalence of inflammatory bowel disease (IBD) has increased worldwide. However, there are few studies that described the epidemiology and clinical behavior of IBD in South America. The aim of this study was to describe phenotype and clinical evolution of IBD in a central city from Argentina.

Methods: We performed a descriptive observational study in order to describe all patients with IBD diagnosis that assisted to ten centers (public and private) from Córdoba city (Argentina) between 06/2014–09/2016. Córdoba is the second largest city in population from Argentina with 1,300,000 inhabitants and represents almost 3.3% of the country population. During the registry data were recorded on standardized forms and information on demography, clinical evolution, endoscopic finding, and therapy were evaluated.

Results: A total of 454 patients were included. The ratio of ulcerative colitis (UC) ($n=394$, 86.8%) and Crohn's disease (CD) ($n=56$, 12.3%) was 7.04: 1. Mean age at diagnosis was 39.5 years (SD 16.4), with similar distribution by gender. At the moment of diagnosis, diarrhea and bleeding were more frequent manifestations in patients with UC; and abdominal pain and weight loss were the main presentation in patients with CD. Extra intestinal manifestations (with a predominance of joint involvement) were present in 20.2% of patients and were similar in UC and CD. The distribution of UC was: 34.18% proctitis, 48.72% left colitis and 17.1% pancolitis. The most common site of involvement in CD patients was: 45% colonic, 25.7% ileocolonic, 17% ileum, and 2.3% had upper gastrointestinal tract involvement. The phenotype of CD was 42.1% inflammatory, 31.6% fibrostenotic, 10.5% perianal, and 15.8% fistulizing/perforating. Anti-TNF therapy was used in 2.3% of patients with UC compared to 26.7% of patients with CD ($p<0.001$). The rate of surgery was 3.8% for patients with UC compared to 41% in patients with CD ($p<0.001$). CD patients with inflammatory and fibrostenotic behavior presented a lower percentage of surgery.

Conclusions: We observed a predominance of UC in our population with lower rate of anti-TNF therapy and surgery. Compared to other series in South America, patients with CD diagnosis presented a higher frequency colonic involvement and lower need of anti-TNF therapy.

P718**The epidemiology of IBD differs in South Asian migrants compared to Caucasians; results from a systematic review and meta-analysis**

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Background: Migrants from eastern low incidence countries are reported to develop the incidence of their adopted country. The South Asian (SA) community has a wide diaspora and presents an ideal group to study migration. We aimed to summarise the epidemiology of IBD in SA migrants through a systematic literature review and meta-analysis.

Methods: Studies reporting the incidence of IBD in SA migrants compared with Caucasian groups were eligible for inclusion. Quality as-

Abstract P718 – Table 1. Description of studies comparing South Asians and Caucasian incidence in ulcerative colitis and Crohn's disease

Study	Study characteristics and demographics					Study quality characteristics		
	Country (region)	Study period	Number of cases	Incidence rate/100,000		Diagnosis based on recognised criteria	Ethnicity reporting method	Sample frame
				SA	Caucasian			
ULCERATIVE COLITIS								
Probert (1992)	UK (Leicester)	1972-1989	1003	10.8	5.3	No	Surname	Population
Jayanthi (1992)	UK (East London)	1972-1989	112	1.8	6.2	No	Medical records	Hospital
Mayberry (1999)	UK (Leicester)	1991-1994	74	17.2	9.1	Yes	Self-reported	Population
Pinsk (2007)	Canada (Vancouver)	1985-2005	120	6.4	3.7	No	Medical records	Hospital
CROHN'S DISEASE								
Fellow (1985)	UK (Derby)	1966-1985	221	4.4	7.5	No	Self-reported	Hospital
Probert (1992)	UK (East London)	1970-79	45	1.2	3.8	Yes	Medical records	Hospital
		1980-89	54	2.3	3.8			
Jayanthi (1992)	UK (Leicester)	1972-1980	80	1.2	3.5	Yes	Surname	Population
		1981-1989	104	3.1	5.3			
Pinsk (2007)	Canada (Vancouver)	1985-2005	397	6.7	1.0	Yes	Self-reported	Hospital

assessment of the studies was performed by examining the number of studies which fulfilled the following criteria: use of recognised diagnostic criteria, self-reporting of ethnic background and whether the study was population based. The p-value from the test of heterogeneity is given, with the I² value. Size of difference between both groups is reported as a rate ratio, along with corresponding confidence intervals. This is quantified as the incidence in SA relative to the incidence in Caucasians.

Results: Eight studies met the inclusion criteria for Crohn's disease (CD) and Ulcerative Colitis (UC), seven in the UK and one study in Canada (Table 1). The total population was 2,569,074. The UC incidence was higher in SA in 3/4 studies with a rate ratio of UC 1.39 (0.84, 2.32) whereas CD incidence was lower in 5/6 CD studies with a rate ratio of 0.78 (0.22, 2.78) compared with Caucasians (Table 2). There was significant heterogeneity between both UC and CD studies. (I² – 83%, p<0.001 and I² – 95%, p<0.001).

Table 2. Summary statistic of incidence studies showing rate ratio of South Asians to Caucasians

Disease	Number of Studies	Heterogeneity		Effect size	
		I ²	P-value	Rate Ratio (95% CI)	P-value
Crohn's Disease	6	95%	<0.001	0.78 (0.22, 2.78)	0.7
Ulcerative Colitis	4	83%	0.001	1.39 (0.84, 2.32)	0.2

Conclusions: There is a lack of good quality recent data in the literature. One UC study reported a lower incidence rate (Jayanthi) but only studied the Bangladeshi subgroup of the SA population whereas the others reported on a predominantly North Indian population. This finding suggests a difference in the presentation of IBD within the SA population. One study showed a higher incidence of CD in SA group than Caucasians which included a paediatric population. Early environmental influences may be more important for the pathogenesis of CD than UC. We conclude that SA migrants have increased risk of developing UC potentially due to exposure to new environmental factors in the adopted country. Larger prospective population based studies are needed to support these findings including differences between first and second generation migrants to implicate the environmental exposure.

P719**Determinants of tobacco consumption in the Swiss IBD cohort**M. Grueber^{*1}, C. Clair Willi², M. Allez³, L. Biedermann⁴,N. Fournier⁵, A. Schöpfer⁶, S. Vavricka⁷, P. Juillerat⁸, A.J. Macpherson⁹

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Background: Tobacco consumption is an important environmental factor in inflammatory bowel diseases (IBD). Our aim was to identify characteristics associated with smoking in Crohn's disease (CD) and Ulcerative colitis (UC).

Methods: Adult UC and CD patients included in the Swiss IBD cohort study (SIBDCS) from Nov. 2006 to Nov. 2015 were asked about their smoking status. Patients were separated in two groups (active smokers vs. non-smokers). A logistic regression analysis was performed with smoking as main outcome.

Results: 999 UC and 1386 CD patients were included in the study. In the univariate analysis, smoking was positively associated with the female gender in CD patients. Smoking CD patients had more stenosis and used significantly more oral Budesonide, whereas UC patients used more topical treatments. A high anxiety and depression score was significantly associated with smoking among CD patients. The use of invalidity insurance was significantly higher in smoking UC and CD patients in the univariate analysis and was confirmed in the multivariate analysis (OR 1.8 [1.1–3.0], p=0.02 for UC and OR 3.4 [1.3–9.1], p=0.015 for CD).

Conclusions: After adjustment for disease pattern and activity, the only factor significantly associated with tobacco consumption in IBD patients is the need for invalidity insurance.

This positive association between active smoking and invalidity insurance is, however, not specific to IBD patients but also known in the Swiss population

P720**Use of proton pump inhibitors associated with a markedly increased risk of microscopic colitis**O. Bonderup^{*1}, G. Lauge Nielsen², M. Dall³, A. Pottegård³, J. Hallas³

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Background: Microscopic colitis (MC) is a chronic inflammatory bowel disease with unknown etiology. Proton pump inhibitor (PPI) use has been consistently linked to an increased risk of MC. The specific role of the different classes of PPI is unknown. Based on the nationwide Danish registries we explored the association between MC and use of PPI and in addition the effect of different classes of PPIs and dose-dependency. Secondly we explored the effect of concomitant use of PPI and NSAID.

Methods: In a ten-year period (January 2004 to December 2013) we identified 10652 patients with a first-time recorded diagnosis of MC including 6254 (59%) with collagenous colitis (CC) and 4398 (41%) with lymphocytic colitis (LC). MC cases were identified via the Danish Pathology Registry. For each MC case, we sampled 10 population controls. Information on PPI use was obtained from the Danish Prescription Register. The analysis conformed to a case-control design, estimating the odds ratio (OR) for the association between PPI use and the risk MC using conditional logistic regression, while adjusting for potential confounders.

Results: We found strong associations between current PPI use and both CC (adjusted OR [aOR] 8.75; 95% CI: 8.12–9.43) and LC (aOR 5.03; 95% CI: 4.61–5.49). This association was seen across all individual PPIs, however, the strongest association was seen with current use of lansoprazole, for both CC (aOR 20.10; 95% CI: 18.05–22.37) and LC (aOR 7.70; 95% CI: 6.79–8.73). When considering timing, ORs were highest for current use of PPI, while the association quickly diminished when considering recent or past exposure. When analyzing the prescribed strength of PPI, we found no apparent dose-response pattern. The use of NSAID was associated with a modest increased risk of CC (aOR 1.70; 95% CI: 1.55–1.87). However, the combination of NSAID and PPI and was associated with a higher risk for CC (aOR 9.72; 95% CI: 8.65–10.92) compared to the use of one of the drugs alone.

Conclusions: In a large comprehensive case-control study based on nationwide Danish registries we found an increased risk of MC associated with the use of PPI and especially an increased risk with the use of lansoprazole. The combination of NSAID and PPI and was associated with a high risk for CC.

P721

A switch in the prevalence ratio of Crohn's disease vs. ulcerative colitis in Israel between 2003 and 2015 – a report from the epi-IIRN group

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Background: Crohn's disease (CD) has been considered a condition limited mostly to westernized countries, while ulcerative colitis (UC) may be more common in some developing countries. We aimed to utilize data from all four Israeli health maintenance organizations (HMOs), covering 98% of the Israeli population, to determine population-based epidemiological trends of CD and UC.

Methods: IBD patients were identified from 2003 (the first year of computerization in the HMOs) until 2015 and differentiated as CD or UC patients using algorithms validated to accurately identify cases from within the dataset (case ascertainment accuracy: 99% and 94%, respectively). Standardized prevalence per 100,000 population per year were derived from the Israeli National Insurance Institute.

Results: At the end of 2015, a total of 38,291 IBD patients were residing in Israel, corresponding to a prevalence rate of 459/100,000 (0.46%), double the prevalence rate 12 years earlier (0.23%). UC was more prevalent than CD until 2010 after which CD became more common, and this difference has increased each year (CD/UC: 2003- 6306/7665 (p<0.0001), 2010 - 14628/14427 (p=0.1), 2015 - 20196/17810 (p<0.0001) (Figure 1)). Patients in the 25–34 years and 35–44 years age groups contributed most to the upsurge in CD rates, suggesting a link to environmental and economic changes in Israel during childhood years.

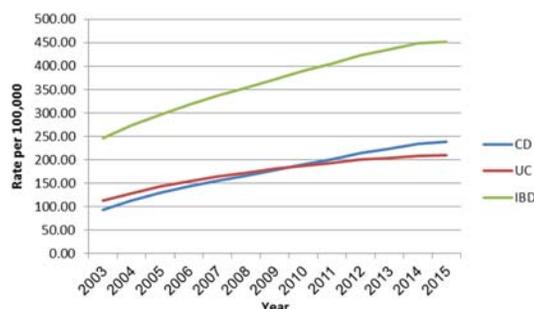


Figure 1. IBD prevalence trends in Israel between 2003 and 2015.

Conclusions: Israeli IBD prevalence is the third highest in the world, and has nearly doubled in the past decade. The increased preponderance of CD over UC has occurred in parallel with an increase in the economic state of Israel; this possible link requires further study.

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P722

Pre-diagnostic serum vitamin D levels and risk of inflammatory bowel disease: a pan-European, nested case-control study

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Background: A causal link between a low vitamin D status and the development of inflammatory bowel disease (IBD) has previously been suggested. The aim of this study was to investigate the association between prediagnostic circulating vitamin D concentrations and dietary intakes of vitamin D, and the risk of Crohn's disease (CD) and ulcerative colitis (UC).

Methods: Among 359,728 participants of the European Prospective Investigation into Cancer and Nutrition cohort, individuals who developed CD or UC after enrolment were identified. Each case was matched with two controls by center, gender, age, date of recruitment and follow-up time. At cohort entry, blood samples were collected and dietary vitamin D intakes were obtained from validated food frequency questionnaires. Serum 25-hydroxyvitamin D levels were measured using liquid chromatography-tandem mass spectrometry. Conditional logistic regression was performed to determine the odds of CD and UC.

Results: Seventy-two participants developed CD and 169 participants developed UC after a median follow-up of 4.7 and 4.1 years, respectively. The median serum vitamin D level was 59.1 nmol/L for CD cases and 60.1 nmol/L for their controls. The corresponding

values for UC cases and their controls were 54.2 nmol/L and 54.9 nmol/L, respectively. Compared with the lowest quartile, no associations with the three higher quartiles of vitamin D concentrations were observed for CD ($p_{\text{trend}}=0.34$) or UC ($p_{\text{trend}}=0.66$). Similarly, no associations were detected when serum vitamin D levels were analyzed as a continuous variable. Dietary vitamin D intakes were not associated with CD ($p_{\text{trend}}=0.39$) or UC ($p_{\text{trend}}=0.83$).

Conclusions: Vitamin D status was not associated with the development of CD or UC. These findings do not suggest a major role for vitamin D deficiency in the etiology of IBD.

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SexDI study – sexual satisfaction in inflammatory bowel disease

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Background: Sexual satisfaction is among the concerns of patients with Inflammatory Bowel Disease (IBD) being rarely addressed in the outpatient clinic and Quality of Life (QoL) questionnaires. At a time where patient-reported outcomes (PRO) grow in importance, the impact of the disease on sexual health must be valued. Objective: To assess the impact of IBD on the sexual satisfaction of patients.

Methods: A cross-sectional, self-administered, multimodal questionnaire was distributed to 18–65 year-old patients at the IBD outpatient clinic. It included the following validated instruments: The Short IBD Questionnaire (SIBDQ), Social Desirability Scale (SDS-SF), Sexual QoL Questionnaire-Male/Female (SQoL-M/F), Nine-item Patient Health Questionnaire (PHQ-9). Comparison with healthy controls. Statistics: ρ (rho) Test, t (t-student) Test and Kruskal-Wallis-Test.

Results: The study included 92 patients (38 Crohn's disease, 54 ulcerative colitis) and 100 healthy controls (49% vs. 43% <40 years old, 58.7% vs. 28% women), most with high-school education (56.5% vs. 60%) and stable relationships (mean 13.3 vs. 13.3 years).

A cut-off = 54 in the SIBDQ was identified to differentiate the self-perception of higher activity/less control of IBD. There was no difference in the social desirability scale in active, inactive and control patients (mean SDS-9 vs. 8.8 vs 9.8), so the reliability of the responses was homogeneous between groups.

The sexual satisfaction of the patients with controlled disease was similar to that of the control group (median 83.3% vs. 84.8%) but it was impacted in active disease (68.6%, $p<0.1$). Similarly, the incidence of depression was equivalent in inactive disease and in controls, being higher in active disease (PHQ-9 median 1 vs. 3 vs. 7, $p<0.05$). Indeed, patient-perceived disease activity was negatively correlated with sexual satisfaction, as measured by SQoL (ρ test, $p=0.01$) and strongly associated with a higher incidence of depression (score PHQ-9, ρ test $p<0.001$). Likewise, the degree of depression evolved alongside with sexual dissatisfaction (tTest, $p=0.002$).

Conclusions: The patient who considers his or hers disease controlled, has the same sexual satisfaction as a healthy individual. Sexual satisfaction is strongly influenced by the IBD activity perceived by the patient, but also by the increase in the degree of depression that the disease activity correlates to. Sexual health should therefore be addressed in the IBD outpatient clinic.

P724**Appendectomy is not a treatment option for ulcerative colitis**

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Background: Ulcerative colitis (UC) is a chronic inflammatory disease usually responding well to anti-inflammatory drugs but many patients will eventually need a colectomy, due to severe acute colitis or chronically active disease. Appendectomy has previously been shown to be associated with a lower risk of developing UC later in life. We aimed to assess the association between appendectomy and disease activity and the risk of having a colectomy in UC patients.

Methods: All patients in Sweden with a UC diagnosis between 1964 and 2010 were identified from the National Patient Register. Information regarding appendectomy with or without appendicitis was gathered, including appendectomy both prior to and after the UC diagnosis. Planned and unplanned hospital admissions for UC as well as colectomy were used as markers of disease activity.

Results: Appendectomy was performed in 2,143 of the 63,711 UC patients, prior to the UC diagnosis in 1,537 patients and after in 606 patients.

In all, 7,690 patients underwent colectomy. The cumulative risk of colectomy for patients without appendectomy was 0.10 (95% CI 0.09 to 0.10) and 0.13 (0.12 to 0.13) after 5 and 10 years, respectively. For patients with appendectomy for appendicitis before the age of 20 and prior to UC diagnosis, the cumulative risk of colectomy was 0.05 (0.03 to 0.09) and 0.07 (0.04 to 0.11), respectively. In multivariable analysis the hazard ratio for this group was 0.44 (0.27 to 0.72) compared to UC patients without appendectomy. Appendectomy prior to UC diagnosis but at age 20 years or older did not affect the risk of colectomy after UC diagnosis (HR 0.97 (0.80 to 1.18)). Appendectomy for appendicitis after the UC diagnosis was associated with an increased risk of colectomy with HR 1.55 (1.20 to 2.02). Appendectomy after UC diagnosis for other reasons did not affect the risk of colectomy (HR 1.14 (0.57 to 2.28)).

Appendectomy prior to UC diagnosis was associated with fewer planned and unplanned admissions for UC (Incidence rate ratio 0.71 (0.64 to 0.77)), whereas appendectomy after UC diagnosis was associated with more admissions for UC (IRR 1.10 (1.00 to 1.21)).

Conclusions: UC patients with a history of appendicitis before the age of 20 years and preceding the UC diagnosis have a lower risk for colectomy. Appendectomy for appendicitis after the UC diagnosis is associated with more admissions and increased risk of colectomy. Appendectomy for other reasons after the UC diagnosis does not seem to affect the severity of UC. Appendectomy therefore does not appear to be a treatment option in UC.

P725**The impact of an integrated model of care for patients with inflammatory bowel disease in Canada**

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Background: Integrated models of care (IMC) for inflammatory bowel disease (IBD) have been implemented to improve the quality of care and disease management, and reduce adverse outcomes. Studies providing a systematic assessment of the impact of IMC for IBD on health care utilization have not previously been undertaken. This study compared health care services and medication use for IBD patients who were and were not exposed to an IMC.

Methods: A retrospective population-based cohort study was conducted between 2009 and 2015 using administrative health data for the province of Saskatchewan (SK), Canada. The SK IMC for IBD (the Multidisciplinary IBD Clinic—MDIBDC) was introduced in 2009. Patients with IBD were identified with a validated administrative case definition applied to hospital and physician billing records. The criteria for measuring exposure to the IMC included baseline and follow-up visits with MDIBDC physicians. Cox proportional hazard regression models with propensity-score matching were used to test for differences in IBD-related hospitalizations, surgeries, and medications use (5-aminosalicylic acid—5-ASA, immune modulator—IM, and biologics) between patients with and without MDIBDC exposure. Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated. Conditional logistic regression was used to test for differences in the probability of corticosteroid dependency (CsD) over a 6-month period.

Results: The study included 2312 IBD patients. In the sample, the mean age was 44.1 (SD=15.8) years, 51.5% were women, 74.7% had urban residence, 39.6% had ulcerative colitis (UC), and 24.3% were defined as exposed. The exposed group had a lower rate of IBD-related surgeries (HR=0.72, 95% CI 0.57–0.91), higher rate of IM (HR=1.75, 95% CI 1.48–2.05), higher biologic use (HR=1.75, 95% CI 1.48–2.05), and lower 5-ASA use (HR=0.79, 95% CI 0.68–0.92) than the non-exposed group. Analyses stratified by disease type revealed a lower rate of IBD-related hospitalization in exposed UC patients (HR=0.71, 95% CI 0.53–0.94). The odds of CsD amongst patients with UC in the exposed group was 0.39 (95% CI 0.15–0.98) that of the non-exposed group. No significant differences in CsD were identified in the full group analysis.

Conclusions: Differences in adverse disease outcomes between exposed and non-exposed patients reflect the improved quality of care provided within an IMC for IBD. Increased use of steroid-sparing maintenance therapies, specifically IM and biologics, is an indicator of improved access to IBD therapies, as is the lower CsD use amongst patients with UC. Integrated models can positively impact the health care outcomes of patients with IBD, and, subsequently, lead to effective use of health care resources.

P726**High mortality risk after first hospital admission for inflammatory bowel disease: a nationwide registry linkage study**

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Background: The aims of this study were to determine the incidence of hospitalization for inflammatory bowel disease (IBD) and to determine outcomes after hospital admission.

Methods: A cohort of patients who were admitted to the hospital because of IBD for the first time between 1995 and 2010 was identified by linkage of nationwide Dutch registries. Incidence rates, mortality risks and causes of death for Crohn's disease (CD) and ulcerative colitis (UC) were assessed. Cox regression models were used to determine differences between CD and UC.

Results: A total of 28,843 individuals (56.0% men, mean age 47.7 years) were at least once hospitalized for IBD. Incidence rates of hospital admission increased from 7.18 to 8.28 per 100,000 person-years in CD and from 5.71 to 6.30 per 100,000 person-years in UC. During a mean follow-up of 5.69 years, all-cause mortality was 15.9% and 21.5% after hospital admission for CD and UC, respectively. Main causes of death were cancer and cardiovascular disease. Patients admitted for UC had a lower risk of all-cause mortality (adjusted relative risk [RR] 0.88, 95% confidence interval [CI] 0.83–0.92), death from cardiovascular disease (adjusted RR 0.89, 95% CI 0.80–0.98) and death from cancer (adjusted RR 0.81, 95% CI 0.74–0.89) than those admitted for CD. No difference in risk of death from colon cancer between CD and UC was observed (adjusted RR 0.89, 95% CI 0.70–1.12).

Conclusions: The incidence of hospitalization for IBD did not decrease over time and the all-cause mortality risk of patients after first admission to the hospital was high.

P727**Change in Crohn's disease behavior in a prospective European population-based inception cohort – the ECCO-EpiCom cohort**

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Background: Crohn's disease (CD) is a progressive disease that over time can lead to the development of complications such as strictures or internal penetrating disease that will ultimately lead to surgery. Only few population-based studies from the biological era and widespread use of immunomodulators have investigated the change in disease behaviour and subsequent risk of surgery in CD.

Methods: The EpiCom-cohort is a population-based cohort of unselected patients with inflammatory bowel disease diagnosed in 2010 in Eastern and Western European centres. Patients were followed prospectively for five years and clinical data were captured throughout the follow-up period and entered in a validated web-based database. Disease behaviour as defined according the Montreal classification as B1: non-stricturing, non-penetrating, B2: stricturing; B3: penetrating based on endoscopy, cross-sectional imaging or surgery. The risk of changing behaviour from B1 to B2 or B3 as well as the risk of surgical resection was analysed by Cox regression analyses using the proportional hazard assumption including multiple covariates (age, gender, disease location, diagnostic delay, smoking status, change in behaviour, geographic region, and early treatment with biologics).

Results: The EpiCom-cohort is a population-based cohort of unselected patients with inflammatory bowel disease diagnosed in 2010 in Eastern and Western European centres. Patients were followed prospectively for five years and clinical data were captured throughout the follow-up period and entered in a validated web-based database. Disease behaviour as defined according the Montreal classification as B1: non-stricturing, non-penetrating, B2: stricturing; B3: penetrating based on endoscopy, cross-sectional imaging or surgery. The risk of changing behaviour from B1 to B2 or B3 as well as the risk of surgical resection was analysed by Cox regression analyses using the proportional hazard assumption including multiple covari-

Table 1. Disease behaviour in Crohn's disease at diagnosis and follow-up

At diagnosis	At follow-up			Total (diagnosis)
	B1: non-stricturing, non-penetrating	B2: stricturing	B3: penetrating	
B1: non-stricturing, non-penetrating	248 (58%)	35 (8%)	12 (3%)	295 (70%)
B2: stricturing	–	80 (19%)	14 (3%)	94 (22%)
B3: penetrating	–	–	35 (8%)	35 (8%)
Total (follow-up)	248 (58%)	115 (27%)	61 (14%)	424 (100%)

ates (age, gender, disease location, diagnostic delay, smoking status, change in behaviour, geographic region and treatment with biologics within 6 months from diagnosis).

Conclusions: In this European population-based inception cohort of unselected CD patients 14% of patients progressed to B2 or B3 after five years of follow-up. The risk of surgery was increased in patients with B1 who progressed to B2/B3. No clinical predictors for progression in behaviour including smoking and treatment with biological therapy could be identified.

P728

Changes in the use of biologics in the treatment of IBD patients over time. Results from a comprehensive Norwegian registry study

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Background: During the last decade, several new and expensive drugs (including TNF α inhibitors and anti-integrins) have been introduced in IBD treatment. Little is known about the overall treatment pattern for these new biologic pharmaceuticals: What proportion of patients eventually receive biologics and how has this changed over time.

Methods: Data was collected from the Norwegian Patient Registry and included information about every individual hospital treatment episode for patients with Crohn's disease and ulcerative colitis from 2008 to 2015 (ICD codes K50 and K51). Altogether 45,767 IBD patients were identified in the registry. The data included a unique patient identifier and information about gender, age, the date of the treatment (month and year) and the use of biologics.

The date of diagnosis was set to the earliest observation in which the individual was observed with a K50 or K51 treatment episode. In order to examine development over time, the patients were stratified based on the year of the first diagnosis. Only patients with at least two registered events in which an IBD diagnosis was used, were included when calculating the results.

Results: During 2010 to 2014, there were 14,168 new IBD patients. 4,796 (33.8%) were diagnosed with Crohn's disease (CD) and 9,372 (66.2%) with ulcerative colitis (UC). Among CD patients the proportion that received a biological pharmaceutical within one year after being diagnosed, increased from 15.4% in 2010 to about 26% in 2013 and 2014. For UC the share increased from 5% in 2010 and 2011 to 10.3% in 2014.

For CD patients, the use of biologics one year after diagnosis increased steadily by about 3 percentage points for every cohort from 2010 to 2013, but there was no increase between 2013 and 2014. For UC patients the increase was more uneven. One year after diagnosis, between 5.1% and 5.6% of the patients from the 2010 and

2011 cohorts had received a biologic. This increased to 7.8% for the 2012 and 2013 cohorts, and among patients diagnosed in 2014 10.3% had received a biologic one year after diagnosis.

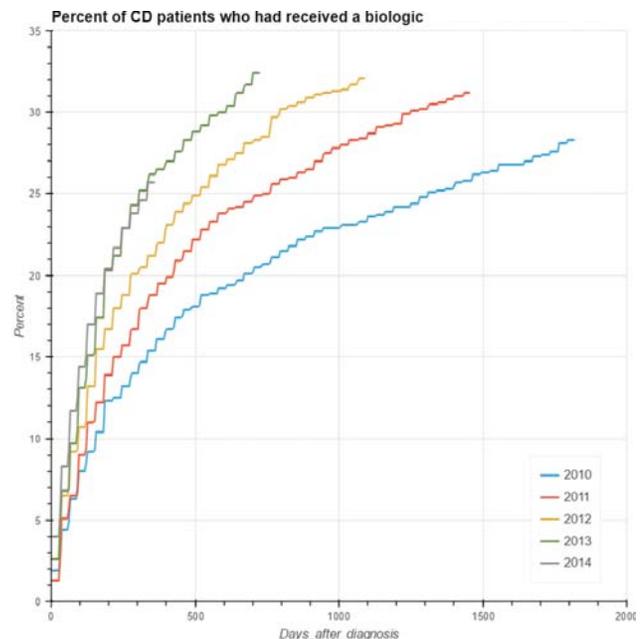


Figure 1. Percent of CD patients who had received a biologic.

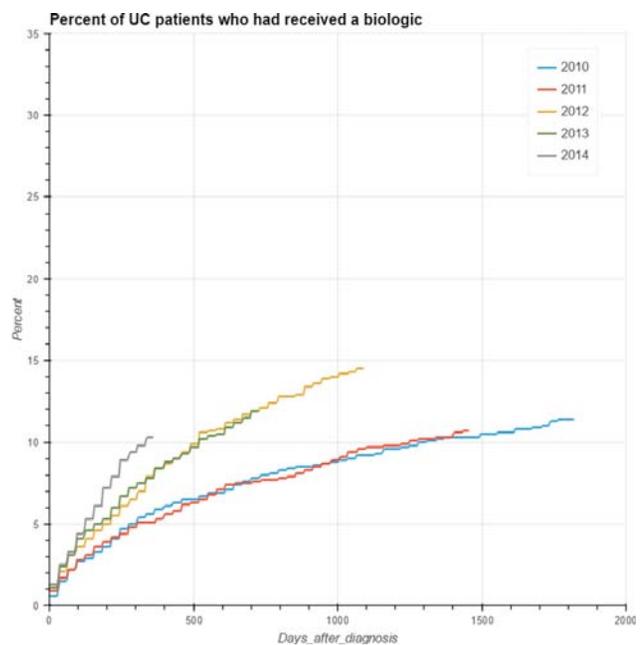


Figure 2. Percentage of UC patients who had received a biologic.

Conclusions: There was a consistent trend towards an increased use of biological pharmaceuticals over time, but it is still a treatment that is only used on a minority of the patients.

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Increased requirement for steroids, thiopurines and intestinal surgery in Crohn's patients who are smokers at IBD diagnosis; a nationwide population based study

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Background: An association between tobacco smoking and outcomes in IBD has been established. We aimed to investigate the impact of smoking status at IBD diagnosis on clinical outcomes including corticosteroid (CS) and thiopurine (TP) use as well as the need for surgery using a nationally representative research database.

Methods: Using the UK Clinical Practice Research Datalink, which contains data for approximately 8% of the UK population, we identified incident cases of patients with IBD between 1998 and 2014. Prescription data for IBD medications including CS and TP were obtained. Surrogate markers for disease severity included early CS use (within 3 months of diagnosis) in ulcerative colitis (UC) and the modified Beaugerie Index in Crohn's disease (CD). Smoking status at diagnosis was defined using Read codes for tobacco consumption. Patients were classified as either smokers or non-smokers at IBD diagnosis. The surgical endpoints were colectomy in UC and first intestinal resection (IR) in CD. Medical endpoints included CS use and TP use. Kaplan Meier survival analysis was used to study differences in the rates of surgery and medication use between smoking subgroups. A multivariate Cox regression model was used to calculate the risk of surgery given smoking status at IBD diagnosis.

Results: 12302 patients with IBD were identified (UC 7497, CD 4805). There were fewer smokers at diagnosis with UC compared to CD (16.5% vs 30.2%, $p < 0.0001$). The proportion of male smokers at diagnosis was higher in UC than CD (56.4% vs 41.2%, $p < 0.0001$). There were no differences in disease severity indices between smokers and non-smokers in either UC or CD. The 1, 3 and 5 year cumulative probability for IR in CD was 5.3%, 9.0% and 10.1% in smokers compared to 4.1%, 6.0% and 7.7% in non-smokers (log rank test for trend, $p = 0.008$). The 1, 3 and 5 year cumulative probability of CS use in CD was 27.1%, 34.6% and 39.4% in smokers and 24.2%, 30.7% and 35.2% in non-smokers ($p = 0.01$). Furthermore, the 1, 3 and 5 year cumulative probability of TP use in CD was 24.3%, 34.1% and 35.3% in smokers compared to 21.7%, 28.5% and 31.9% in non-smokers ($p = 0.001$). In patients with UC, there was no difference in the rates of colectomy, CS or TP use between smokers and non-smokers. In the multivariate Cox regression analysis for patients with CD, smokers at IBD diagnosis had a 27% increased risk of IR compared to non-smokers (HR 1.27, 95% CI 1.02–1.56, $p = 0.03$). No association was found in a similar analysis for colectomy in UC patients.

Conclusions: In Crohn's disease, smoking at diagnosis is associated with increased steroid use, thiopurine use and intestinal resection. Conversely, smoking at diagnosis in ulcerative colitis does not appear to impact on these outcomes.

P730

Disease phenotype of Korean paediatric Crohn's disease patients at diagnosis: a multicentre retrospective comparative study with EUROKIDS

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Background: There is limited data regarding the disease phenotype of paediatric Crohn's disease (CD) patients in the Asian population. We aimed to investigate the disease phenotype of Korean paediatric CD patients at diagnosis according to the Paris classification by comparison with patients from the EUROKIDS registry.

Methods: Paediatric CD patients who were newly diagnosed before 18 years-old from 9 tertiary medical centers in Korea during January 2013 to October 2016 were included in this retrospective study. Medical charts were reviewed and disease phenotype at diagnosis was classified according to the Paris classification. Regarding disease phenotype, only the patients who had conducted a complete diagnostic workup of the entire gastrointestinal (GI) tract were included. A complete workup required ileocolonoscopy, upper GI endoscopy, and small bowel imaging by at least one of the following modalities; magnetic resonance enterography, computed tomography enterography, capsule endoscopy. Comparison was performed by utilizing data from the previously published 5-year analysis of the EUROKIDS registry [1].

Results: A total 230 subjects [150 males (M), 80 females (F)] were included. The median age at diagnosis was 14.7 years (range: 1.2–17.9). No significant difference was observed in M:F ratio compared with EUROKIDS (1.88:1 vs. 1.46:1, $p = 0.088$). A complete workup was done in 213 subjects. The proportion of children <10 years (A1a) was significantly lower in Koreans (6.6% vs. 19.6%, $p < 0.001$). Colonic disease was less prominent (9.9% vs. 27.3%, $p < 0.001$), while upper GI involvement was more prominent in Korean children (60.1% vs. 46.2%, $p < 0.001$). Although no significant difference was observed in luminal disease behaviour, the proportion with perianal modifiers were significantly higher in Korean patients (46.5% vs. 8.2%, $p < 0.001$). Meanwhile, a first-degree family history of inflammatory bowel disease was significantly lower in Korean children (4.8% vs. 10.8%, $p = 0.005$).

Table 1. Comparison of paediatric Crohn's disease phenotype at diagnosis between Korea and EUROKIDS according to the Paris classification

	Korea (n=213)	EUROKIDS (n=582)	p
Diagnosis age, n (%)			
A1a	14 (6.6%)	114 (19.6%)	< 0.001
A1b/A2	213 (93.4%)	468 (80.4%)	
Lower GI tract location, n (%)			
L1	29 (13.6%)	95 (16.3%)	< 0.001
L2	21 (9.9%)	159 (27.3%)	
L3	161 (75.6%)	307 (52.8%)	
No involvement	2 (0.9%)	21 (3.6%)	
Upper GI tract location, n (%)			
L4a	60 (28.2%)	129 (22.1%)	0.006
L4b	45 (21.1%)	97 (16.7%)	
L4ab	23 (10.8%)	43 (7.4%)	
No involvement	85 (39.9%)	313 (53.8%)	
Luminal disease behaviour, n (%)			
B1	183 (85.9%)	477 (82%)	0.241
B2	25 (11.7%)	77 (13.2%)	
B3/B2B3	5 (2.4%)	28 (4.8%)	
Perianal modifier, n (%)	99 (46.5%)	48 (8.2%)	< 0.001

Conclusions: Newly diagnosed paediatric CD patients in Korea are more likely to present at an older age, with more ileocolonic and upper GI tract involvement, and perianal fistulas and/or abscesses, compared to their counterparts in Europe. An underlying genetic difference between races may play a role in the different expression of phenotypes in paediatric CD.

References:

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P731

Abstract has been withdrawn

P732

Clinical characteristics of inflammatory bowel disease in Belgian immigrants from Moroccan and Caucasian origin

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Background: Moroccans are a growing minority in Belgium since the 1960s. Few studies have examined the characteristics of inflammatory bowel disease (IBD) in this population. The aim of our study was to compare IBD characteristics between immigrants from Moroccan and Caucasian origin.

Methods: We performed a retrospective chart review of all first and second generation immigrants with Crohn's disease (CD) or Ulcerative colitis (UC) followed in our IBD Center from 2010 to 2016. Disease characteristics (Montreal classification), clinical variables and treatment were extracted to define disease severity and prognosis.

Results: A total of 83 Moroccans (57 CD/26 UC, 53 men) and 72 Caucasian immigrants (42 CD/30 UC, 37 men) patients were analysed. For CD patients, penetrating disease (26/57 vs 11/42), perineal localisation (24/57 vs 12/42) were more frequent in Moroccan. Although there were no significant differences in medication prescription between the two groups (immunosuppressive:IS (49/57 vs 32/42), biologics (32/57 vs 23/42), there was a higher number of hospitalisations (37/57 vs 15/42) and surgeries (33/57 vs 19/42) in the Moroccan population especially with the most severe disease who needed a definitive stoma (5/57 vs 0/42). For UC patients (26 Moroccans, 30 Caucasians), no differences in localisation, medications

or need for hospitalisation were observed. Colectomy was performed in 4 Moroccans and 3 Caucasians.

Conclusions: We report a higher proportion of CD in Moroccan compared to Caucasian immigrants in our active IBD cohort. Moreover, Moroccan CD patients tend to have more severe disease, characterized by more penetrating disease, more perineal disease leading to higher rates of CD-related surgery and definitive stoma. Further research is required to confirm these observations and determine if these findings reflect genetic or environmental differences.

P733

Past history of bariatric surgery associated with increased risk of new onset inflammatory bowel disease

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Background: Case series suggest a possible association between bariatric surgery and incident inflammatory bowel disease (IBD). The aim of this study was to evaluate the association between bariatric surgery and new onset IBD in a U.S. health claims database.

Methods: We conducted a matched case-control study using medical and pharmacy claims from 2008 through 2012 in a national database from Source Healthcare Analytics LLC. Patients age 18 or older in the database since 2008 were included. New onset IBD was defined as having at least 3 ICD-9 codes for Crohn's disease (CD, 555.x) or ulcerative colitis (UC, 556.x) in 2012 with no IBD code or medication from 2008 through 2011. Each case had up to 10 age group, gender, race, and geographically matched controls with no IBD codes, associated diseases or medications. Bariatric surgery was defined as at least one ICD-9 or CPT code for sleeve gastrectomy, roux-en-Y gastroenterostomy, gastric band, or other gastric bypass prior to first IBD code. Past history of bariatric surgery was determined using ICD-9 code V45.86. Patients with history of peptic ulcer disease or malignancy in the esophagus, stomach, small intestine, or pancreas were excluded. Bariatric surgery was evaluated as recent (code in database timeframe), past history (V45.86 code but no bariatric surgery code in database timeframe), or no history. Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for new onset IBD, CD and UC. Analyses were adjusted for age, obesity, antibiotics, hormone replacement therapy and statins.

Results: A total of 8,968 cases and 42,929 controls were included in the analysis. Adjusting for potential confounders, any bariatric surgery (combining recent and past history) was associated with significantly increased odds of new IBD (OR 1.46, 95% CI 1.09–1.96). Patients who had recent bariatric surgery (within the 4 years prior to diagnosis) did not appear to be at shorter term risk of IBD (OR 0.95, 95% CI 0.58–1.54). However, past history of bariatric surgery was

Table 1. Summary of results

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	Moroccan	Caucasian		Moroccan	Caucasian
	Crohn's disease			Ulcerative Colitis	
Number	57	42		26	30
Median age at Diagnostic	26,1 y	26,7 y	Median age at Diagnostic	29,3 y	34,2 y
Gender	34M/23F	17M/25F	Gender	19M/7F	20M/10F
B1	19 (33%)	22 (52%)	E1	3 (12%)	6 (20%)
B2	12 (21%)	9 (21%)	E2	13 (50%)	9 (30%)
B3	26 (46%)	11 (26%)	E3	10 (38%)	15 (50%)
perineal	24 (42%)	12 (29%)			
IS	49 (86%)	32 (76%)	IS	14(54%)	20 (67%)
Biologics	32 (56%)	23 (55%)	Biologics	11(42%)	11(37%)
Hospitalisations	37 (65%)	15(36%)	Hospitalisations	13(50%)	12(40%)
Surgeries	33(58%)	19(45%)			
Definitive stoma	5(9%)	0 (0%)	Colectomy	4 (15%)	3 (10%)

Table 1. Odds ratios (OR) for new onset CD and UC and gastric bypass surgery

	OR	95% Confidence Interval
CD		
Recent gastric bypass	1.12	0.60–2.09
History gastric bypass	1.86	1.10–3.14
UC		
Recent gastric bypass	0.89	0.40–1.98
History gastric bypass	2.17	1.28–3.66

associated with an increased risk of new onset IBD (OR 1.95, 95% CI 1.36–2.82). This association was stronger for UC than CD (Table 1). Of note, obesity was also associated with new IBD in this cohort (OR 1.50, 95% CI 1.39–1.63).

Conclusions: New onset IBD was significantly associated with past history of bariatric surgery. This potential association should be evaluated in prospective studies.

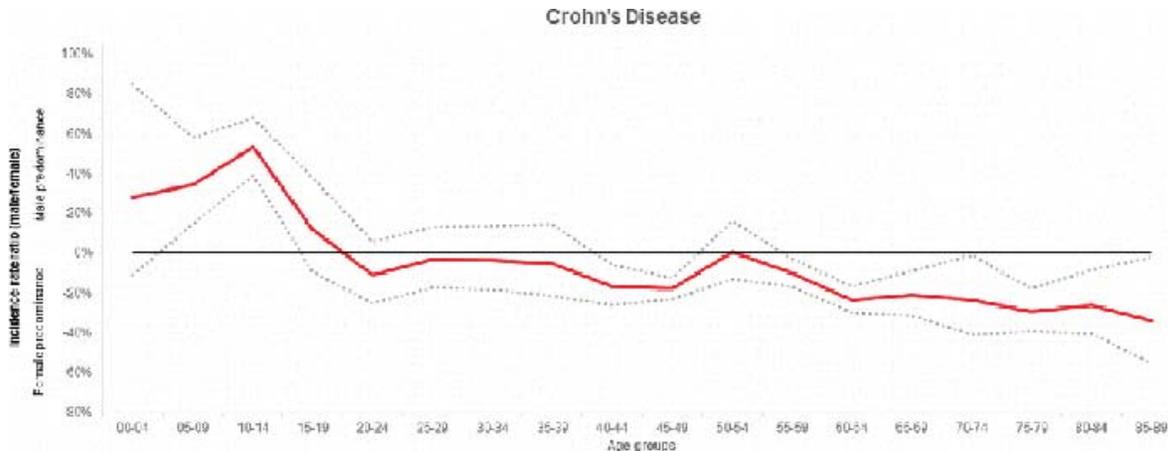
P734
The sex ratio of inflammatory bowel disease varies according to age at onset: results from a worldwide survey

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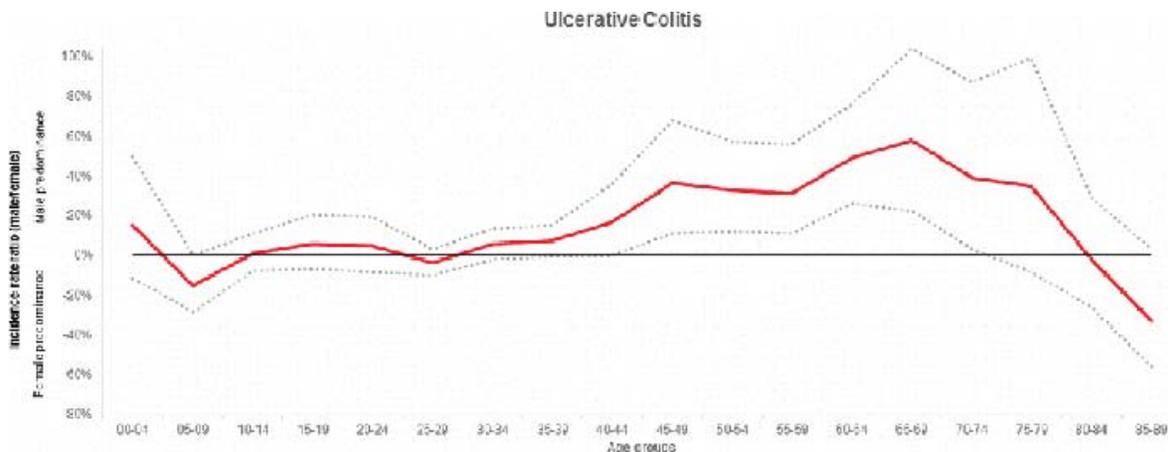
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Background: Among patients with inflammatory bowel disease (IBD), age is a strong and well-known determinant of disease risk. Although peak incidence rates according to age have been widely reported, little is known about how these estimates vary according to sex. We aimed to explore the incidence of Crohn's disease (CD) and ulcerative colitis (UC) according to age and sex in population-based studies across the world.

Methods: A comprehensive literature search was conducted to identify representative population-based cohorts with IBD incidence data available for the full age spectrum starting from birth divided into 5-year or less intervals. Authors and guarantors of these cohorts were invited to share their data as collaborators. Background population data were also obtained. Incidence rates for CD and UC were calculated according to age and sex. We pooled incidence rate ratios



Abstract P734 – Figure 1. Crohn's disease age of onset according to sex worldwide.



Abstract P734 – Figure 2. Ulcerative colitis age of onset according to sex worldwide.

(pIRR) for males:females (M:F) by random-effects meta-analysis according to the method of Desimonian and Laird.

Results: Data from 22 population-based or nationwide cohorts from 1988–2013 were included in the analysis. Among 269,136,094 males and 277,683,752 females, there were 69,689 total cases of CD (32,300 M/37,389 F) and 80,739 total cases of UC (41,807 M/38,932F). In CD, males younger than age 15 had a significantly higher incidence, peaking between age 10–14, compared to females (pIRR age 10–14 M:F 1.53, 95% CI: 1.39–1.68, $p < 0.001$). There was an inversion of sex ratio after age 15, with females having increasingly higher incidence of CD, reaching statistical significance after age 40–44 (pIRR age 40–44 M:F 0.83, 95% CI: 0.74–0.94) [Figure 1]. Age of onset for UC in males and females was similar until age 40–44 (pIRR age 40–44 M:F 1.17, 95% CI: 1.0–1.36), after which males had a significantly higher incidence rate compared to females until age 75 (pIRR age 75–89 M:F 1.39, 95% CI: 1.03–1.87) [Figure 2].

Conclusions: Worldwide, there is significant variability in the sex ratio of IBD according to age at onset with males having higher incidence of CD before the age of 15, after which there is a female predominance, with an opposite trend in age at onset for UC where there is a striking male predominance after age 40. Variations in incidence rates according to sex across the globe may help identify unique, previously unrecognized genetic and environmental risk factors.

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Indirect burden of patients with moderate inflammatory bowel disease in Uppsala County Council, Sweden: a retrospective study using real-world data

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Background: Inflammatory bowel disease (IBD) is often diagnosed in early adulthood in the working-age population and substantial work productivity losses among patients with moderate to severe disease have been reported [1,2]. The aim of this study was to examine the indirect burden among adult patients in the workforce (18–65 years of age) with Crohn's disease (CD) and ulcerative colitis (UC) in a moderate disease state.

Methods: Electronic medical records of patients diagnosed with CD and UC between 2005 and 2014 in Uppsala County Council in Sweden were extracted (N=3,999) and enriched with data from the Swedish longitudinal integration database for health insurance and labour market studies (LISA). Patients were classified into the moderate disease state if (a) they were steroid dependent and (b) they had a Harvey-Bradshaw index score of 8–16 (for patients with CD) or partial Mayo index score of 2–4 (for patients with UC). Medical records that did not include sufficient information to designate reliable scoring were excluded and classification was based on steroid use alone. Indirect burden outcomes were assessed within 2 years after entering the moderate disease state. Annual productivity losses (sick leave and retirement) were collected from the LISA database. Indirect costs were calculated by multiplying the average annual number of sick

leave days times the average annual Swedish salary, adjusting for gender. The average annual Swedish salary from 2014 was 350,400 SEK for women and 403,200 SEK for men (including legislated social fees of 47%).

Results: In this study, 797 patients with CD (of 1,549) and 1,361 patients with UC (of 2,450) were classified as having moderate disease, 698 (88%) and 1,145 (84%) of which were aged between 18 and 65 years and included in the analysis. The average annual sick leave was long: 16 and 9 weeks for CD and UC, respectively (compared with an average 5.6 days/year in Sweden), which equaled an average annual cost of 86,440 SEK for patients with CD and 50,925 SEK for patients with UC. Few patients (17 CD and 21 UC) retired early, but the average age of retirement among those who did was 47 years for both patients with CD and those with UC.

Conclusions: This study demonstrates high indirect costs in moderate IBD, which might be decreased with improved monitoring and treatment and should be taken into account when evaluating new therapies. This is particularly important as IBD often is diagnosed in early adulthood and the incidence now is rising.

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P736

Psychological impact of inflammatory bowel disease: differences by gender and age. The ENMENTE Project

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Background: Inflammatory bowel disease (IBD) may cause psychological morbidity. Age and gender are factors that may condition quality of life perceived by patients and therefore may have important psychological impact. The aim of ENMENTE was to understand the psychological impact of IBD and whether age and gender are factors to be considered in patients' management.

Methods: During April 2016 two surveys were made available online, one for IBD patients, on the ACCU Spain website (Confederation of IBD Spanish Patients' Associations) and another one for physicians (n=665) members of GETECCU (Spanish Group for IBD treatment). Both invited their members to participate by email and the patients' survey was announced in social networks. Closed questions were asked by patients about the impact of IBD on their feel-

Abstract P736 – Table 1

	Gender, n (%)			Age, years n (%)			
	Men	Women	P-value	< 30	30-50	> 50	P-value
Have you ever felt anxious or stressed due to IBD? ^a	98 (38)	253 (48)	0.006	93 (53)	210 (46)	40 (30)	<0.001
Have you ever felt sad or depressed due to IBD ^a	82 (32)	207 (39)	0.001	85 (48)	165 (36)	31 (23)	<0.001
I consider IBD influences on my psychological status ^a	189 (69)	400 (74)	ns	129 (71)	363 (76)	84 (63)	0.008
I consider IBD influences on my personal relationships ^a	142 (52)	313 (58)	ns	100 (55)	286 (60)	59 (44)	0.004
I consider IBD influences on my every-day life ^a	175 (65)	382 (71)	ns	126 (70)	341 (72)	77 (57)	0.005

^aPatients responding always or mostly

^aPatients responding "agree" or "totally agree"

ings of anxiety and depression and how they perceived that IBD influenced their psychological status, relationships and every-day life. Differences by gender and age were analysed with the chi-square test, age ranges were set considering mean age and SD.

Results: The survey was responded by 912 patients. Mean age was 39 years (SD±10), 67% were women. Mean disease duration was 11 years (SD± 9). Up to 58% of the patients described their illness as moderate or severe (56% men/70% women). A total of 45% of patients reported having feelings of anxiety/stress due to IBD "always" or "mostly", whilst the figure for feelings of depression/sadness was 37%. Women ($p<0.05$) and younger patients ($p<0.001$) reported a higher frequency of such feelings in comparison to men and older patients (table). Most patients agreed on that IBD had a negative influence on their psychological status (72%), their personal relationships (56%), and their every-day life (69%). No differences were found by gender, but younger patients perceived a significant higher impact of IBD on all these aspects compared to older patients (Table 1).

On the other hand, younger patients reported to have been referred to consult psychologists less frequently than older patients (13% <30 years, 25% 30–50 years and 28% >50 years, $p=0.002$).

Conclusions: Feelings of anxiety/stress and depression/sadness are frequent in IBD patients, and more frequent in women and younger patients. The latter also perceive a higher impact of IBD on their psychological status and every-day life, although, compared with older patients, they are not more frequently referred to the psychologist. Acknowledgements. Funded by Merck Sharp & Dohme of Spain and endorsed by ACCU España and by GETECCU

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Early life microbial exposure, lifestyle and comorbidity as risk factors for microscopic colitis: a case-control study

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Background: The pathophysiology of microscopic colitis (MC) is not fully understood. A dysregulation of the adaptive immune response of which the maturation and function is imprinted in early life, has been hypothesized. Lack of early childhood exposure to infectious agents and symbiotic microorganisms may increase the risk of MC in

later life. Various other factors (e.g. female hormone exposure, educational level) have been associated with MC, but often with minimal or conflicting evidence. Therefore, we aimed to evaluate whether exposure to (microbial) agents in early life might be protective for MC development and to assess the role of several less well-established risk factors for MC in one study.

Methods: A case-control study was performed including MC cases diagnosed in the southern part of the Netherlands between 2000–2012. Cases were identified in the national pathology registry and biopsy slides were revised to confirm the diagnosis. All included cases were matched to non-MC controls from the same geographical area, based on gender and year of birth. All subjects filled out a questionnaire on various risk factors, including e.g. proxy measures for early life microbial exposure, female hormone exposure, passive smoking and self-reported comorbidities. For the cases, the index date was defined as the date of diagnosis, controls were assigned the same index date as their matched case.

Results: In total, 171 MC cases and 361 controls were included. Based on the univariate analyses a lower educational level, cardiac disease, non-asthmatic pulmonary disorder, gastric disorder, liver disorder, depressive disorder, arthrosis, chronic back pain, rheumatoid arthritis, esophageal disorder and celiac disease (all prior to the index date) were selected for the multivariable analysis. In the multivariable model, current smoking (OR 6.23, 95% CI 3.10–12.49), arthrosis (OR 2.23, 95% CI 1.15–4.34) and a cardiac disorder (OR 3.31, 95% CI 1.31–8.38) were associated with MC. No association was observed for factors related to early life microbial exposure, passive smoking, rheumatoid arthritis, celiac disease or female hormone exposure.

Conclusions: Early life exposure to microbial antigens was not protective for MC in later life. Furthermore, female hormone exposure, educational level and passive nicotine exposure were not associated with MC. We did confirm the association between smoking and MC. Exposure to environmental risk factors in later life may be of relevance in MC pathogenesis and warrants further investigation.

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Assessing aCCess to investigations in IBD (ACCID) – results from an international inflammatory bowel disease survey

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Background: In recent years, several new investigations to aid diagnosis and monitoring of IBD have become available. These include faecal calprotectin (FC), widely regarded as a surrogate for intestinal inflammatory activity and therapeutic drug monitoring (TDM) for thiopurine metabolites and anti-TNF therapy. However, uptake and access has not been uniform. We aimed to assess barriers to access of these investigations.

Methods: Questionnaires were distributed to delegates at the 11th Congress of ECCO. Analysis of responses was performed using R statistical software including binomial linear regression analysis for potential barriers to access, including health economic data extracted from the WHO Global Health Expenditure database. <https://planner.smart-abstract.com/ecco2017/submission/en/abstract/3800/content#>

Results: 195 valid responses were obtained from participants from 38 countries, including paediatricians (14%), adult gastroenterologists (42%) and gastroenterologists-in-training (35%). 135 (39%) of respondents were practicing in an academic hospital. High volume IBD work (≥ 1 IBD patient/day) was reported by 61.8%.

FC was available to 92.3%, most using at least weekly (80.3%). Access to anti-TNF TDM was less widespread (78.9%; $p=0.0002$) and less heavily used (45.8% using at least weekly; $p<0.0001$). Access to TDM for infliximab was better than for adalimumab ($p=0.0004$). Thiopurine TDM was least widely available (67.7%; $p=0.0001$ vs FC, $p=0.02$ vs anti-TNF TDM) but used at an intermediate level where available (56.5% reporting at least weekly usage; $p<0.01$ vs both other groups). There was heterogeneity and lack of consensus when asked to identify situations where they might use each investigation. Access to all 3 investigations within Europe showed a significant East (E)–West (W) and North (N)–South (S) divide. For FC we found W vs E: 95.1% vs 82.0% ($p=0.04$) and N vs S: 97.3% vs 80.4% ($p=0.001$), with similar statistically significant comparisons for both other tests. Multivariable analysis showed that the strongest independent predictors of access to all 3 tests was health-care spending per capita ($p=0.005$ for FC; $p<0.0001$ for both TDM). Working in an academic centre was an independent predictor of access to TDM ($p=0.03$ for anti-TNF; $p=0.02$ for thiopurine). Respondents were more likely to cite cost as a barrier to accessing anti-TNF TDM (30.8%) or FC (24.6%) than thiopurine TDM (12.3%; $p<0.0001$ and 0.003).

Conclusions: Investigations for the purpose of personalizing therapy have revolutionized IBD care. FC, anti-TNF and thiopurine TDM have been incorporated into routine practice in much of Europe. Increased healthcare spending in IBD care with a focus on Eastern and Southern European countries may improve access to these integral investigations.

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Characteristic of IBD related colorectal cancers observed in different Hungarian centers

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Background: Patients with extended, colonic inflammatory bowel diseases (IBD) have an increased risk for development of colorectal cancer (CRC) mainly due to the chronic, uncontrolled mucosal inflammation in the bowel. The aim of our nationwide study was to evaluate the demographic characteristic, the clinical features and the molecular pathogenetic alterations of IBD-associated CRCs in a relatively large cohort of patients.

Methods: Electric medical databases, personal queries and IBD registries have been used for data collection regarding clinical and demographic characteristic of IBD-related CRC. Gene expression profiles of p53, MLH1, MSH2, β -catenin, PTEN, APC, K-ras, Cox-2, NOS, NF κ B and VEGF were also investigated with tissue microarray technique (TMT) in the tumour in selected cases.

Results: In our retrospective observational study between 1976 and 2016, we identified 14 Crohn's disease (CD) and 26 ulcerative colitis (UC) patients with histologically confirmed adenocarcinoma. CRC occurred at a median age of 50 years (min.–max. 34–78) and 56 years (min.–max. 24–87) in patients with CD (female n=5, male n=9) and UC (female n=5, male n=21), respectively. Median time elapsed between IBD diagnosis and the diagnosis of CRC was 18 years. Duke's A, B, C and D stage carcinomas were represented in 18.4%, 39.5%, 21.1% and 21.1%. Among UC patients, 76.9% (n=20) of carcinomas were localized in the rectosigmoidum, 15.4% (n=4) in the other part of the colon and 7.7% (n=2) of the carcinomas were multifocal. Among CD patients, 28.6% (n=4) of the carcinomas localized to the rectosigmoidum, while 71.4% (n=10) in the more proximal part of colon. Overall, 61.9% and 28.5% of UC patients demonstrated extended colitis and left-sided colitis, respectively (mean disease durations of 23 and 18 years). Altogether, 87.5% of UC- and 33.3% of CD-associated CRC seem to be IBD-related according to TMT. The timing between the last endoscopy and the diagnosis of CRC was average 6.5 (1–30) years in those 18 patients, when these data were available.

Conclusions: CRC occurs earlier in IBD than that in general population after a long disease duration and mainly in pancolitis. UC-associated CRC seems to be more distal and disease related, while CD-associated CRC may be more proximal and mainly sporadic. Lack of regular screening can increase the chance of advanced CRC.

P740 What kind of IBD patients succeed in smoking cessation? Insights from the Swiss IBD cohort study

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Background: Tobacco consumption is known to have a differential effect in Crohn's disease (CD) and Ulcerative colitis (UC). Smoking cessation can transiently worsen disease course in UC whereas it should be beneficial to CD patients. Our aim was to identify whether this effect drives success in smoking cessation.

Methods: Retrospective analysis of prospectively yearly collected data from adult UC and CD patients included in the Swiss IBD cohort study (SIBDCS) from November 2006 to November 2015.

Results: 999 UC and 1368 CD patients were included in the study and separated in three groups (smokers, past-smokers and non-smokers at enrollment). In general, past smokers who succeed in smoking cessation are males, older, with a higher BMI ($p < 0.001$). The disease location was less extensive in UC (mostly left sided colitis and proctitis) ($p = 0.121$) and less ileal in CD (compared to active CD smokers) ($p = 0.009$). Concerning treatment, UC past smokers used significantly more topical treatment and CD past smokers required less anti-TNF and conventional immunosuppressants. The disease severity measured by clinical scores and CRP/albumin showed no significant difference.

Conclusions: UC and CD patients in the Swiss IBD cohort who succeed in smoking cessation seem to be patients with a pattern of disease which is less likely to be influenced by smoking. Further investigations are needed to identify whether this phenotype is due to smoking cessation or likely to ease it.

P741 IBD-related work disability in Brazil

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Background: Given the increasing prevalence of Inflammatory Bowel Diseases (IBD) in Brazil [7] and considering that the highest peak incidence occurs in young patients; the work disability generates relevant economic and social impacts. This study aimed at assessing disability due to IBD in the Brazilian population.

Methods: Analysis was obtained through the computerized Single System of Social Security Benefits Information with the crosscheck of

aid pension and disability retirement, for ulcerative colitis (UC) and Crohn's disease (CD) between 2010 and 2014. Additional data were obtained within the platform including the average values, benefit duration, gender, age, and region of the country.

Results: In terms of costs, the value of benefits paid from 2010 to 2014 for IBD was US\$ 98,098,212, representing approximately 1% of the total of all benefits paid by the social security. Benefits paid for CD were higher than for UC, whereas both tend to decrease from 2010 to 2014.

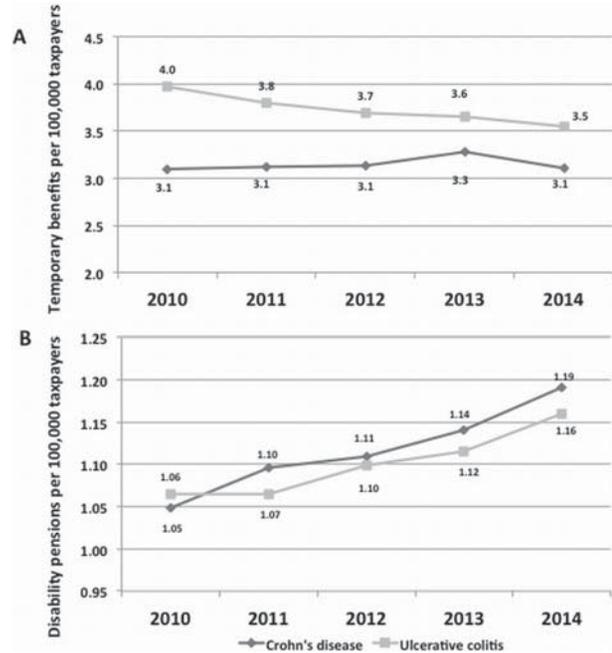


Figure 1. Rates of temporary benefits and disability pensions due to Crohn's disease and ulcerative colitis, per 100,000 taxpayers, from 2010 to 2014.

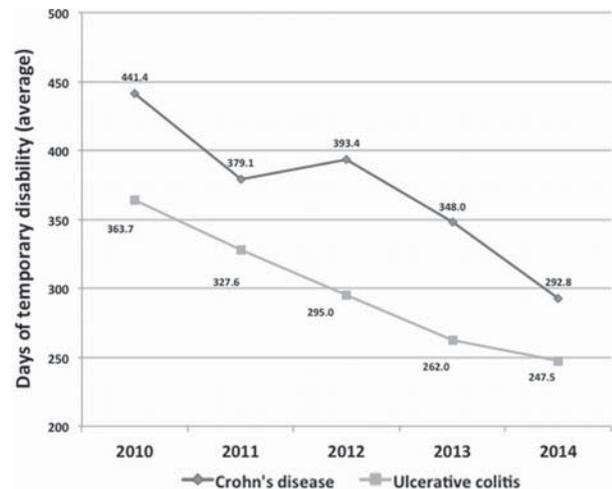


Figure 2. Average number of days of temporary disability due to Crohn's disease and ulcerative colitis, from 2010 to 2014.

Temporary disability was more frequent in UC, while permanent disability in CD. Temporary disability affected younger patients with CD than UC. Rates for temporary and permanent disability were greater among women. Temporary work absences due to UC and CD were greater in the South, while the lowest rates in the North and Northeast, due to CD. Permanent disability rates were higher in the South (UC) and Southeast (CD). Absence from work was longer in CD (355 days) compared to UC (305 days), reaching almost a year.

Abstract P741

Table 1: Rates of active temporary benefits due to IBD per 100,000 taxpayers from 2010 to 2014

IBD subtype	2010		2011		2012		2013		2014	
	CD	UC								
Gender										
Male	2.8	3.5	2.8	3.4	2.9	3.2	2.9	3.2	2.6	3.0
Female	3.6	4.6	3.5	4.4	3.5	4.3	3.8	4.2	3.7	4.2
Age range (years)										
< 19	0.7	0.9	0.7	0.7	0.7	0.7	1.0	0.7	1.0	0.7
20–29	2.5	2.5	2.7	2.2	2.8	2.2	2.9	2.4	2.8	2.6
30–39	3.8	4.3	3.7	4.1	3.8	4.0	3.7	4.0	3.7	3.8
40–49	4.0	5.6	3.9	5.7	3.8	5.5	4.2	5.0	3.5	4.7
50–59	2.8	5.8	3.0	5.3	3.0	5.0	3.4	5.1	3.3	4.7
> 60	1.3	2.3	1.2	2.5	1.2	2.3	1.2	2.3	0.8	2.3
Region										
North	0.78	3.02	1.08	3.41	1.04	2.85	1.35	2.55	0.99	2.85
Northeast	1.73	3.43	1.54	3.57	1.51	3.42	1.72	3.48	1.78	3.46
Southeast	3.48	4.01	3.60	3.59	3.69	3.48	3.80	3.43	3.57	3.33
South	4.26	5.34	4.25	5.35	4.02	5.28	4.31	5.20	4.01	4.92
Center-West	2.04	2.25	1.96	2.43	2.18	2.67	2.16	2.74	2.18	2.60

Rates are defined according to gender, age ranges, and the geographic region of origin. CD, Crohn’s disease; UC, ulcerative colitis.

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Table 2: Rates of disability pensions due to IBD per 100,000 taxpayers from 2010 to 2014

IBD subtype	2010		2011		2012		2013		2014	
	CD	UC								
Gender										
Male	0.90	0.96	0.95	0.96	0.97	1.00	1.02	1.03	1.04	1.06
Female	1.24	1.21	1.29	1.20	1.28	1.22	1.29	1.22	1.38	1.29
Age range (years)										
< 19	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
20–29	0.23	0.12	0.25	0.12	0.26	0.14	0.25	0.13	0.25	0.14
30–39	0.96	0.71	0.97	0.71	1.00	0.71	1.03	0.74	1.07	0.77
40–49	1.86	1.81	1.95	1.79	1.99	1.84	2.10	1.84	2.14	1.90
50–59	2.07	2.69	2.20	2.70	2.09	2.73	2.07	2.74	2.15	2.73
> 60	2.01	3.65	1.93	3.36	1.84	3.34	1.93	3.32	1.85	3.20
Region										
North	0.21	0.78	0.20	0.79	0.18	0.83	0.18	0.79	0.20	0.79
Northeast	0.41	0.96	0.47	0.95	0.46	0.97	0.50	0.96	0.55	0.99
Southeast	1.40	1.12	1.45	1.11	1.49	1.11	1.51	1.14	1.58	1.20
South	1.09	1.28	1.18	1.31	1.17	1.49	1.25	1.52	1.28	1.58
Center-West	0.35	0.60	0.37	0.60	0.38	0.59	0.40	0.58	0.44	0.58

Rates are defined according to gender, age ranges, and the geographic region of origin. CD, Crohn’s disease; UC, ulcerative colitis.

Conclusions: IBD-related work disability rates are much longer in Brazil, compared to the ones seen in developed countries [1]. Reduction trends may reflect improvements in access to health care and medication. Vocational rehabilitation programs may positively impact social security and quality of life of patients.

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Arterial stiffness as a marker of vascular aging in IBD patients – a pilot study

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Background: Chronic systemic inflammation can contribute to development of arterial stiffness increase and accelerated vascular aging. Recent research has demonstrated higher risk of developing atherosclerosis in inflammatory bowel disease (IBD). Noninvasive measurement of aortic pulse wave velocity (PWV) has predictive value for future fatal cardiovascular events and total cardiovascular mortality. The aim of our study was to assess the level of arterial stiffness by measuring aortic PWV as an index of arterial stiffness in IBD patients.

Methods: We conducted a pilot observational study on a cohort of IBD patients during the period from December 2015 to October 2016. We measured PWV with validated, noninvasive oscillometric device (Tensiomed Arteriograph device (Medexpert Ltd., Budapest, Hungary)) in all patients enrolled in this study. Select laboratory data were collected, as well as patients' medical history relevant for the analysis.

Results: A total of 40 patients diagnosed with IBD with median age of 31 years (range: 18–66 yr) were enrolled: 24 Crohn's disease (CD) patients – median age 28.5 yr (range: 18–58 yr, 62% males), and 16 ulcerative colitis (UC) patients – median age 41.5 yr (range: 18–66 yr, 62% males). Mean±SEM PWV value was 8.11±0.35 m/s, 7.83±0.28 m/s, and 8.52±0.78 m/s for IBD, CD and UC groups, respectively. There was no statistically significant difference between the CD and UC in PWV values (p=0.34) nor age (p=0.10). Structuring (Montreal classification-B2) and penetrating phenotype (B3) of CD were associated with higher PWV values comparing to non-structuring, non-penetrating phenotype (B1) (8.23±0.43 m/s (n=8) and 8.39±0.6 m/s (n=7) vs 7.03±0.28 m/s (n=9); p=0.033 and p=0.057, respectively). Significant correlation was found between PWV values and patients' age (p<0.0001, r=0.71) and cholesterol levels (p=0.0206, r=0.3649). Also, patients on steroid therapy (n=8) had higher measured PWV values than the ones on immunomodulatory therapy (n=13) (9.29±0.88 m/s vs 7.58±0.42 m/s), although this result did not reach level of statistical significance (p=0.06).

Conclusions: According to our data, CD phenotype and patients' age have a significant impact on arterial stiffness in IBD. Higher PWV values in B2 and B3 CD phenotype could be an effect of more pro-

found systemic inflammation in these patients. Also, higher PWV values in steroid therapy subgroup could be related to current disease activity. There seems to be no difference in aortic PWV between CD and UC patients. However, next step in our research is to measure PWV in a larger cohort of patients with a goal to further elucidate the differences within IBD patient groups, according to disease phenotype, disease length and treatment regimens.

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What information is available on the internet and social media for faecal microbiota transplantation?

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Background: The use of the internet has become an increasingly popular resource for medical information. Various investigators have critically evaluated the websites and the patient-oriented medical information on internet in the past and found them scientifically inaccurate and incomplete [3–7]. Faecal microbiota transplantation (FMT) has changed the treatment of *Clostridium difficile* with cure rates of 81% following one infusion of FMT [1], further studies have since validated these findings [8]. The National Institute of Health and Care excellence recommended the use of FMT for recurrent *C. difficile* as studies have shown it to be over 90% effective in achieving remission [1,5]. It is not known in the UK the uptake and utilisation of this treatment and how readily available it is. The Medicines and Healthcare Products Regulatory Agency has now classified FMT as a medicine [2] and hence should be only utilised in strict clinical settings

Methods: We searched Facebook, Twitter, Google and YouTube using the words “Faecal Microbiota Transplantation” and “FMT”. A sub search using the term “FMT clinics” was also searched in Google We then categorised the results into: education material by medical professions, information from generic hospital and clinic information, information from scientific journals or books, Communication between healthcare professionals to patients, Education material by another group, charity, support group, news article, self-administration group and medical professional clinic. We utilised the first 50 hits on each site. We analysed the percentage of articles that fell outside regulated medical practice.

Results: Google, YouTube, and Facebook had a variety of information regarding FMT available. Nine out of fifty (18%) of the top 50 google searches can be considered articles that fall outside regulated practice. YouTube highlighted four videos describing how to self-administer FMT, one of these was for the treatment ulcerative colitis. Fourteen percent of the top fifty YouTube videos fall outside regulated practice and 8% of the top 50 Facebook searches falling outside regulated clinical practice. A Search for “FMT clinics” found 48 of the top 50 advertising to clinics within the UK, both advertising FMT outside regulated practice. One of these clinics advertise FMT treatment for a variety of conditions including inflammatory bowel disease, multiple sclerosis and Parkinsons disease, all of which so far have limited data on efficacy and safety.

Conclusions: Clinicians and patients need to be aware of the resources available through social media and the internet. It should be appreciated that some websites fall outside regulated clinical practice. Private clinics offering FMT need to ensure that they are offering FMT within a regulated framework.

P744 Risk factors for faecal incontinence in patients with Crohn's disease

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Background: Faecal incontinence (FI) has a great impact on daily (quality of) life and many patients are too embarrassed to report it spontaneously. Prevalence of FI in patients with Crohn's disease (CD) has barely been studied and little is known about factors predicting FI in these patients. To estimate its prevalence and evaluate potential causes in patients with complex CD, we studied a tertiary CD population and related outcome with quality of life.

Methods: Consecutive patients with CD treated between 2003 and July 2013 at our centre were identified in the prospectively maintained departments' IBD-database. A questionnaire was sent out in October 2013 to evaluate current complaints of FI, perianal disease and the Faecal Incontinence Quality of Life questionnaire. Demographic characteristics and medical history were collected by use of the IBD-database and additional chart review. Multivariate regression analysis was performed.

Results: The questionnaire was responded by 325 out of 528 patients (62%). Median age of patients was 42 years (range 18–91), 215 (66%) were female and diagnosis of CD was established for a median period of 12 years (interquartile range 6–21). FI was reported by 65 patients (20%), median St. Marks Incontinence score was 11. FI was associated with liquid stools ($p=0.0001$), previously performed IBD-related bowel resections ($p=0.001$), stricturing behaviour of disease ($p=0.02$) and perianal disease ($p=0.03$). Quality of life (lifestyle, coping, depression, embarrassment) was poor in patients with FI, particularly in patients with more frequent episodes of incontinence.

Conclusions: Prevalence of FI in a tertiary CD population is substantially higher than in the community-dwelling population. Considering the reduced quality of life in incontinent patients, active questioning to identify FI is recommended in those with liquid stools, perianal disease or previous (intestinal or perianal) surgery. Multimodality treatment is proposed due to the high impact on quality of life.

P745 Impact of migration on IBD incidence in 8 European populations: results from Epicom 2010 inception cohort study

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Background: Europe has experienced an influx of migrants from Africa and Middle East over the last 5 years. Previous studies have shown that migrants moving to developed countries develop the higher incidence of the host country. We aimed to obtain data on incidence of inflammatory bowel disease (IBD) according to country of origin from the Epicom 2010 inception cohort before this significant migration flow to define the current epidemiology and how this might guide future studies.

Methods: Eight populations from 6 countries in the Epicom collaborative group took part. A new ethnicity field was created and integrated onto the existing validated Epicom database. The participants were asked to submit data on the country of origin of each patient from the 2010 inception cohort. Census data was used to provide the number of people in the background population and each incident case was categorised into indigenous vs migrant groups. Patients born in the host country but with a migrant background were classified as migrant. Crude incidence was calculated as cases/100,000/yr.

Results: Five populations had <13% migrant population (Table 1). Six regions had <5 migrants diagnosed with IBD. In the UK (Brent and Harrow population) the number of IBD cases was 31 in the indigenous population and 43 in migrants with a non-adjusted incidence rate of 15.5/100,000/yr and 15.7/100,000/yr respectively. Similarly, in Denmark (Herlev) the incidence for indigenous and migrant groups was 21.6/100,000/yr and 19.1/100,000/yr.

Conclusions: The 2010 cohort shows limited migration in most European participating countries except for the UK where the majority were South Asians. Incidence rates for migrant and indigenous populations were similar and reflected expected high incidence of western world. The incidence rate in migrants was higher than expected for people coming from less developed countries, which supports hypothesis of the influence of environmental factors. There may be differences between UC and CD but the numbers were too small to explore this distinction. The study was limited by the small migrant population with IBD and incomplete data from two regions. The anticipated change in population demographics following the recent influx of migrants to Europe presents a unique opportunity to study evolution of IBD with migration and explore putative environmental factors. The data from our study will set a baseline on which to compare future trends in disease epidemiology.

Abstract P745 – Table 1. Crude incidence of IBD in Indigenous and Migrant groups in 8 European populations from 2010 Epicom cohort.

Region	No. of cases	IBD Cases by Country of origin				Background population			Crude incidence by country of origin (100,000/yr)	
		Indigenous	Other	S Asia	Not documented	Total	Indigenous (%)	Migrant (%)	Indigenous (%)	Migrant (%)
Amager, Denmark	23	21	1	0	1	133986	109852 (81.2)	24134 (18.8)	19.1	4.1
Herlev, Denmark	48	40	5	0	3	211400	185277 (87.6)	26123 (12.4)	21.6	19.1
Hull and East Yorkshire, UK	91	83	1	0	7	334,179	327,789 (98.0)	6,390 (2.0)	25.3	1.6
Brent and Harrow, UK	76	31	13	31	1	487,554	197,753 (40.5)	289,801 (59.5)	15.7	15.5
Padua, Italy	46	19	4	0	23	210,301	190,532 (90.5)	19,769 (9.5)	10.0	20.2
Vigo, Spain*	102	75	2	2	23	-	-	-	-	-
Tartu, Estonia	30	27	1	0	2	319,813	289,254 (90.4)	30559 (9.6)	9.3	3.3
Malta	40	39	1	0	0	412,655	407290 (98.4)	5365 (1.6)	9.6	18.6

*No census data available

P746 Clinical characteristic of Crohn's disease patients in Polish population

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Background: There is a common impression that the incidence and prevalence of Crohn's disease (CD) in the Polish population have been rising in recent years. In 2005, a nationwide Crohn's disease registry in Poland was established to collect demographic and clinical data of patients diagnosed with Crohn's disease.

The aim of presented study was to characterise demographic and clinical features of Polish population with CD, based on national registry data.

Methods: In a collaborative, prospective registry of a consecutive CD patients conducted in 95 gastroenterology centers across the country 5942 adult patients have been enrolled. Patient's phenotype according to: Montreal classification, demographics, smoking, family history, comorbidity, extraintestinal manifestation, medical treatment and surgical interventions have been evaluated.

Results: The age of diagnosis of CD in Polish population was under 40 in more than 77% of patients [22.8% <16 (A1), 55.2% 17–40 (A2)] and only in 22% over 40 (A3). Although there was no gender difference in the overall population (males/females ratio 1.025), males predominated among young patients (759/565 in <16 group and 1723/1474 in 17–40 group, $p < 0.001$). Males more often sustain penetrating disease and localization in ileum and upper gastrointestinal tract. On the other hand females more often suffer from extraintestinal manifestations. The location of the disease was as follows: ileal (L1): 13.4%, colonic (L2): 30.3%, ileocolonic (L3): 56%, upper gastrointestinal tract (L4): 9.9%. The disease behaviour presented: non stricturing, non penetrating (B1): 58.6%, stricturing (B2): 28%, penetrating (B3): 19.8%, perianal disease (p): 26.4%. The disease was more common in urban areas and in patients with higher education. Family history was positive in 4.4%. Rheumatoid arthritis among women (2.6%) and ankylosing spondylitis among men (1.1%) were the most prevalent coexisting diseases. There were more smokers among men than women (15.6% vs. 11.0% $p < 0.001$). Smoking was associated with a higher risk of strictures (36.4% vs 28.5%, $p < 0.001$), abscesses (19.3% vs 15.3%, $p = 0.013$) and over-

all need for surgery (41.8% vs 30.5%). However smokers less likely suffer from extraintestinal manifestations and localization in upper gastrointestinal tract. 31.6% of the patients had at least one surgery. **Conclusions:** The prevalence of IBD in this cohort falls in the intermediate range of that reported for white populations in Europe and North America. Young age of diagnosis, smoking and male gender are the main risk factors for the complications, which will require surgery. Future studies are needed to examine more local risk factors and epidemiologic time trends.

P747 Extracolonic and colonic cancer risk in patients with ulcerative colitis and primary sclerosing cholangitis

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Background: Ulcerative colitis (UC) and primary sclerosing cholangitis (PSC) frequently co-occur. Ulcerative colitis in PSC patients represents a distinctive phenotype characterized by a milder clinical course and inflammation but increased risk for colorectal cancer (CRC) and other solid tumors. We aimed to investigate these correlations in our IBD cohort.

Methods: We evaluated medical charts from patients diagnosed with UC alone and PSC/UC in our referral center for inflammatory bowel diseases from 2011–2015. Descriptive statistical analysis was conducted for comparison of clinical characteristics between two groups. Multivariate logistic regression was performed to identify the association of PSC with overall cancer, CRC and other tumors outside the digestive tract. Analysis was adjusted for age, gender, immunomodulator and biologics use. A two-sided p -value < 0.05 indicated independent statistical significance.

Results: A total of 349 patients with UC and 25 with distinctive PSC/UC phenotype were identified. Patients with PSC/UC were younger (38.4 ± 10.85 vs 45.53 ± 16.02 ; $p = 0.029$), diagnosed for UC at younger age (28.04 ± 9.64 vs 36.35 ± 15.29 ; $p = 0.005$), more likely to be male compared to the patients with only UC ($p = 0.013$) and have pancolitis at initial presentation (94% vs 43%; $p < 0.001$). PSC/UC patients were less likely to require UC-related hospitalization, steroids, immunomodulators and biologics but these differences were not statistically significant. PSC/UC patients had significantly increased overall risk of cancer compared to UC patients (OR 3.66; 95% CI: 1.17–11.41; $p = 0.025$). Regarding CRC incidence PSC/UC patients revealed also a significantly increased risk compared to UC patients (OR 7.80; 95% CI: 1.75–35.20; $p = 0.008$).

Conclusions: PSC/UC patients represent a distinctive phenotype with male predominance, younger age and pancolitis in most patients. PSC/UC phenotype is associated with increased risk for CRC and increased overall risk for cancer. It is possible that we failed to find the connection between other specific solid tumors and PSC/UC except cholangiocarcinoma due to a relatively small sample size. However, it is important to maintain rigorous surveillance programme in patients with PSC/UC phenotype regarding cancer.

P748 High stress and significant decrease in productivity in caregivers of IBD patients

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Background: Inflammatory Bowel Diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are known to alternate episodes of active disease with frequent symptoms with periods of remission. This significantly impacts everyday life of the IBD patient but it does not stop there. Caregivers of IBD patients, usually spouses, partners or friends, assist them with medical responsibilities and daily activities. In this study, we target to assess the impact associated with caregiving for an IBD patient to provide decision support for potential interventions.

Methods: IBD patients of the UCLA Center for Inflammatory Bowel Diseases and their self-identified caregivers were approached through email, in the outpatient clinic and the Medical Procedures Unit (MPU) to fill out online questionnaires; the Work Productivity and Activity Impairment questionnaire (WPAI), the short Inflammatory Bowel Disease Questionnaire (sIBDQ) for QoL and the Mobile Health Index (mHI) for disease activity. The caregivers filled out the Zarit Burden Interview (ZBI) and a caregiver version of the WPAI. Both IBD patients and their caregivers provided information about their medical history and demographics. The results were assessed for caregiver burden and potential predictors of this burden.

Results: 143 IBD patients (42.8±15.3 years, 55.2% females, 74.1% employed, 48.9% CD) and 65 caregivers (47.3±15.4 years, 46.2% females, 69.3% wife/husband of patient, 69.2% employed) were included in the study. The mHI showed that 73.7% of the IBD patients were in remission. Also, 12.3% of the caregivers suffer from a chronic disease themselves. An average of 9±22 hours were spent on caregiving per week. Due to caregiving, 27.3% of the employed caregivers had missed (4±8 hours) work and 51.1% had experienced decreased productivity at work. Additionally, 40% of caregivers experienced mild to moderate burden and 36% felt stressed because of caregiving. Also, the ZBI showed that 46.9% of caregivers felt they could do a better job in caregiving. The odds of caregiver burden were increased for IBD patients with active disease (OR 13.1; 95% CI: 2.75–63.07) compared to remissive IBD patients.

Conclusions: When looking at the impact of IBD on the caregivers of patients, our results show, that even when IBD patients are in remission, there is still significant impact. Caregivers are stressed about the future and their productivity is affected. Although this problem tends to be regularly unnoticed by physicians, interventions could possibly be tremendously valuable in providing support to caregivers of IBD patients.

P749 Impact of psycho-social variables on the activity of inflammatory bowel disease

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Background: While the medical causes for exacerbation of Inflammatory Bowel Disease (IBD) are well known, the impact of psycho-social variables on the activity of Crohn's disease (CD) and ulcerative colitis (UC) are poorly understood. We determined the impact of psycho-social variables in active CD and UC.

Methods: Our ongoing nation-wide psycho-social research in IBD has generated data on 818 patients. UC patients with Simple Clinical Colitis Activity Index >3 and CD patients with Harvey-Bradshaw Index >5 were entered in a cross-sectional study. Patients completed demographics, economic status (ES), medical history, and six psychological questionnaires: Brief Symptom Inventory (GSI, psychological stress measure), List of Threatening Experiences Questionnaire (LTE, exposure to major stress events), Brief COPE Inventory (coping strategies), Satisfaction with Life Scale (SWLS), SF-36 (generic health-related quality-of-life measure yielding Physical Health and Mental Health scores). Data are means (SD) or medians (IQR).

Results: The cohort comprised 122 UC patients (age 38.6 (14.0) years, 60.0% women, disease duration 8.0 (3.0–14.0) years, 40.5% smokers) and 305 CD patients (age 45.2 (15.1) years, 60.1% women, disease duration 9.0 (4.0–16.0) years, 2.6% smokers). Psychological scores for UC vs. CD were: GSI 1.24 (0.8) vs. 0.9 (0.8) p<0.001, LTE 2.0 (1.0–4.0) vs. 1.5 (0–3.0), COPE Emotion-focused-strategies 24.5 (5.7) vs. 23.0 (5.7) p<0.03, COPE Planning-focused-strategies 16.4 (4.5) vs. 15.4 (4.2) p<0.04, COPE Dysfunctional-strategies 23.7 (5.7) vs. 22.0 (5.0) p<0.01, SWLS 20.1 (8.0) vs. 21.0 (8.0), SF-36-Physical 37.8 (29.2–44.6) vs. 38.5 (32.4–46.1), SF-36-Mental 37.8 (30.0–45.6) vs. 33.0 (26.6–44.6). ES was moderate (3 on scale 1–5) in UC and CD. UC disease activity was significantly associated with female gender, age, ES, GSI, LTE, all COPE strategies, SWLS and both SF-36 (p<0.02–0.001). CD activity was significantly associated with work status, smoking, ES, GSI, LTE, Dysfunctional COPE, SWLS and both SF-36 (p<0.05–0.001). A multiple linear regression model was created for UC (adjusted R square 0.11, model significance <0.001) and CD (0.185, <0.001). UC activity was predicted (R squared change) by GSI (9.1% of the variance), ES (6.9%), COPE Planning (4.2%), LTE (1.3%). CD activity was predicted by LTE (5%), GSI (4%), older age (1%).

Conclusions: In this model, psychological stress impacted on both active UC (GSI) and active CD (LTE), whereas economic status impacted on UC only. Planning-focused coping was significant for active UC but not CD. Additional research is required to determine whether other psycho-social variables predict activity in these diseases.

P750 Prevalence and risk factors of cholelithiasis in patients with Crohn's disease

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Background: In thus far published literature, the cholelithiasis in patients with Crohn disease (CD) is twice more frequent than in the general population, the reported prevalence ranges from 13% to 34%. The reason for this difference has not been satisfactorily explained. The aim of our study was to assess the prevalence of cholelithiasis in patients with CD and analyze the risk factors of gallstone formation.

Methods: We retrospectively evaluated all CD patients who underwent an abdominal ultrasound performed by one sonographer at a single tertiary IBD center between years 2007 and 2015. Medical records were reviewed and patients demographics, behavior, localisation, duration and number of flare of CD, number and type of bowel resections, number and length of total hospitalization, number of total parenteral nutrition treatment and presence of cholelithiasis

and its characterization were noted. An univariate and a multivariate analysis were performed using logistic regression analysis (with cholelithiasis as the dependent variable). Prevalence and odds ratios were calculated with their 95% confidence intervals.

Results: In total, 111 CD patients (median age 38 [21 to 77 years]; 53% of males) were evaluated. We observed 13 cases (12%) of cholelithiasis confirmed by ultrasound, all cases were cholecystolithiasis. The majority of patients with cholelithiasis remained asymptomatic during follow-up mean 141 months, only 5 (4.5%) cases had biliary symptoms. The prevalence of cholelithiasis was more common in fistulizing CD compared with the inflammatory behavior of CD, 20% vs 4.9%. The median age of CD patients with cholelithiasis was higher compared to patients without cholelithiasis, 53 vs 38 years, respectively. We observed no association between cholelithiasis and CD localisation, duration and number of flares, neither with number and type of bowel resections, number of hospitalizations and parenteral nutrition episodes.

Conclusions: Cholelithiasis is a frequent complication of CD. In our cohort, the prevalence of cholelithiasis in CD patients was 12%. In multivariate analysis only fistulizing CD and median age were the only significant risk factors of cholelithiasis.

P751 Trends in incidence of inflammatory bowel disease in northwest Greece

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Background: Inflammatory bowel disease (IBD) is changing profile and surveys conducted in areas with homogenous population have shown important changes in incidence. Herein we present a large Greek population based study for IBD in a well-defined area of Greece.

Methods: A retrospective epidemiological survey was conducted for the years 1982–2015. Only cases that met the diagnostic criteria of IBD at least twice in a time span of six months or more were included in the study. Confidence intervals were calculated at the 95% level of significance using the form of the Poisson distribution. The referral population was derived from the 2011 census. All numbers were calculated for every 105 inhabitants.

Results: In total we recorded 1647 patients with IBD, of whom 1018 were males and 619 were females. The mean age of the patients was 50.59±15.35. It was also found that the first peak regarding the number of patients per 5-year classes, located in the class of 45–50, with a constantly increasing number of patients under 25 years old. Men are more affected than women (2:1) and Ioannina patients have the most severe extraintestinal manifestations. The mean annual incidence of Crohn's disease was 2.36/100000 (1.16–3.56) and of ulcerative colitis was 7.31/100000 (4.85–9.75). We also recorded 97 patients with indeterminate colitis. In our previous epidemiological registry for the whole period 1981–1997 the mean annual incidence of CD was 0.5/100000 and of UC was 6.6/100000.

Conclusions: This recent population based IBD registry in our area shows that incidence of Crohn's disease is increasing more rapidly compared to UC (also increasing) and so the ratio gap of UC to CD is also decreasing, showing similarities in IBD epidemiology pro-

files like in Northern European countries. This changing profile of Crohn's disease strengthens the hypothesis of some environmental factor(s), which, probably in correlation with the genetic factor(s), are responsible for the expression of IBD

Genetics

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Abstract has been withdrawn

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X-linked inhibitor of apoptosis protein genetic variants in paediatric-onset inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD) has a multifactorial aetiology, with complex interactions between genetic and environmental factors. Recent studies have suggested an increasing spectrum of human monogenic diseases that can present with IBD-like intestinal inflammation. Mutations in X-linked inhibitor of apoptosis protein (XIAP) result in an X-linked recessive disorder whose phenotype is highly heterogeneous with respect to age at presentation and severity of disease and is poorly understood. Due to X chromosome inactivation heterozygous female carriers can also be symptomatic. Although a severe phenotype with infantile onset disease and predisposition to hemophagocytic lymphohistiocytosis (HLH) or X-linked lymphoproliferative syndrome (XLP) is recognized, one recent study has reported XIAP variants in 4% of male pediatric IBD patients.

Methods: 1250 individual Hospital for Sick Children pediatric IBD patients have undergone whole exome sequencing in collaboration with the Regeneron Genetics Center. Within the cohort, 39 variants were called across the XIAP gene – 29 of which were high quality, rare (maf <0.01), protein coding variants predicted to be deleterious. 13 of these variants were present in 15 affected patients all of which have been Sanger validated. Case notes were retrospectively reviewed to ascertain phenotypic features of IBD in these 15 pediatric patients.

Results: Of the 15 patients (80% males), 14 (93%) were diagnosed with IBD. 13 (92%) of these with Crohn's disease and 1 (7%) with ulcerative colitis. At the time of diagnosis, CD involved small bowel and colon (L3) in 50% children, colon (L2) in 14% and ileum (L1) in

28%. 21% of the children had perianal disease, with a further 21% having extra intestinal manifestations of IBD (erythema nodosum, fevers, large joint arthritis). A further infant was diagnosed with primary HLH and received a bone marrow transplant. This infant did have some gastrointestinal involvement with diffuse damage noted in the colonic mucosa and frequent apoptotic cells. 14% of these children had a first degree relative with IBD. 21% underwent ileocaecal resection with 57% progressing to biologic therapy. Patient samples, monocytes, are now undergoing a functional test to determine tumour necrosis factor (TNF) production of monocytes in response to NOD2 stimulation by muramyl dipeptides (L18-MDP) for the functional diagnosis of XIAP deficiency.

Conclusions: Analysis of this large pediatric cohort confirms the highly varied phenotypic spectrum of IBD associated with XIAP mutations. Functional studies may more completely explain the observed variation.

P755

NUDT15 polymorphism is associated with thiopurine-related leukopenia independently of 6-thioguanine nucleotide levels in Korean paediatric inflammatory bowel disease patients

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Background: Polymorphisms in the *NUDT15* gene are associated with thiopurine-related myelosuppression in patients with inflammatory bowel disease (IBD). We aimed to investigate factors associated with leukopenia including *NUDT15* polymorphisms in Korean paediatric IBD patients during treatment with thiopurines.

Methods: This retrospective study was conducted in 167 paediatric IBD patients who had performed *NUDT15* genotyping and had been treated with azathiopurine (AZA) from January 2006 to August 2016 at the Department of Pediatrics, Samsung Medical Center. Subjects were divided into 3 groups according to *NUDT15* activity based on *NUDT15* diplotypic groups; normal activity (wild type), intermediate activity (heterozygous at a single variant with one prototype allele) and low activity (with both variant allele). The lowest white blood cell count during AZA treatment as well as 6-thioguanine nucleotide (6-TGN) levels, AZA dosage, concomitant drug usage, *TPMT* polymorphism status, and other clinicodemographic factors were investigated.

Results: *NUDT15* groups of normal, intermediate, and low activity consisted of 71% (119/167), 27% (45/167), and 2% (3/167) of the enrolled subjects, respectively. Leukopenia was observed in 16% (19/119), 44% (20/45), and 100% (3/3) of the normal, intermediate, and low activity groups ($p < 0.001$), and early leukopenia (within 8 weeks from AZA initiation) in 1% (1/119), 2% (1/45), and 100% (3/3) of each group, respectively ($p < 0.001$).

Among patients with leukopenia, 6-TGN levels were significantly lower in patients with low activity compared to intermediate activity (median 91.8 vs. 365.6, $p = 0.025$) and to normal activity (median 91.8 vs. 308.3 pmol/8 × 10⁸ RBC, $p = 0.024$).

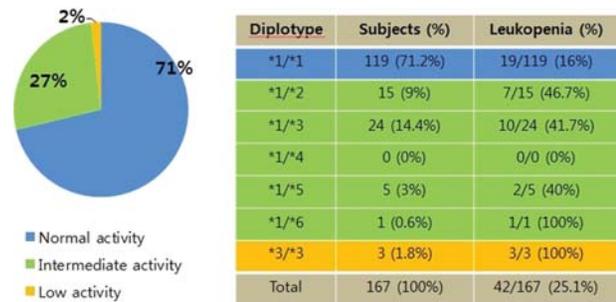


Figure 1. Composition of subjects and leukopenia occurrence according to *NUDT15* activity.

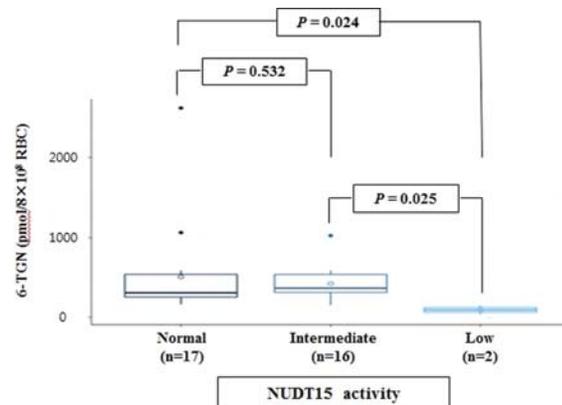


Figure 2. 6-TGN levels according to *NUDT15* activity in patients with leukopenia.

According to multivariable logistic regression, *NUDT15* polymorphism was the only factor associated with leukopenia (odds ratio=4.719, 95% confidence interval=1.986–11.214, $p < 0.001$). Among patients with *NUDT15* variants, no significant difference was observed in 6-TGN levels between patients with and without leukopenia (median 343.9 vs. 273.1 pmol/8 × 10⁸ RBC, $p = 0.088$).

Conclusions: *NUDT15* polymorphism is the major factor associated with thiopurine-related leukopenia in Korean paediatric IBD patients under AZA treatment, which is independent of 6-TGN levels. Genetic evaluation of the *NUDT15* gene is required in order to prevent leukopenia during AZA treatment.

P756

Diagnosing rare inherited disorders using targeted next generation sequencing in patients with early-onset inflammatory bowel disease: a population-based study

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Background: Several recent referral center studies showed that a significant proportion (3–10%) of children with early-onset (EO, defined by an age at diagnosis <12 years) inflammatory bowel dis-

ease (IBD) present with an underlying monogenic disorder. Currently, more than sixty disorders of this type have been identified and their pathophysiological mechanisms are very heterogeneous. Most of them affect the intestinal epithelial barrier and are associated with defects in phagocytosis, immune deficiency, or are hyper- and auto-inflammatory disorders. However, they are all characterized by an EO intestinal inflammation.

Methods: Using a next-generation sequencing (NGS) of the 63 genes whose abnormalities are responsible for these disorders, and a targeted CGH array analysis of their chromosomal loci, 91 patients with an initial diagnosis of EO-IBD between 1988 and 2004 (54% of the whole EO-IBD cohort) issued from EPIMAD population-based registry were screened; 71 with Crohn's disease and 20 with ulcerative colitis.

Results: Analysis isolated 24 patients (26.4%) with very rare or not yet reported potential pathogenic variants in a total of 17 genes. Seven of them (7/91; 7.6%) had a genotype compatible with one of the tested disorders: Burton agammaglobulinemia, familial diarrhea, familial C γ 2 defect, hyper-IgM syndrome or Omenn syndrome. The remaining 17 patients (17/91; 18.7%) were heterozygous carriers of gene variants involved in autosomal recessive traits. The genotype identified in these patients were not likely to be the underlying cause of one of these disorders. However, it cannot be excluded that they may contribute to IBD as suggested by the unusually high prevalence of these genotypes.

Conclusions: Our study issued from a population-based registry, provides further evidence to recommend screening for inherited disorders using targeted NGS in children with an EO-IBD with the potential to enhance optimal selection of treatment options and adequate counseling of families. This study also indicates that targeted NGS used in this study may be an adequate and efficient tool for the reappraisal of the diagnosis in these patients.

P757

Genotype-serotype interactions shed light on of the pathophysiology inflammatory bowel diseases

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Background: Multiple genetic variants are associated with inflammatory bowel diseases (IBD) but their role in IBD pathophysiology is mostly unclear. Variants in *NOD2* and *ATG16L1* genes were related to defects in microorganism sensing in IBD. These variants are more prevalent Crohn's disease (CD), but not ulcerative colitis (UC), compared with controls. Serologic responses may reflect loss of tolerance towards luminal microorganisms. The study aim was To evaluate the effect of having variants in *NOD2* and *ATG16L1* genes on serologic responses in IBD patients

Methods: IBD patients and healthy controls were recruited in a tertiary IBD Center. *NOD2* variants (1007fs, G908R, R702W) and the *ATG16L1* A300T variant were analyzed in leukocytes DNA using TaqMan chemistry. Anti-glycan-antibodies: Anti- *S. cerevisiae* antibodies (ASCA), anti-mannobioside carbohydrate antibodies (AMCA), anti-chitobioside carbohydrate antibodies (ACCA) and anti-laminaribioside carbohydrate antibodies (ALCA), were analyzed using Elisa.

Results: Patients [144 CD, 195 UC of whom 126 underwent pouch

surgery (pouch group)], and healthy controls (90) were recruited. *NOD2* G908 allele was detected in 15% of CD patients compared with up to 4% in the other groups. The *ATG16L1* A300T variant was detected in 61% of controls compared with 79–85% in the IBD groups ($p < 0.05$). ASCA levels were elevated in CD compared to all other groups ($p < 0.01$). CD patients with the *NOD2* 1007fs variant had increased ASCA levels compared with CD patients negative for the variant (64% vs. 36% positive ASCA, $p < 0.01$, and 78.0 ± 31.1 IU vs. 52.9 ± 50.5 IU absolute levels, $p < 0.05$). No increased ASCA levels were detected in CD patients with the missense *NOD2* variants compared to those without the variants. Similarly, pouch patients having the *NOD2* 1007fs variant had elevated ASCA levels with 33% of them showing positive ASCA levels compared to 8% in these without this variant ($p < 0.05$). The 1007fs variant, detected in two UC patients and six controls, did not affect serologic responses. ACCA levels were highest in CD, and significantly elevated in UC compared to normal controls ($p < 0.05$). Positive ACCA was detected in 26% of CD patients having an *ATG16L1* A300T variant (either heterozygote or homozygote state) compared with zero among those without the *ATG16L1* A300T variant ($p < 0.01$). Concordantly, ACCA levels were doubled in CD patients with compared to those without the *ATG16L1* A300T variant ($p < 0.05$).

Conclusions: Genetic variants impact serologic responses in CD and pouch patients, but not in UC and healthy controls. The difference in genotype-serotype interactions may imply diverse response towards microorganisms in IBD patients with different genetic backgrounds, such as the *NOD2* and *ATG16L1* functional variants.

P758

Elevation in ribosomal and cell cycle gene transcription in macroscopically normal colonic tissue from Icelandic patients with ulcerative colitis

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Background: A complex interplay of genetic and environmental factors are implicated in the pathogenesis of ulcerative colitis (UC), resulting in an abnormal immune response and subsequent destruction of the colonic epithelium. The Icelandic population has a restricted gene pool with extensive medical records in combination with one of the highest incidence of UC in the world [1]. We aimed to assess the exomic genetic data and colonic transcriptomics of patients with UC and healthy controls to identify novel deleterious mutations and its influence on the colonic mucosa.

Methods: We performed exome sequencing and whole genome wide microarray analysis on macroscopically normal colonic mucosa from patients with a histological diagnosis of UC and healthy patients with no family history of UC undergoing colonoscopy. Gene-ontology analysis was used to identify common processes and pathways differentially expressed in diseased tissue. Exon sequencing screening for rare or novel mutations was performed on both cohorts.

Results: Non-inflamed colonic tissue from UC patients demonstrated significant alteration in the transcriptomic profile when compared with control tissue. Over 2,000 genes were differentially expressed in the rectum. Gene-ontology analysis identified up-regulation in genes associated with cell cycle and protein metabolism in patients with

Abstract P758 – Table 1. Significantly enriched deleterious mutations in the Icelandic UC cohort with corresponding allele frequency from EXAC and UCLex variant databases

Gene name	Variant	ID	Consequence amino acid	CADD	Condel	EXAC non-finnish European	UCLex	UC ICE	Chi-square p-value	Yates corection
TPMT	6_18130918_T_C	rs1142345	missense Y/C	19.88	deleterious	0.040	0.035		0.138 (0.0001)	
TPMT	6_18139228_C_T	rs1800460	missense A/T	21.7	deleterious	0.036	0.028		0.138 (0.0001)	
SLC26A3	7_107427322_A_C	rs34407351	missense C/W	13.76	deleterious	0.049	0.046		0.103 (0.014)	

UC. Exome sequencing identified 2 missense mutations in thiopurine S-methyltransferase (TPMT) in 7/13 of the UC biopsies compared to 1/14 controls. The mutations identified are known to result in a loss of enzyme function leading to high levels of toxic metabolites from thiopurine analogues, which cause liver toxicity and bone marrow suppression. [2] This variant seems to be significantly more prevalent in this population. We identified 2 significant possibly damaging mutations which have influence on rectal gene expression.

The mutations correspond with differential expression of SPOP with TPMT variant and DUOXA2 and DUOX2 with SLC26A3 variant.

Conclusions: Rectal mucosal samples from UC patients show an elevation in cell cycle activity and protein metabolism. The perceived increase in the TPMT variant would suggest screening of the UC population to avoid the serious toxicity associated with thiopurine analogue therapy. Significantly enriched deleterious mutations in the UC cohort, also have an influence on rectal gene expression of DUOXA2, DUOX2 and SPOP.

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P759

MiRNA expression patterns in colon of active and inactive ulcerative colitis

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Background: MicroRNAs (miRNAs) are highly tissue-specific, small non-coding RNAs that post-transcriptionally regulate gene expression. These molecules are strongly implicated in the pathogenesis of various immune-related diseases, including ulcerative colitis (UC). Recent studies identified numerous frequently deregulated miRNAs in UC, but there is a lack of information on miRNAs which are deregulated in different forms of the disease's severity. To get further insight into the pathogenesis of UC, the aim of this study was to examine miRNA profiles in active and inactive forms of UC.

Methods: In the discovery phase, small RNA transcriptomes of 76 individuals (HC =32, UCa =23, UCi =21) were sequenced using Illumina HiSeq 2500 NGS platform. Small RNA-seq data pre-processing and quantification were performed using miRDeep2 package (reference database miRBase v20). Normalization, quality control, statistical analysis, and assessment of miRNA differential expression were performed using DESeq2 package. Validation of the most def-

erentially expressed miRNAs was determined in the independent cohort of 122 individuals (HC =38, UCa =38, UCi =36) using Custom TaqMan[®] Low Density Array (TLDA). The TLDA expression data was normalized using the $\Delta\Delta CT$ method to the expression values of U6 snRNA, statistical analysis was performed by using HTqPCR package. In order to identify the overall similarity structure of the miRNA expression profiles, a multidimensional scaling (MDS) analysis using Spearman's correlation distance (1-correlation coefficient) was performed.

Results: The comparative analysis of small RNA-seq data identified 108 differentially expressed miRNAs between active UC and normal controls. In contrast, in inactive UC vs. normal controls, 31 miRNAs were found to be differentially expressed. Comparison of the miRNA expression profiles between active UC and inactive UC identified 74 differentially expressed miRNAs. To further validate the findings of small RNA-seq data, 22 highly differentially expressed miRNAs were selected for TLDA analysis in the independent cohort. The expression levels of 11 miRNAs showed significant differential expression in the same direction as in the sequencing data. The MDS analysis either on small RNA-seq or TLDA data revealed two clearly resolved clusters corresponding to active UC and healthy controls and one intermediate cluster corresponding to the inactive UC.

Conclusions: The expression profiles of miRNAs differ among active UC, inactive UC and healthy controls. The patients with inactive UC have an intermediate miRNA expression profile that has similarities to both healthy and active UC-affected individuals.

P760

microRNA expression profiling of inflammatory bowel disease

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Background: Crohn's disease (CD) and ulcerative colitis (UC) are the two major diseases that make up the inflammatory bowel disease (IBD). The etiology is multifactorial, is an interaction between individual genetic characteristics, predisposition and environment. These factors must be involved in the modification of the immune response with consequent formation of altered inflammatory response. Studies indicate that several genes, in addition to those involved in the modulation of the immune response, are differentially expressed in patients with CD. vsUC. Considering that microRNAs (miRNAs) are important gene expression regulators with a role in human diseases, including inflammatory and chronic degenerative diseases, they may be good candidates to investigate as biomarkers with diagnostic, prognostic and therapeutic applications. An important feature of miRNAs is their stability and reliable detection in body fluids.

Methods: A meta-analysis was performed for the identification of miRNA expression data in IBD. Inclusion and exclusion criteria were applied and 10 studies were selected, from which relevant miRNAs

with statistically significant, increased or decreased expression as compared to controls were identified. We also collected information on the type and number of analyzed samples (serum, plasma or tissue) with CD or UC, type of platforms used for analysis of global miRNA expression and data validation, author name and date of publication. Significantly deregulated miRNAs were used in bioinformatic analysis to predict the target genes regulated by these miRNAs. Prediction analyzes of miRNA target transcripts and enrichment of biological functions of the target genes were performed.

Results: The results showed 6 CD miRNAs with increased expression and 51 UC. On the other hand, miRNAs with decreased expression were found on 51 CD and 26 UC.

The miRNAs that showed the greatest number of interactions with IBD deregulated genes were let-7a-5p, let-7b-5p and miR-199a-5p, miR-150-5p, miR-362-3p and miR-224-5p. For patients with RCU, deregulated miRNAs were miR-155-5p, miR-24-5p, miR-335-5p and miR-16-5p. Such miRNAs may play an important role in the molecular mechanisms of disease. In addition, results were used to identify gene interactions and biological processes within inflammation and immune response. Studies such as this may contribute to the identification of miRNAs and target genes as useful biomarkers for the development of new therapeutic strategies for patients with IBD.

Conclusions: miRNA-mRNA networks identified may play important roles in the development and progression of inflammatory bowel disease. Future validation studies with large patient cohorts are required to demonstrate the role of miRNAs and target genes in IBD.

P761

Gene expression differences between Crohn's disease aphthous ulcers and healthy Peyer's patches highlights potential treatment strategies

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Background: The earliest macroscopic lesion in Crohn's disease (CD) is the aphthous ulcer, which overlies Peyer's patches and lymphoid follicles. Our aim was to characterize differences in gene expression of aphthous ulcers and Peyer's patches.

Methods: Biopsies were obtained from the terminal ileum of 12 patients (6 with CD, 6 healthy controls). Aphthous ulcers and adjacent unaffected mucosa were obtained from CD patients, and Peyer's patches and adjacent mucosa from the controls. All patients were medication-free, except one. RNA was extracted using Qiagen kits. NextSeq 500 libraries were constructed using NextSeq 500/550 High output kits (Illumina) in a 150 bp paired-end format. Transcripts were assessed for quality using FASTQC, trimmed using Trimmomatic, and aligned to the human reference genome using *subread* mapper. Fragment counts were obtained using *featureCount*, and expression values normalized using the trimmed mean of M-values normalization method (TMM). Differential gene expression analyses were performed using generalized linear models in edgeR. Cell-specific gene expression was determined using *ImSig*.

Results: We obtained 36 million tags per sample, 87% were retained for downstream processing, and 93% of these mapped to the human genome. 685 genes were significantly differentially expressed between aphthous ulcers and Peyer's patches, all were upregulated in aphthous ulcers. Differential gene expression analysis revealed 34 pathways that were upregulated in aphthous ulcers relative to Peyer's patches. Receptors for the constant region of immunoglobulin (Ig) G were represented in 13 of these pathways. Expression of the high affinity FCGR1A (CD64), and low affinity FCGR3A (CD16), FCGR2A and FCGR2C (CD32), was significantly upregulated in aphthous ulcers ($p=1.14E-12$), but not the inhibitory FCGR2B (CD32B). Other pathways that were highly upregulated in aphthous ulcers included those involved in responding to bacteria, leukocyte chemotaxis, inflammatory response, and creation of C2 and C4 activators. *ImSig*, which is capable of using transcriptome data to indicate cell types and their activation state, revealed that core marker genes for plasma cells were overrepresented in aphthous ulcers relative to Peyer's patches and unaffected/normal mucosa.

Conclusions: The most significantly upregulated Fc gamma receptors in aphthous ulcers are the major receptors expressed on monocytes/macrophages, which are involved in regulating innate and adaptive immune responses, as well as plasma cell survival (FCGR2B), making them an attractive target for immunotherapy.

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Gene expression profiling of immune adaptive response in the colonic mucosa from patients with ulcerative colitis

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Background: Ulcerative Colitis (UC) is caused by an aberrant immune response. Recent advances highlight the crucial role of the ubiquitination pathway dependent autophagy targeting of intracellular pathogens has implications for regulation of inflammatory responses. **Methods:** We studied a total of 100 patients with definitive diagnosis of UC (50 active and 50 in remission) and healthy control group (50 subjects) without endoscopic evidence of intestinal inflammation. In all groups, the gene expression was measured by RT-PCR.

Results: Patients with UC in remission had significantly higher IRGM gene expression in the colonic mucosa compared to active UC patients and normal controls ($p=0.012$ and $p=0.013$). The medical treatment response was associated with high gene expression of IRGM ($p=0.001$). Conversely, XBP1 and AGR2 gene expression was decreased in remission UC compared to active UC patients and controls ($p=0.04$ and $p=0.04$). The ORDML3 expression was decreased in patients with active UC compared to UC patients in remission and the normal control group ($p=0.024$ and $p=0.0001$). The ORDML3 levels were decreased in UC remission compared to the control group ($p=0.003$). The patients with active UC had significantly higher FCGR2A gene expression in colonic mucosa compared to remission UC patients and controls ($p=0.035$ and $p=0.050$). TNFRS14 gene expression was increased in patients with active UC compared with remission UC and controls ($p=0.010$ and $p=0.000$). The LAMP3 expression was increased in patients with active UC compared to UC patients in remission and the control group ($p=0.020$ and $p=0.0005$). The patients with active UC had significantly higher HSPA5 and UBE2L3 gene expression in colonic mucosa compared to

controls ($p=0.007$, $p=0.007$). Conversely, CUL2 gene expression was decreased in active and remission UC groups compared to controls ($p=0.000$ and $p=0.020$). The UBD gene expression was decreased in patients with active UC compared to UC patients in remission and the control group ($p=0.022$ and $p=0.015$). Conversely, DOK3 gene expression was decreased in active and remission UC groups compared to controls ($p=0.024$ and $p=0.010$). The SNX20 expression was decreased in patients with active UC compared to UC patients in remission and the control group ($p=0.000$ and $p=0.00001$). The gene expression of LSP1, CTLA4 and HSP9 were higher in patients with active UC compared to remission UC ($p=0.003$, $p=0.008$ and $p=0.036$) and controls ($p=0.001$, $p=0.010$, $p=0.035$). CTLA4 gene was associated with histological activity index score ($p=0.05$ OR=14, 95% CI: 0.83–235).

Conclusions: This is the first transcriptomic analyses of a panel genes in the colonic mucosa from Mexican patients with UC.

P763

Fucosyltransferase 2 non-secretor status in Crohn's disease: a prospective observational analysis

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Background: The FUT2 gene encodes fucosyltransferase 2 (FUT2), regulating intestinal antigen secretion and bacterial adherence. FUT2 homozygous mutations (FUT2M) and subsequent non-secretor status is associated with Crohn's disease (CD). A nucleotide polymorphism encoding a nonsense variant may predispose to CD by disrupting bacterial adherence or mucin fucosylation. This alters bacterial and mucous protection against pathogens, causing immune disequilibrium and mucosal inflammation. FUT2 products also interact with the IL 12/23 inflammatory pathways. Supporting genome wide association studies strongly associate homozygous FUT2 SNPs in strong linkage disequilibrium (LD) (rs602662 (A), rs676388 (C), rs492602 (G), rs504963 (A), rs601338 (A), rs485186 (G)), non-secretion, and CD. rs601338 (W143X) is the common null allele in Caucasians associated with the ABO non-secretory phenotype.

Methods: We conducted a cross-sectional observational study of consecutive adult CD outpatients at the McGill University Health Center (2013–2015). Clinical and biochemical data were prospectively collected at a single routine office visit. We analyzed associations between CD and FUT2 mutation status.

Results: Sixty-two CD patients were recruited. FUT2M homozygotes (rs602662, rs601338 or any mutation in LD) were detected in 27% of CD (17/62). Compared to Wild type ($n=18$), CD FUT2M homozygotes ($n=17$) had less penetrating CD (18% vs. 56%, $p=0.02$) and higher clinical remission without biologic or immunomodulator therapy (47% vs 6%, $p=0.006$). The latter was not observed in heterozygotes (22%, $n=27$, $p=0.15$). CD FUT2M homozygotes had similar disease location in the ileum (L2 $p=0.31$) and colon (L1, L3, $p=0.56$). Similarly, patients with homozygous rs601338 ($n=15$) had increased clinical remission rates without biologic or immunomodulator therapy (53% vs 5%, $p=0.0016$) compared to patients with wild type status ($n=19$). This was not observed in heterozygotes (24%, $n=25$, $p=0.09$). Both rs601338 homozygotes (20%) and heterozygotes (24%) had less penetrating disease than Wild type (53%,

$p=0.0495$, 0.0478). rs601338 homozygotes (67%) but not heterozygotes (56%) had more luminal phenotype compared to non-mutants (32%, $p=0.042$).

Conclusions: FUT2 homozygous mutations in CD was associated with a milder disease course: lower rates of penetrating disease and higher rates of remission without need for biologic or immunomodulator therapy. FUT2 may play a role in the natural history of CD through modification of expression of adherence molecules and gut dysbiosis. Further studies are needed to confirm these findings.

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Response to thiopurines is independent of ATG16L1 genotype

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Background: Thiopurines, like azathioprine (AZA) and 6-mercaptopurine (6-MP), are effective in maintaining remission in Crohn's disease (CD). Due to potential adverse effects and the increased availability of biological therapies, their role might be questioned. We looked at clinical characteristics associated with an increased response to thiopurines. Moreover, ATG16L1 T300A genotyping has recently been suggested to identify patients who will benefit most from thiopurine treatment [1]. Hence we evaluated this single nucleotide polymorphism (SNP) in our cohort.

Methods: Medical records of 230 British CD patients were retrospectively assessed. Response to thiopurines was defined as continued usage up to chart assessment or termination because of prolonged disease remission on thiopurine monotherapy; non-response as requirement for significant additional therapy (>1 course corticosteroid/year or addition of biologics) after 4 months on thiopurine. Patients who stopped thiopurines because of intolerance or immediately started combo therapy were excluded from genetic association analysis. Genotyping data (rs2241880, T300A) were available for 128 patients (UK IBDGC). Association analysis was performed via PLINK (chi-square test). A p -value <0.05 was considered significant.

Results: Most (87.0%) of the 230 included patients (111 men, median age at diagnosis 21 years) were administered AZA, with 23.9% ever receiving 6-MP. 24.8% of all patients had to stop thiopurines due to side effects (6 leukopenia, 5 abnormal LFT's, 6 pancreatitis, 1 lymphoma and 39 patients - intolerance unknown). A response rate of 57.8% was observed in patients who tolerated therapy. No difference in response rates was noticed depending on either disease location, disease behaviour, sex or smoking status. Conversely, absence of perianal disease was significantly associated with response to thiopurines (OR=2.8, $p=0.003$). The ATG16L1 minor allele, A, was not represented more often in responders compared to non-responders (minor allele frequency 41.8% vs 43.0% respectively, $p=0.85$). Additionally we could not identify a significantly higher proportion of AA homozygotes in thiopurine responders (14/71 vs 9/34, $p=0.63$), as identified in a Dutch cohort.

Conclusions: Although thiopurines have to be stopped due to intolerance in approximately one quarter of patients, they can still maintain

clinical remission in an important subset. Apart from the absence of perianal disease, we could not identify any clinical parameters which might help to stratify patients towards thiopurine monotherapy. Similarly, we could not validate the previously reported predictive value of ATG16L1 genotyping.

References:

- [1] Wildenberg et al. (2016), The ATG16L1 risk allele associated with Crohn's disease results in a Rac1-dependent defect in dendritic cell migration that is corrected by thiopurines. *Mucosal Immunol*

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Transcriptome of intestinal epithelial barrier genes in the colonic mucosa from patients with ulcerative colitis

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Background: Defects in the intestinal epithelial barrier function have been observed in patients with Ulcerative Colitis (UC). It is now becoming evident that an aberrant epithelial barrier function plays a central role in the pathophysiology of UC. Truncated forms of the adherens junction protein E-cadherin (encoded by CDH1) are associated with Crohn's disease. However, genes involved in the epithelial barrier function (ECM1, LAMB1, CDH1, NLRP6, PTGER4 and LRG5) has not been yet described in patients with UC. The aim was to study the transcriptome panel of genes (ECM1, LAMB1, CDH1, NLRP6, PTGER4 and LRG5) in the colonic mucosa from UC patients.

Methods: We studied a total of 100 patients with definitive diagnosis of UC (50 active and 50 remission) and non-inflamed control group (N=50) without endoscopic evidence of intestinal inflammation. In all groups, the ECM1, LAMB1, CDH1, NLRP6, PTGER4 and LRG5 gene expression were measured by real-time polymerase chain reaction (RT-PCR). Expression of GAPDH a housekeeping gene was analyzed for normalization purposes and quality controls. Statistical analysis was performed using the SPSS 19 program by the Kruskal-Wallis One Way Analysis of Variance on Ranks Data were expressed as the median, range and mean \pm SE. A P value ≤ 0.05 was considered as significant.

Results: LAMB1 gene expression was decreased in remission UC compared to active UC patients and controls (p=0.024 and p=0.03, respectively). CDH1 expression was increased in colonic mucosa from patients with active UC when compared with control group (p=0.043 and p=0.05). Conversely, the ECM1 expression was decreased in patients with active UC compared to UC patients in remission and normal control group (p=0.05 and p=0.003, respectively). The ECM1 levels were decreased in UC remission compared to the normal control group (p=0.017). NLRP6 gene expression was increased in UC patients with histological remission compared with active UC and control group (p=0.013 and p=0.022). PTGER4 expression was increased in patients with UC remission compared to active group and normal control group (p=0.055 and p=0.050). LRG5 gene expression was increased in patients with active UC compared with remission and normal control group (p=0.043 and p=0.028).

Conclusions: This is the first depiction of the description of gene expression of CDH1, LAMB1, ECM1, NLRP6, PTGER4 and LRG5 genes in the colonic mucosa from patients with UC, suggesting that

these genes could be involved with defects in the intestinal epithelial barrier in patients with Ulcerative Colitis (UC).

Microbiology

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Combination therapy of fresh fecal microbial transplantation and antibiotics for ulcerative colitis

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Background: Fecal microbiota transplantation (FMT) is a potential therapeutic approach to restore normal intestinal microbiota in patients with ulcerative colitis (UC), which is associated with dysbiosis; however, treatment efficacy remains unclear. Hence, we studied the impact of antibiotic pretreatment with amoxicillin, fosfomycin, and metronidazole (AFM therapy) and FMT versus AFM alone.

Methods: Patients with mild-to-severe active UC (n=21 combination-therapy group; n=20 AFM monotherapy group) were included. AFM therapy was administered to patients for 2 weeks until 2 days before FMT. Patients' spouses or relatives were selected as donor candidates. Donor fecal samples were collected on the day of administration and transferred into the patient's colon via colonoscopy within 6 h. Microbiome analysis was performed by 16S rRNA next-generation sequencing.

Results: Thirty-six patients completed this assessment (n=17 combination-therapy group; n=19 AFM monotherapy group). At 4 weeks after treatment with FMT, clinical responses were observed in 14 patients (82.3%), and the Lichtiger's CAI score decreased from 10.1 ± 3.2 to 5.1 ± 3.7 (mean \pm standard deviation; p<0.001). Nine of 14 responders achieved clinical remission (53.0%). A higher clinical response was observed following combination therapy compared to AFM monotherapy. The relative abundance of Bacteroidetes decreased significantly from $20.4\% \pm 11.1\%$ before treatment to $0.3\% \pm 0.5\%$ after 2 weeks of AFM pretreatment (p<0.0001). Among 17 cases treated with combination FMT and AFM therapy, the proportion of Bacteroidetes in 14 cases recovered was $27.4\% \pm 10.8\%$ at 4 weeks after FMT therapy following AFM. We also observed improvements in patients' clinical symptoms scores in all responders. The Bacteroidetes proportion recovered in clinical responders at 4 weeks after FMT was not observed in the AFM monotherapy group. Persistent antimicrobial-associated dysbiosis found in the AFM monotherapy group was reversed by FMT. Furthermore, in endoscopic findings, a highly negative linear correlation was observed between the proportion of Bacteroidetes and the endoscopic sum score in patients treated with combination therapy with AFM and FMT (n=17, r=-0.74, p=0.001). In patients with severe clinical symptoms based on endoscopic scores, the relative abundance of Bacteroidetes did not increase, and improvement of UC symptoms was not observed.

Conclusions: FMT following antimicrobial bowel cleansing synergistically contributes to the recovery of the Bacteroidetes composition, which is associated with clinical response and UC severity. Thus, this therapeutic protocol may be useful for managing UC.

P767**The FIT trial: anti-inflammatory dietary intervention effects on the intestinal microbiota**

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Background: The intestinal microbiota is implicated in the pathogenesis of several immune-mediated disorders including inflammatory bowel diseases and has subsequently been the target of different therapeutic interventions. We designed the Food influence on the Intestinal microbiota (FIT) trial to study the effects of diet on intestinal microbiota changes and inflammation in healthy individuals (part 1) and patients with ulcerative colitis (part 2). We here report the results of the first part of the study.

Methods: The FIT diet consists of a semi-vegetarian diet, high in fibre (>30g/day), low in saturated fat and sulphites and exclusion of added sugar, processed foods, carrageenan, and polysorbate-80. Following informed consent, 29 volunteers followed the diet for 1 month and were followed up for 6 months. Faecal calprotectin was measured on fresh faecal samples (Bühlmann ELISA). Dietary compliance was followed with food frequency questionnaires and 3-day food records.

16S rDNA paired-end sequencing targeting the V4 hypervariable region was performed using Illumina MiSeq sequencer. Sequencing depth was downsized to 10000 reads/sample. The RDP classifier was used for taxonomic annotation. Statistical analyses were performed with R.

Results: A significant weight loss was observed after 4 weeks following the FIT diet (t-test, $p < 0.0001$, mean -2.3 kg, SD -1.5). Strikingly, faecal calprotectin – although within normal ranges in all but 1 individual – significantly decreased after dietary intervention (Wilcoxon test, $p = 0.0008$) and microbial richness significantly increased (OTU observed richness, Wilcoxon test, $p = 0.004$). There was an inverse correlation between the microbial richness at baseline and the magnitude of increase in richness following the diet (Spearman's $\rho = -0.51$, $p = 0.0113$). At genus level, Roseburia decreased after the diet, although after multiple testing correction, this was no longer significant. At enterotype level, 27% of individuals which were Bacteroides at baseline shifted towards the Ruminococcus enterotype, 11% of Ruminococcus shifted towards Bacteroides and no shifts were observed in the Prevotella enterotype.

Conclusions: The FIT diet significantly increased intestinal microbial richness in healthy individuals, especially in individuals with low richness at baseline. The Bacteroides enterotype, frequently associated with dysbiosis, was less resilient to dietary changes. Furthermore, a significant decrease in faecal calprotectin was seen after the diet suggesting additional anti-inflammatory metabolic effects beyond microbial richness and composition. A proof-of-concept study using the FIT diet is currently ongoing in patients with quiescent ulcerative colitis but recent flare, to see if the diet could prevent relapse.

P768**Co-housing DSS treated mice with healthy mice results in faster recovery and normalization of the intestinal microbiota**

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Background: The intestine is populated with myriads of bacteria, which form a complex ecosystem and have tremendous impact on our health. In inflammatory bowel disease (IBD), shifts in the microbial composition and a reduction in bacterial diversity have been described. There are attempts to therapeutically transfer the microbiota from healthy subjects to persons suffering from intestinal disease. While in case of *Clostridium difficile* infections, this approach proves to be very efficient, the therapeutic value of fecal microbial transfer (FMT) in IBD is still unclear. In mouse models of intestinal inflammation, the effect of FMT has been studied poorly and if so, germ-free or antibiotic-treated animals have been used – models that poorly reflect the situation in human IBD patients. Here, we addressed how transfer of microbiota from healthy to diseased mice affects recovery from acute colitis.

Methods: Acute colitis was induced in 12 week old C57B6 mice by administration of 2% DSS in the drinking water for 7 days. Mice with colitis were co-housed with healthy mice after removal of DSS. Due to coprophagy, this results in fast transfer of the microbiota between co-housed mice. To analyze changes in the microbial composition over time, stool samples were taken every second day and sequenced for the V4 hyper-variable region in the bacterial 16S DNA.

Results: As expected, DSS treatment resulted in severe weight loss, and even 7 days after withdraw of DSS (day 15), histology confirmed severe colitis. Intestinal inflammation was accompanied by an overall reduction of microbial diversity (decreased Shannon index, $p < 0.01$), and a marked shift in the composition of the microbiota (increased abundance of *Verrucomicrobia*, *Cyanobacteria* and some families of *Firmicutes* [mainly *Clostridiaceae*], although overall abundance of *Firmicutes* was decreased [$p < 0.01$ for all]). However, on day 15, these changes were less pronounced, indicating a normalization of the microbiota composition upon recovery. DSS-treated mice which were co-housed with healthy littermates after colitis induction, showed faster recovery (earlier weight gain, reduced histological scores, reduced levels of the infiltration marker myeloperoxidase (MPO), less pronounced shortening of the colon, $p < 0.01$ for all) and an earlier normalization of the microbiota composition.

Conclusions: Our results indicate that co-housing of DSS-treated mice with healthy mice results in transfer of the “healthy” microbiota to diseased mice, and promotes recovery from colitis. This indicates that introduction of a healthy microbiota might have beneficial effects during intestinal inflammation and opens the possibility to systematically study the effect of genetic alterations in donor and/or recipient on the efficacy of FMT.

P769**In Crohn's disease, an aggressive disease course is related to an increased abundance of proteobacteria: a seven year follow up study**

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Background: Many studies have found an imbalance of the gut microbiota – termed dysbiosis – in inflammatory bowel disease (IBD) patients, with an overall loss of diversity, a depletion of Firmicutes and an increase of Proteobacteria. Differences in abundance seem to depend on disease activity and are found significantly lower in IBD patients with active disease compared to patients with inactive disease. However, studies have emerged from tertiary centers and selected cohorts. The aim of this study was to investigate the microbiota in 139 IBD patients from an unselected inception cohort of patients diagnosed in Copenhagen, Denmark year 2003–04 after 7 years of disease duration.

Methods: Sixty Crohn's disease (CD) and 79 ulcerative colitis (UC) patients were included. Disease activity was assessed by the Harvey-Bradshaw Index for CD and Simple Clinical Colitis Activity Index for UC and fecal samples were collected at a follow-up (FU) visit after 7 years of disease duration. The diversity of the fecal microbiome was assessed by 16S rDNA MiSeq sequencing. Medical and surgical data was registered retrospectively at the follow-up visit. An aggressive disease course was defined as ≥ 3 courses of ≥ 50 mg/day systemic steroids and/or biological therapy (any dose) and/or surgical resection (CD) or colectomy (UC) during the 7 years of FU.

Results: The diversity of microbiota measured both as OTUs and Shannon index was significantly lower for active compared to inactive IBD ($p=0.005$ and $p=0.038$ respectively). The abundance of Firmicutes ($p=0.001$) decreased and the abundance of Proteobacteria ($p=0.004$) increased in patients with active IBD. For CD, a significant decrease was observed in the number of OTUs in patients with aggressive disease compared to patients with non-aggressive disease ($p=0.007$), but not in Shannon index ($p=0.13$). There was no change

in diversity or the number of OTUs or Shannon index observed between non-aggressive and aggressive disease for UC ($p>0.20$). Only Proteobacteria was significantly more abundant in CD patients with aggressive disease compared to non-aggressive ($p=0.049$). There were no significant phyla-level differences in abundance for UC.

Conclusions: In this unselected cohort of patients with 7 years of follow-up, we found a lower microbial diversity in IBD patients with active disease. The abundance changed with loss of Firmicutes and an increase in Proteobacteria. The abundance of Proteobacteria was also found to be increased in CD patients with aggressive disease. These results are in accordance with former studies, suggesting that dysbiosis of the gut in CD patients is not only related to activity but also to severity of disease.

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First analysis from UK IBD Twin Biobank; 16S rRNA gene sequencing identifies reduced diversity in IBD and bacterial taxa associated with disease

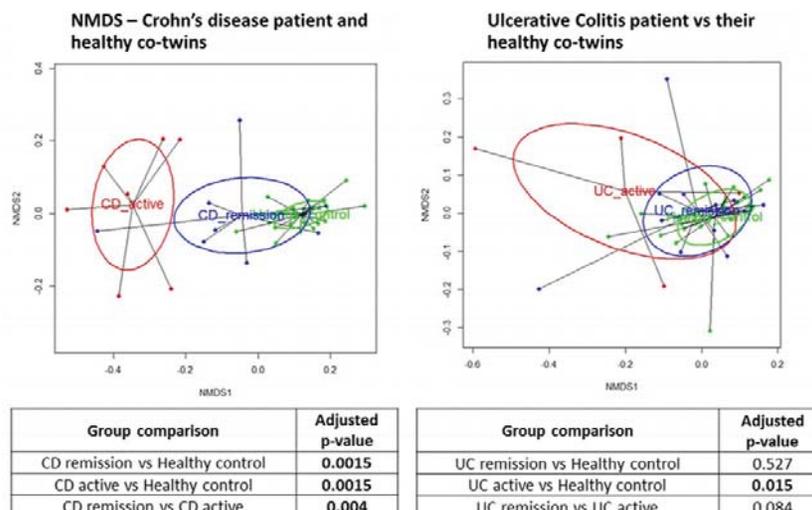
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Background: Previous studies have shown that the gut microbiota plays an important role in IBD. However there is no consensus on which bacteria are responsible for the disease. 16S gene profiling studies generate large amounts of information, but are confounded by genetic and environmental factors. Twin studies are instrumental in controlling these variables.

In this study we investigated the microbiota of twin pairs discordant for Crohn's disease (CD) and ulcerative colitis (UC) using 16S rRNA gene sequencing, with the aim of identifying taxa associated with disease.

Methods: Participants were recruited via the UK IBD Twin Registry. Stool samples were collected and frozen using standard methods. Participants who had received antibiotics within 3 months were excluded. Harvey Bradshaw Index and Simple Clinical Colitis Activity Index were recorded. Full medical history was available from the UK IBD Twin Registry.



Abstract P770 – Figure 1. NMDS CD and UC.

Samples underwent 16S rRNA sequencing using the Illumina MiSeq platform and analysed using our data analysis pipeline. PERMANOVA was used to evaluate associations with clinical metadata, which included matching of twin pairs for analysis, and STAMP was used to identify taxonomic differences between groups.

Results: 20 twin pairs discordant for CD (5MZ:15DZ mean age 52 years) and 17 discordant for UC (6MZ:11DZ mean age 59.7 years) were recruited. 7 subjects with CD had active disease as did 4 with UC.

Gut microbiota from active CD patients had lower bacterial diversity compared to remission CD patients and healthy twins (Shannon diversity index, $p < 0.001$ healthy vs active CD, active vs remission CD, 1-way ANOVA post-hoc = Tukey). Active UC patients also had lower bacterial diversity compared to remission UC patients and healthy twins (Shannon diversity index, $p < 0.01$ healthy vs active UC, $p < 0.05$ active vs remission). NMDS plots show more definitive clustering to phenotype in CD.

Active CD patients had a higher proportion of *Clostridium hylemonae* and *Lactobacillus delbrueckii* compared to healthy twins, and a lower proportion of *Bacteroides uniformis*, *Bacteroides vulgatus*, and *Faecalibacterium prausnitzii* ($p < 0.05$). Active UC patients had a lower proportion of *Alistipes* spp. compared to healthy co-twins and UC patients in remission ($p < 0.05$).

Conclusions: This study confirms previous findings showing decreased diversity in IBD patients and changes in some bacterial taxa. Our study is the first to show decreases in *Alistipes* spp. in active UC.

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The recombinant NZ9000SHD-5 attenuates the inflammation and mucosal lesions in dextran sodium sulfate-induced colitis

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Background: Defensin, as a family member of antimicrobial peptide, plays an important role in host immunity and maintaining the gut barrier function. Meanwhile, probiotics were reported to be a protective role in patients of IBD.

Methods: In this study, we optimized a defensin mHD-5 mainly consisted by the mature peptide of human defensin 5 (HD-5) and constructed vector-pN8148-SHD-5 and transfected into *Lactococcus lactis* to build the recombinant NZ9000SHD-5 based on the nisin-controlled gene expression and gene splicing technology.

Results: We found that recombinant NZ9000SHD-5 attenuated inflammatory cells infiltration, histopathological changes in colonic gland, and protected the intensity of epithelial cells in DSS-induced colitis. Recombinant NZ9000SHD-5 remarkably suppressed the production of inflammatory cytokine, such as interleukin-1B (IL-1B), IL-6 and tumor necrosis factor- α (TNF- α). Meanwhile, NZ9000SHD-5 increased the expression of zonula occludens-1 and occluding mRNA and proteins, and it decreased the permeability of FITC-D while preserving the structure and function of Tight junctions in the DSS-induced models. We tested the mechanism of protective effects of NZ9000SHD-5 on LPS-induced model of mouse macrophage RAW264.7 cell. Pretreated with the supernatant of NZ9000SHD-5 for 4h before exposed to LPS significantly reduce the concentrations of IL-6, IL-1B and TNF- α , inhibited the expression of LPS-induced phosphorylation nuclear transcription factor-kappa B (NF- κ B) p65 protein and its inhibitor I κ B α of NF- κ B signaling pathways. In accordance with the protective effect of NZ9000SHD-5 on

gut barrier of DSS-induced colitis, we observed the positive effect of NZ9000SHD-5 in mucosal injury and the disruption of epithelial barrier on Caco-2 cells. We found that NZ9000SHD-5 increased the transepithelial electrical resistance, and it decreased the permeability of FITC-D and the damage the of skeleton of TJs against the dextran sodium sulfate

Conclusions: The results indicate that the NZ9000SHD-5 relieves the changes in DSS-induced mucosal damage and paracellular permeability possibly through attenuating the colon inflammation by downregulating the activation of NF- κ B signaling pathway, and therefore the administration of NZ9000SHD-5 may be a possible option for colitis.

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The presence of adherent-invasive *Escherichia coli* strains on the surgical specimen is a predictor of severe endoscopic postoperative recurrence in Crohn's disease

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Background: The majority of Crohn's disease (CD) patients undergo at least one intestinal resection during the course of their disease. Since surgery is not a curative treatment, postoperative recurrence (RPO) is a major issue in these patients, as up to 70% of patients have endoscopic RPO within one year of surgery. The aim was to determine whether the presence of adherent and invasive *Escherichia coli* (AIEC) bacteria at the time of surgery was associated with endoscopic RPO at 6 months.

Methods: REMIND group has established a homogeneous, prospective, multicenter cohort (POP-REMIND) of operated CD patients. Samples were performed on the surgical specimen (M0) and at endoscopy (M6), and stored centrally in a bio-bank. The inclusion criteria were: age ≥ 18 years, ileal or ileocaecal CD requiring intestinal resection. Post-operative treatment was prescribed according to a pre-established algorithm. Clinical outcome, therapeutic, biological and endoscopic data (Rutgeerts score) were collected 6 months after surgery. Clinical factors (demographic variables, phenotypic and postoperative treatments) associated with endoscopic recurrence were investigated by univariate analysis and logistic (multivariate) regression. The search for AIEC bacteria was carried out by culturing and investigating the characteristics of adhesion, invasion in Int-407 cells, and survival within THP-1 macrophages.

Results: Presence of AIEC strains was determined on the surgical specimen in 226 patients; 30 had a positive AIEC status. Descriptive analysis of the population at M0 showed that the presence of AIEC was inversely associated with a penetrating phenotype of the disease (13% for AIEC+ versus 38% for AIEC- patients, $p=0.005$). On the other hand, presence of AIEC on the surgical specimen was not correlated with age, disease duration, smoking, previous surgical resection and with preoperative anti-TNF exposure. Of the 226 patients included, 170 had a postoperative colonoscopy (M6). At time of surgery, only 26 of the 170 patients (15.3%) were carriers of AIEC. Presence of AIEC on the surgical specimen was not associated with an increased risk of post-operative recurrence (i1-i4). However, the presence of AIEC on the surgical specimen was pre-

dictive of severe endoscopic post-operative recurrence (i3 and i4): 10 among 26 patients AIEC+ (38%) versus 24/143 (17%) for AIEC-; $p=0.01$). After adjusting for age, sex, pre- or post-operative exposure to TNF antagonists and antibiotics, the presence of AIEC on the surgical specimen was associated with severe endoscopic recurrence i3-i4 (OR =3.42 CI95% [1.31–8.84], $p=0.011$).

Conclusions: The presence of AIEC on the surgical specimen was an independent risk factor for severe endoscopic post-operative recurrence of Crohn's disease.

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Post-operative Crohn's disease recurrence is associated with specific changes in the faecal microbiome – potential pathogenic and protective roles

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Background: Crohn's disease usually recurs after "curative" resection. This may relate to specific microbial populations playing a pathogenic role.

Methods: Faecal samples were obtained peri-operatively (baseline) and at 6, 12 and 18 months after surgery from 130 patients enrolled in the prospective POCER study. Endoscopic disease recurrence was assessed (Rutgeerts Score ≥ 2) at six months (in 2/3 of patients in the active endoscopic care arm) and at 18 months in all patients. DNA was extracted using the MoBio Powersoil DNA extraction kit, and the V2 region of the bacterial 16S rRNA gene sequenced (MiSeq).

Data were processed using the QIIME pipeline; alpha and beta diversity were assessed on samples after rarefaction to 10,000 reads per sample. Alpha diversity was compared using the Shannon's index. Weighted UniFrac distances assessing beta diversity were compared using the vegan package (adonis function) in R. Differential abundance between remission and recurrence was assessed at genus level using MetagenomeSeq with cumulative sum scaling normalisation, FDR correction (FDR P value), further adjustment for the number of comparisons (Adj. P Value), and adjustment for baseline patient characteristics (smoking, age, gender, body mass index and antibiotics) in R.

Results: Diversity increased significantly after surgery (all patients, baseline versus 18 months ($p=0.048$)). At 6 months, diversity was significantly greater for patients who remained in remission compared to those with recurrence ($p=0.04$); at 18 months, a similar trend was observed but the results were not significant ($p=0.185$).

Overall bacterial composition differed between recurrence and remission at 18 months ($p=0.008$), as well as over time (all patients and all samples: baseline, six, 12 and 18 months; $p=0.001$).

Nine genera (four from the order Clostridiales, two from the orders Lactobacillales and Bacteroidales) were differentially abundant between subjects with disease recurrence compared to remission as shown.

Conclusions: Specific bacterial genera are associated with disease recurrence after Crohn's disease resection. Positive associations need to be investigated for a possible causative role, while negative associations (decreases within the orders Clostridiales and Lactobacillales) require investigation for a possible protective role.

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Metagenomics and metabolomics of patients with inflammatory bowel disease and their unaffected relatives

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Abstract P773 – Table 1. Differentially abundant genera in patients with endoscopic disease recurrence compared to patients in remission

Differentially Abundant Genera between Timepoints	Phylum	Class	Order	Family	Genus	Log Fold Change in Patients with Recurrence	FDR P values	Adj. P values
Baseline samples for 18 Month outcomes	Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	<i>Corynebacterium</i>	1.595	0.006	0.038
Baseline samples for 6 month outcomes	Firmicutes	Clostridia	Clostridiales	Tissierellaceae	<i>Peptoniphilus</i>	-3.436	0.001	0.004
	Firmicutes	Bacilli	Lactobacillales	Streptococcaceae	<i>Lactococcus</i>	-2.216	0.036	0.215
	Firmicutes	Clostridia	Clostridiales	Clostridiaceae	<i>SMB53</i>	-1.630	0.036	0.215
	Firmicutes	Clostridia	Clostridiales	Eubacteriaceae	<i>Anaerofustis</i>	-1.218	0.042	0.255
6 month samples for 6 month outcomes	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	<i>Odoribacter</i>	2.101	0.000	0.002
	Firmicutes	Clostridia	Clostridiales	Lachnospiraceae	<i>Oribacterium</i>	-1.851	0.000	0.002
18 month samples for 18 month outcomes	Bacteroidetes	Bacteroidia	Bacteroidales	Odoribacteraceae	<i>Butyricimonas</i>	2.446	0.003	0.016
	Firmicutes	Bacilli	Lactobacillales	Carnobacteriaceae	<i>Granulicatella</i>	-0.847	0.014	0.084

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Background: Dysbiosis, intestinal barrier dysfunction and metabolic alterations of the gut microbiota have been implicated in the pathogenesis of inflammatory bowel disease. We studied the faecal microbiome and metabolome, as well as intestinal permeability of multiple-affected families with Crohn's disease (CD) or ulcerative colitis (UC) to investigate which factors are associated with disease. **Methods:** Faecal and urine samples were obtained from 84 individuals of 19 families (37 CD, 11 UC and 36 unaffected first-degree relatives (FDR)). Faecal microbial profiling was done using 16S rDNA paired-end sequencing (Illumina MiSeq). Sequencing depth was downsized to 10,000 reads/sample. Taxonomic annotation was performed with the RDP classifier. Faecal volatile organic metabolites were measured using GC-MS. Metabolite data were relatively quantified to an internal standard, and subject-specific compounds were discarded. Metabolite profiles were clustered by PLS-DA (Unscrambler). Small intestinal permeability (IP) was measured using a 2-hour lactulose-mannitol urine test. Statistical analyses were conducted in R with multiple testing correction (Benjamini-Hochberg). **Results:** Microbial richness and composition were significantly different in patients with CD compared to UC and FDR ($p < 0.05$), whereas these comparisons were not significant for UC versus FDR. Vector fitting confirmed diagnosis as the main driver of the variability in microbial composition ($p < 0.001$), followed by family ID ($p = 0.02$). The genera discriminating CD and FDR included 16 known and new genera, such as *Faecalibacterium*, *Ruminococcus* and *Gemmiger* (corrected $p < 0.05$). Analysis of the metabolites also showed separate clusters for CD and FDR, while samples from UC patients partially overlapped with both groups. In contrast to the microbiota results, family did not significantly drive the metabolic profiles. The chemical classes associated with FDR were short- and medium-chain fatty acids, while samples from CD patients were associated with esters. Comparison of individual metabolites identified eight compounds with significantly different levels for CD versus FDR (corrected $p < 0.05$). Among these, acetic acid and butyric acid are known for their anti-inflammatory properties and beneficial effect on gut barrier function. A subset of CD patients (30%) had increased small IP values, but this trait was not associated with any of the individual metabolites, nor bacterial genera.

Conclusions: Significantly different metagenomic and metabolomic profiles were observed between CD patients and healthy individuals with a shared familial background. *Faecalibacterium*, *Ruminococcus* and *Gemmiger* genera, amongst others, drive the phenotype of CD, as do esters and lower levels of short-chain fatty acids.

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Fibre intake is associated with microbiome changes in pediatric Crohn's disease patients following remission induction with exclusive enteral nutrition

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Background: Changes in gut microbiome community structure are associated with the development of Crohn's Disease (CD) and can be altered by environmental factors such as diet. Exclusive enteral nutrition (EEN) can induce disease remission in more than 80% of pediatric CD patients. However, the mechanism of EEN effectiveness remains unclear and evidence-based dietary recommendations for remission maintenance after EEN cessation do not exist. We aimed to assess the influence of dietary fibre intake on microbiome composition and sustained remission.

Methods: We conducted a cross-sectional analysis of 11 pediatric CD patients aged 11–17 years old who are participants in an ongoing study of microbiome changes in response to EEN. Participants had returned to their regular ad libitum diet for at least 3 months following 12-week EEN therapy, and completed a 79-item validated food frequency questionnaire (FFQ) to assess their fibre intake. Clinical sustained remission (SR) was indicated by weighted Pediatric Crohn's Disease Activity Index (wPCDAI) < 12.5 by 6 month follow-up, otherwise participants were classified as non-sustained remission (NSR). 16S rRNA from participant stool samples collected at 12-week intervals was analysed using QIIME to assess changes in gut microbial diversity at time of EEN and following return to regular diet.

Results: The dietary data revealed general low fibre intake (only 1 of 11 respondents consumed recommended amount of daily dietary fibre), so participants were classified as "higher fibre" if they consumed at least half the daily fibre recommendation for their age and sex, and "lower fibre" if they did not. Microbial beta diversity was significantly lower in patients consuming lower fibre compared to those consuming higher fibre ($p = 0.04$, ANOSIM). There were no significant differences in alpha or beta diversity between patients consuming < 600 g of oral solid food ($n = 3$) at time of FFQ and those consuming > 600 g. Microbial alpha diversity (Chao-1) analysis of patients' stool samples, after return to regular diet, showed the lowest gut microbial richness in patients who achieved remission with EEN but experienced disease flare (NSR) flare by 6 months follow-up ($n = 3$), compared to EEN primary non-responders ($n = 2$) and those in SR ($n = 4$).

Conclusions: Lower fibre intake is associated with decreased gut microbial diversity in pediatric CD patients after completing induction treatment with EEN. Persistence of decreased gut microbiome diversity with return to regular diet after EEN may indicate increased risk of disease flare. Further longitudinal analysis of microbiome changes associated with return to an oral diet after EEN are required to inform dietary therapy recommendations for maintenance of remission in pediatric CD.

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Dysbiosis in Nlrp6/Asc-deficient mice does not result from inflammasome deficiency

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Background: Shifts in intestinal microbial composition, termed dysbiosis, have been associated with Inflammatory Bowel Diseases (IBD). Genetic mouse models lacking Nlrp6 or Asc, which were proposed to regulate intestinal inflammasome activation, were reported with dysbiosis when compared to unrelated C57BL/6 controls, which conferred increased susceptibility to colon inflammation [1]. The Nlrp6/ASC inflammasome therefore was proposed as a host-encoded machinery that determines gut microbiota composition and thereby regulates intestinal health, suggesting that Nlrp6/ASC inflammasome deregulation may be a causal factor in eliciting dysbiosis-associated IBD.

Methods: Using unrelated separately housed wild-type mice as controls is prone to non-genetic factors such as housing conditions and maternal inheritance influencing the gut microbiota. We therefore subjected littermate and ex-germfree mice from distinct breeding schemes and housing conditions to faecal 16S sequencing in order to thoroughly delineate the contributions of host genetics, housing conditions and maternal inheritance to the gut microbiota composition in Nlrp6- or Asc-deficient mice.

Results: When comparing separately housed offspring from unrelated homozygous C57BL/6 and Nlrp6KO breeding couples, Nlrp6KO mice did not display overall gut microbial dysbiosis but did show statistically significant alterations in a number of individual bacterial taxa. In addition, cage and mother co-variables had bigger effects on the gut microbiota composition than the host genetic Nlrp6 status. Therefore, to minimise differential maternal inheritance as a confounding factor we next generated Nlrp6 and Asc^{+/-} mice and intercrossed those to obtain littermates of the three distinct ^{+/+}, ^{+/-} and ^{-/-} genotypes. Upon weaning, we housed these littermates separately according to their ^{+/+}, ^{+/-} and ^{-/-} genotype, thus avoiding coprophagy-mediated balancing of the gut microbiota. This tightly controlled experimental set-up allowed investigating whether the host Nlrp6 or Asc genetic status exerts an impact on the gut microbiota composition. In this controlled experimental set-up, Nlrp6^{-/-} and Asc^{-/-} mice did not display gut microbial dysbiosis when compared with wild-type littermates and none of the individual bacterial taxa differences in gut microbial alterations observed in Nlrp6KO vs C57BL/6 mice could be reproduced in these littermates.

Conclusions: These results show that the Nlrp6/Asc host genetic status does not influence the composition of the faecal microbiota and suggest that prior dysbiosis findings in inflammasome-deficient mice may result rather from differential maternal inheritance and/or long-term separate housing.

References:

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Ursodeoxycholic acid and its taurine/glycine conjugated species reduce colitogenic dysbiosis and equally suppress experimental colitis in mice

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Background: The promising results with secondary bile acids in experimental colitis suggest that they may represent an attractive and safe class of drugs for the treatment of inflammatory bowel diseases (IBD). However, the exact mechanism by which bile acid therapy confers protection from colitogenesis is currently unknown. Since the gut microbiota plays a crucial role in the pathogenesis of IBD, and exogenous bile acid administration may affect the community structure of the microbiota, we examined the impact of the secondary bile acid ursodeoxycholic acid (UDCA) and its taurine/glycine conjugates on the faecal microbial community structure during experimental colitis.

Methods: Acute colitis was induced in mice by administration of 4% dextran sodium sulfate to the drinking water for 7 days. Mice were treated with 500 mg/kg/d UDCA, tauroursodeoxycholic acid (TUDCA), glyoursodeoxycholic acid (GUDCA), or placebo by oral gavage. At day 9 of colitis, faecal microbiota profiles were determined through 16S rRNA Illumina MiSeq sequencing and mice were sacrificed at day 10 to assess the severity of inflammation. Ultra-high performance liquid chromatography and high resolution mass spectrometry were performed on faecal samples to analyse the extent of biotransformation of orally administered UDCA, TUDCA and GUDCA.

Results: Daily administration of UDCA, TUDCA and GUDCA equally lowered the severity of colitis, as evidenced by reduced body weight loss, colonic shortening and expression of inflammatory cytokines. Illumina sequencing demonstrated that bile acid therapy during colitis did not restore faecal bacterial richness and diversity but normalized the colitis-associated increased ratio of Firmicutes to Bacteroidetes. Interestingly, administration of bile acids prevented the loss of Clostridium cluster XIVa and increased the abundance of Akkermansia muciniphila, bacterial species known to be particularly decreased in IBD patients. Orally administered UDCA, TUDCA and GUDCA were extensively metabolised *in vivo*, resulting in a similar faecal bile acid composition.

Conclusions: We conclude that UDCA, which is an FDA-approved drug for cholestatic liver disorders, could be an attractive treatment option to reduce dysbiosis and improve inflammation in human IBD.

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Microbial characterization of paediatric inflammatory bowel disease and stratification into disease severity groups

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Background: Imbalance in the faecal microbiota with a reduction in biodiversity; dysbiosis, has been identified in inflammatory bowel disease (IBD). Our aim was to study and compare the faecal microbiota in paediatric patients with newly diagnosed untreated IBD with the microbiota of healthy children and paediatric patients with gastrointestinal symptoms but no IBD. We also aimed at studying the microbiota related to IBD subgroups and treatment.

Methods: Faecal samples were collected from 235 children and adolescents. Eighty had Crohn's disease (CD), 27 ulcerative colitis (UC) and 3 IBD unclassified, 50 were non-IBD patients and 75 were healthy children between two and 18 years. The microbiota was analysed using a 16S rRNA DNA based test with the GA-map technology, measuring probe signal intensity (PSI) of 54 DNA probes targeting 300 bacteria on different taxonomic levels. Using non-parametric methods, we selected six probes where the PSI was lower in IBD compared to non-IBD patients. For each of these six probes, IBD patients were given 1 point if their PSI was lower than the median PSI value of non-IBD patients. The points were summarized as a Score ranging from 0–6 points. Logistic regression was used to model possible associations between this Score and risk of having IBD.

Results: Most bacterial PSI were reduced in IBD and non-IBD patients ($p < 0.001$) compared to healthy controls. IBD patients had reduced abundance of Firmicutes (Eubacterium, $p = 0.006$; Holdemania, $p = 0.038$), Tenericutes and Bacteroidetes (Parabacteroidetes $p = 0.02$), $p = 0.002$, and Bifidobacterium, $p = 0.02$, compared to the non-IBD patients. CD patients had lower abundance of Mycoplasma ($p = 0.045$) than UC patients. IBD patients with extensive disease (L3/E3) had more Clostridiales (Ruminococcus gnavus), $p = 0.02$, and CD patients with L3 had more Proteobacteria, $p = 0.04$, than patients with limited disease. IBD patients who later received TNF blockers, 64/110, had lower diversity at baseline for Firmicutes, Tenericutes (Mycoplasma, $p = 0.009$), and Bacteroidetes, $p = 0.015$, compared to IBD patients who were treated with conventional medications, 46/110. Patients who reached 3 or more points using the Score were 2.2 times more likely to have IBD compared to non-IBD (OR=2.1, 95% CI 1.1–4.5, $p = 0.027$).

Conclusions: Microbiota profiles may be of value for stratification of paediatric IBD into diagnostic and prognostic subgroups. A severe dysbiotic microbiota profile in newly diagnosed IBD is associated with a severe phenotype with more extensive disease and subsequent need of TNF blocker treatment.

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CD patients in deep remission harbor a high dysbiosis index similar to active CD at diagnosis, yet both are higher in comparison to healthy controls

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Background: Altered microbial composition (dysbiosis) is detected in Crohn's disease (CD), but it is questionable if this is a primary process that contributes to pathogenesis or is secondary to a survival advantage in inflammatory environment. Murine studies showed that gut dysbiosis from CD patients augments pro-inflammatory responses in the host, suggesting contribution to pathogenesis. We

aimed to test if CD patients under clinical, biomarkers, and capsule-proven deep remission, restore or persist their dysbiosis in comparison to active treatment naïve CD patients (US RISK, $n = 133$), and healthy controls ($n = 1031$ from Israel and US).

Methods: The global pattern of microbial composition was determined by 16S sequencing in fecal samples of CD patients ($n = 38$) from the prospective observational Israeli IBD Research Network (IIRN). Clinical corticosteroid-free remission was defined as CDAI ≤ 150 . Biomarkers remission included fecal calprotectin ≤ 100 $\mu\text{g/g}$ (BÜHLMANN Laboratories) and CRP levels ≤ 5 mg/l. Mucosal healing (MH) was defined by SB-III or PillCam 2 colonic capsules (Given Imaging) with Lewis score (LS) ≤ 135 .

Results: 18 (51%) of 35 patients in clinical remission showed clinical and biomarker remission, and only 10 (29%) showed MH with clinical and biomarker remission. Principal Component analyses of the unweighted UniFrac matrix to summarize the overall microbial dysregulation showed clear separation between CD in remission and healthy controls. Alpha diversity (richness within sample) showed significant reduction in healthy Israeli population in comparison to healthy US population ($p < 0.001$), but no significant differences were detected between healthy Israeli controls, IIRN CD patients irrespective of their remission state, or active US CD. Remarkably the dysbiosis index of Israeli patients in clinical remission was similar to that of active US CD, but was significantly different from that of healthy Israeli and US individuals ($p < 0.001$). Moreover, no differences were noted between Israeli CD patients with and without biomarkers remission and with and without mucosal healing, while all those groups were significantly different from healthy controls.

Conclusions: CD patients in deep remission and in the absence of mucosal inflammation, show significantly higher dysbiosis index as treatment naïve active CD. These results may suggest that the dysbiosis observed in CD, like genetics, is a primary intrinsic component of the pathogenesis that is not affected by current therapeutic approaches. However, as opposed to genetics that is harder to manipulate, future therapeutic and nutritional interventions should aim to target the microbiota to potentially improve CD natural history.

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3-oxo-C12:2-HSL, a new N-acyl-homoserine lactone identified in gut ecosystem exerts an anti-inflammatory effect and does not modify paracellular permeability

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Background: It is now recognized that IBD patients exhibit imbalance in gut microbiome. In this setting, the fact that bacteria can use quorum sensing small signal molecules for cell-cell communication including inter-kingdom (prokaryote-eukaryote) communication is an interesting way to tackle functional impact of dysbiosis on host epithelial cells. In various ecosystems, one of the most studied quorum sensing system relies on amphiphilic molecules called N-acyl-homoserine lactones (AHLs). In a previous study, fecal samples from 49 IBD patients in remission ($n = 24$) and during flare ($n = 25$) and from 26 healthy subjects were analyzed. AHLs profile was determined for each sample using HPLC coupled with tandem mass spectrometry. We detected 10 different AHLs in human gut microbiota and identified a prominent and never described AHL: 3-oxo-C12:2-HSL. Its presence was significantly associated with normobiosis. We

now aimed to look for the impact of the 3-oxo-C12:2-HSL on intestinal inflammatory pathways and the intestinal permeability. To note 3-oxo-C12:2-HSL is close to the well-known quorum sensing molecule 3-oxo-C12-HSL from *Pseudomonas aeruginosa*. This latest has anti-inflammatory properties and is known to increase paracellular permeability.

Methods: Caco-2/TC7 cells were cultured until confluence and then stimulated by IL1B at 25 ng/mL during 18h with increasing concentration of 3-oxo-C12:2-HSL (0, 1, 5, 10, 25, 50, 100 and 200 μ M). The inflammatory response was measured by the level of IL-8 in the supernatant using ELISA. The impact of the 3-oxo-C12:2-HSL (200 μ M) on the paracellular permeability was measured by the passage of a fluorescein-dextran 4kDa (FD4-FITC) tracer, from the apical to the basal side of a monocellular layer of Caco-2/TC7 cells, cultured on Transwell filters. In these experiments, 3-oxo-C12:2-HSL effects were compared to 3-oxo-C12-HSL.

Results: After IL1B stimulation of Caco-2 cells, 3oxoC12:2-HSL (10–50 μ M) as well as 3-oxo-C12-HSL (5 μ M) were able to lower levels of IL-8 ($p < 0.05$). Furthermore, 3-oxo-C12:2-HSL (200 μ M) did not modify paracellular permeability after 4 or 20-hours exposure whereas 3-oxo-C12-HSL (200 μ M) increases paracellular permeability after 4-hour ($\times 2$) or 20-hour ($\times 10$) exposure compared to controls ($p < 0.0001$).

Conclusions: 3-oxo-C12:2-HSL exerts an anti-inflammatory effect on enterocyte like Caco-2/TC7 cells. This anti-inflammatory effect is not associated with an increase of paracellular permeability contrary to what we observed with the 3-oxo-C12-HSL. These results support the hypothesis of a protective role of the 3-oxo-C12:2-HSL in gut ecosystem.

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The stability of the fecal microbiota in Crohn's disease patients with changing disease course

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Background: Microbial shifts have been associated with disease activity in Crohn's disease (CD), but findings on specific taxa are not always consistent. This may be due to differences in populations included, molecular methods applied, potential confounders and the use of cross-sectional study designs. We aimed to prospectively examine the fecal microbiota, by means of next-generation sequencing, in adult well-characterized CD patients with either changing or stable disease course over time.

Methods: Fecal samples were collected at two time points from 15 healthy individuals (HC), 35 CD patients with stable disease course (remission) and 22 CD patients during remission and subsequent exacerbation. The microbial composition was assessed by sequencing of the V4-region of the 16S rRNA gene. The microbial diversity and richness of fecal samples was assessed by the Shannon index and PD whole tree and the observed species and Chao1 index, respectively. Stability of the microbiota composition within individuals as well as differences in the microbiota composition between individuals were assessed by Bray-Curtis dissimilarity and (un)weighted Unifrac distance.

Results: CD patients at baseline had a significantly lower microbial (median (IQR)) richness (Chao1 index (644.7 (440.1–817.2) and 800.4 (711.0–849.7), respectively; $p = 0.004$) and diversity (Shannon index; 6.0 (5.0–6.4) and 6.3 (6.1–7.1), respectively; $p = 0.014$) as compared to HC. However, the microbial richness and diversity did not significantly change over time in CD patients that subsequently developed an exacerbation when compared to HC and CD patients that remained in remission.

When assessing the overall microbial community structure at baseline, a subset of CD patients clustered apart from HC and were characterized by a low microbial diversity and a low relative abundance of *Faecalibacterium* spp. Moreover, the microbiota of both CD patients that maintained in remission (RR) and those that developed an exacerbation (RA) was less stable over time when compared to HC [(unweighted Unifrac median (IQR) RR 0.40 (0.36–0.44), RA 0.38 (0.36–0.42), HC 0.35 (0.31–0.37)]. However, no differences in microbiota stability were observed between these two patient groups ($p = 0.39$), nor was the stability impacted by medication use.

Conclusions: CD patients showed a lower temporal stability than healthy controls, but this was not affected by differences in disease course. Furthermore, a subgroup of CD patients harbored a microbiota composition that deviated from the microbiota of HC, which warrants further investigation.

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A new compatibility test for donor selection for faecal microbiota transplantation in ulcerative colitis

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Background: Faecal Microbiota Transplantation (FMT) is an effective and safe treatment against *Clostridium difficile* infections (CDI). Its usefulness for the treatment of other conditions is being explored. A promising application is ulcerative colitis (UC) treatment, as patients' microbiota contributes to the bowel inflammation in this disease. However, FMT therapeutic success seems to be donor dependent in this setting. The aims of the present work were: 1) To design an individualized test to select the best faecal donor for each UC patient, and 2) To assess the post-FMT implantation of gut microbiota in a UC patient and to compare it with implantation on a CDI patient who used the same faecal donor.

Methods: A 40 year-old male with extensive moderate UC (E3S2) was approached and consented to be studied for protocol design. Disease was refractory to anti-TNF- α , anti-integrin, tacrolimus, and thiopurines. Patient was maintained on 15 mg/day of prednisone. Lymphoid cells from rectal biopsies were obtained by enzymatic digestion with collagenase and DNA-ase. Lymphocytes were faced against three gut microbiota samples from independent healthy donors to determine interleukin production in supernatants using the Cytometric Bead Array kit (B&D). Different incubation times (6, 18, 24 h) and microbiota concentrations (1, 1/100, 1/1000) were tested to select the optimal conditions. Donor faeces resulting in a milder inflammatory response were chosen for FMT. An unrelated CDI patient underwent also FMT with the same faeces, and was used as a positive control of faecal microbiota implantation, which was as

essed by PCR-DGGE of the donor faeces, three UC faecal samples (basal, 15 days and 30 days after FMT) and a single CDI one (30 days after FMT).

Results: The optimal conditions of our test corresponded to a non-diluted faecal sample, combined with an 18 h incubation with lymphocytes. Markers that best discriminated the inflammatory response (higher response range) against the donor microbiota were IL-6 and TNF- α . Our protocol allowed the selection of a faecal donor for our UC patient, preventing the triggering of an inflammatory response in the intestinal immune system. FMT also allowed the reduction of prednisone doses in this patient as well as a clinical improvement of his symptoms. After FMT, PCR-DGGE gut microbiota fingerprints were indistinguishable between the healthy donor and both the UC and CDI patients, demonstrating an adequate microbiota implantation.

Conclusions: We propose this new test to select the most compatible gut microbiota donor for each UC-patient before the FMT. Although the effectiveness of this test should be validated in a higher number of UC-patients and donors, we obtained promising results in our single patient.

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Ciprofloxacin resistance in ESBL producing enterobacteriaceae colonizing the gut in IBD patients

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Background: Ciprofloxacin is one of the most frequently used antibiotics in hospitalized inflammatory bowel disease (IBD) patients. In the last few years an emerging resistance to ciprofloxacin, ranging from 43% to 82%, has been described in extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae colonizing the gut (Lübbert, Christoph et al. 2015; Vervoort, J. et al. 2014). The objective of this study was to evaluate the gut colonization with ESBL producing Enterobacteriaceae in IBD patients, resistance to ciprofloxacin and bacterial plasmid genes determining the resistance to ciprofloxacin.

Methods: Rectal swabs were collected from all consecutive patients hospitalized in Riga East Clinical University Hospital and Pauls Stradins Clinical University Hospital between 2012 and 2015 with clinically, endoscopically and histologically confirmed ulcerative colitis (UC) and Crohn's disease (CD) diagnoses. Enterobacteriaceae were cultured and analyzed for ESBL presence according to EUCAST

guidelines, resistance to ciprofloxacin and bacterial plasmid genes – CTX-M, TEM and SHV were detected.

Results: A total of 130 patients with confirmed IBD diagnosis were included in the study – 92 (71%) with UC, 38 (29%) with CD. We found that 11 (12%) of the UC patients and 3 (8%) of the CD patients were colonized with ESBL producing Enterobacteriaceae. The isolated ESBL producing Enterobacteriaceae strains from UC patients included *Escherichia coli* (n=9), *Klebsiella oxytoca* (n=1) and *Escherichia hermannii* (n=1). The isolated ESBL producing Enterobacteriaceae from CD patients included *Escherichia coli* (n=3). The isolated bacterial plasmid genes associated with ESBL production in UC included CTX-M (n=11), TEM (n=4), SHV (n=2), in CD – TEM (n=3) and CTX-M (n=2). In UC 5 (46%) and in CD 1 (33%) of the isolated ESBL producing Enterobacteriaceae were resistant to ciprofloxacin. In 1 case of ESBL resistance to ciprofloxacin CTX-M, TEM and SHV gene combination was observed, in 2 cases CTX-M and TEM gene combination was observed and in 3 cases only CTX-M gene was present.

Conclusions: 1. High gut colonization rate (12%) with ESBL producing bacteria in UC patients, mostly *E. coli*, expressing CTX-M gene comparing with the literature. 2. High resistance to ciprofloxacin (46%) in UC patients, comparing to CD patients. 3. CTX-M gene associated with resistance to ciprofloxacin.

P784

A comparison study of the mucosa-associated microbiota between inflamed and non-inflamed sites in ulcerative colitis patients

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Background: Gastrointestinal microbiota is suggested to play an important role in the pathogenesis of ulcerative colitis (UC). Despite various efforts to identify disease-related alterations of the microbiota (dysbiosis), interindividual variation has made it difficult to determine the correlation of specific bacterium with the disease. We thus investigated paired mucosa-associated microbiota obtained from both inflamed and non-inflamed colonic sites in patients with UC.

Methods: Paired mucosal biopsies of the non-inflamed site (transverse colon) and the inflamed site (rectum) were obtained from 14 patients with active left-sided or proctitis UC. We also obtained paired mucosal biopsies (transverse colon and rectum) from 14 healthy controls. The compositions of microbiota were investigated using 16S rRNA gene (V4 region) sequences on the Illumina MiSeq platform, followed by the data analysis using Qiime and LEfSe software.

Results: In both transverse-colon and rectum, less mucosal microbial diversities were observed in patients with UC when compared to those in healthy controls. Although a principal coordinate analysis revealed that the general profile of the mucosal microbiome in the inflamed site was similar to that in the non-inflamed site, linear discriminant analysis (LDA) effect size (LEfSe) showed significant increase of genus *Cloacibacterium* and family *Tissierellaceae* in the inflamed site than in the non-inflamed site. On the other hand, neither the profile nor the abundance of mucosal microbiome was different between the transverse colon and rectum in healthy controls.

Conclusions: Mucosal microbial dysbiosis was observed in both inflamed and non-inflamed sites in patients with UC. Genus *Cloacibac-*

terium and family *Tissierellaceae* might be associated with colonic inflammation in UC.

P785

Association of Bacteroidetes with endoscopic activity in patients with inflammatory bowel disease

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Background: The role of gut microbiota on the etiopathogenesis of inflammatory bowel disease (IBD), both in Crohn's disease (CD) and ulcerative colitis (UC), is not well known. Most studies of human gut microbiota rely on the non-invasive collection of stool samples. However, the analysis of the fecal microbiota may not reflect the role of the mucosa-associated microbes. Mucosa-associated germs live in close proximity to the intestinal epithelium and are in contact with the cells of the innate immune system directly involved in the inflammatory response. The aim of this study was to investigate the genotypes of Bacteroidetes microbiota from colon biopsies of IBD patients and to determine their relationship with the endoscopic activity of the disease.

Methods: A single-center, observational cross-sectional study was designed. Consecutive patients with Crohn's disease (CD) and ulcerative colitis (UC) who attended the Endoscopy Unit for colonoscopy were included. Colonic biopsies were taken to characterize microbiota. We did this by using a restriction fragment length polymorphism (RFLP) analysis on PCR products targeting the 16SrRNA genes of Bacteroidetes digested with HinfI, PciI, DpnII and AciI.

Inactive UC was defined as a Mayo endoscopic score of 0. Inactive CD was defined as a SES-CD ≤ 2 . The association of endoscopic activity with demographic (gender, age and smoking habits) and analytical (VSG, PCR and platelets) factors was also evaluated. The results were expressed as prevalence and analyzed using logistic regression. **Results:** 52 consecutive IBD patients (28 CD and 24 UC) were included. 33 patients showed endoscopic activity of the disease (20 CDa and 13 UCa). A total of eight genotypes of Bacteroidetes called N1, C1-C5, CB 10 and CB13 were detected. N1 is probably a strain of *Bacteroides dorei*, and C1 and C2 *B.vulgaris* strains. While the presence of N1 and C1 genotypes was consistent in patients with active and inactive IBD, the percentage of C4 genotypes in patients with UCa and CDa was very high (81.8%) compared to patients without activity (36.8%) ($p=0.001$). C3 genotype was observed in 4/19 inactive IBD patients and in 12/33 of active IBD patients ($p=0.24$). Other genotypes were found sporadically in IBD biopsies. No differences were observed between the genotype of patients with CD or UC. After multivariate analysis, C4 genotype in colon biopsies was associated with endoscopic activity of the disease (OR 8.58, 95% CI 2.16–34.08) ($p=0.02$).

Conclusions: The presence of genotype C4 of Bacteroidetes is associated with the endoscopic activity of IBD, in both CD and UC. Future studies are needed to determinate their role as an activity biomarker.

P786

Correlation between the presence of Bacteroidetes and faecal calprotectin for the detection of endoscopic activity in patients with inflammatory bowel disease

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Background: Faecal calprotectin (FC) levels correlate directly with the endoscopic activity of inflammatory bowel disease (IBD). Microbiota plays a role in the etiopathogenesis of IBD. In this context, the presence of specific genotypes of bacteroidetes has been shown to be associated with the activity of the disease. The aim of this study was to evaluate the correlation between the presence of genotypes of bacteroidetes and the FC levels in relation to the endoscopic activity of IBD.

Methods: A single-center, observational cross-sectional study was designed. Consecutive patients with Crohn's disease (CD) and ulcerative colitis (UC) who performed a colonoscopy were included. Colonic biopsies were taken to characterize microbiota by using a restriction fragment length polymorphism (RFLP) analysis on PCR products targeting the 16SrRNA genes of Bacteroidetes digested with HinfI, PciI, DpnII and AciI. FC levels were measured in faecal samples with a quick test (Quantum blue) the day before starting colon cleansing for colonoscopy. Inactive UC was defined as a Mayo endoscopic score of 0. Inactive CD was defined as a SES-CD ≤ 2 . Results are shown as prevalence and median, and they were analyzed by the Mann-Whitney test, Spearman correlation test and multivariate linear regression.

Results: 22 patients with IBD (12 CD and 10 UC) were included. Endoscopic activity was detected in 15 patients (9 CDa and 6 UCa). 7 different genotypes of Bacteroidetes called N1, C1-C5 and CB10 were detected. The presence of genotype N1 and C1 was constant in patients with active and inactive IBD, while genotype C4 was present in 82.3% of patients with UCa and CDa, and in 17.6% of patients with inactive IBD ($p=0.009$). The median of FC was 30 $\mu\text{g/g}$ (range 30–101) in patients with inactive disease and 315 $\mu\text{g/g}$ (range 30–1128) in patients with active IBD ($p=0.019$). In patients with genotype C4 the median of FC was 280 $\mu\text{g/g}$ (range 30–460), whereas in patients with other genotypes the median of FC was 41 $\mu\text{g/g}$ (range 30–101) ($p=0.01$). A positive correlation was found between C4 genotype and FC levels ($r=0.429$). After multivariable analysis, FC levels were associated with endoscopic activity (coef 473.8, $p=0.018$) and the presence of genotype C4 in biopsies (coef 67.9, $p=0.014$).

Conclusions: FC levels and genotype C4 of bacteroidetes in colon biopsies are associated with the endoscopic activity of IBD. The association of these two biomarkers could help to determinate endoscopic activity in the future.

P787

The microbiota and it's role in anti-TNF therapy non-response

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Background: The human microbiome has an important role in the pathogenesis of inflammatory bowel disease. Dysbiosis is not static and requires evaluation with a longitudinal approach.

Methods: CD patients commencing anti-TNF therapy had 3-monthly visits for 12 months with collection of biofluids (urine, faeces and serum) and disease assessment with biochemistry and faecal calprotectin (FC) or mucosal healing. A response index combining biochemistry (fall in FC or a decrease in CRP) and mucosal healing was used to define therapeutic response in the presence adequate drug level.

Collection of 168 faecal samples from 68 anti-TNF naive CD patients (luminal phenotype undergoing anti-TNF therapy without surgical resections) and 20 healthy controls (HC). Liquid-Chromatography Mass Spectroscopy (LC-MS) with lipid, bile acid and HILIC profiling of faecal metabolites was undertaken. 16SrRNA extraction using powerlyzerkit[®], sequencing with MiseQ illumina[®] and processing using Mothur was performed. 16S changes were then compared to response index to anti-TNF therapy.

Results: There were 18 non-responders and 9 responders to anti-TNF therapy according to biochemical and mucosal healing parameters (response index). Comparison between HC and CD demonstrated that there were 21 OTU (operational taxonomic units) which were different including eschericia, streptococcus and bacteroides. Faecalibacterium was lower in the CD cohort while bacteroides was increased prior to anti-TNF therapy.

With regard to response to anti-TNF therapy, there was no significant change in species richness or beta diversity over time.

Comparing responders and non-responders to anti-TNF therapy, clostridiales was lower while lactobacilles was higher in responders to anti-TNF therapy after bonferroni correction (Fig. 1).

Faecal metabolomic analysis of anti-TNF response				
		Faeces		
		HILIC	Lipid	Bile acid
Response vs Non-response	R2X	0.42	0.28	0.27
	R2Y	0.64	0.47	0.67
	Q2Y	0.32	0.70	0.26
	P-val	0.001	6.87 x 10 ⁻⁴	0.024

Number of sequences for clostridiales and lactobacillus in responders and non-responders

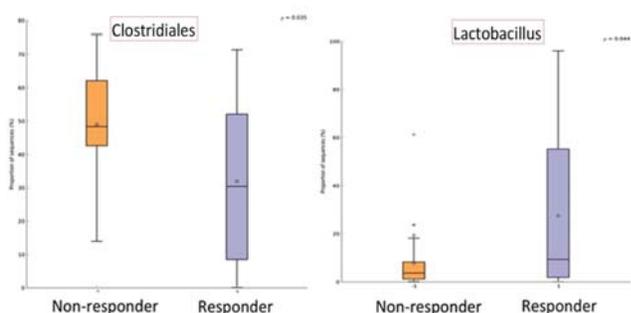


Figure 1. Metabonomic and 16S analysis of response to anti-TNF therapy

Bifidobacterium is elevated in non-responders while faecalibacterium and ruminococcus increased over time responders.

Faecalibacterium and bacteroides were lower in responders while Enterobacteriales and Lactobacilliales are higher in responders compared to HC.

Faecal metabolomic analysis demonstrated models which could separate responders from non responders with HILIC (R2X 0.42, Q2Y 0.32, p=0.001), lipid (R2X 0.28, Q2Y 0.70, p=6.78 x 10⁻⁴) and BA (R2X 0.27, Q2Y 0.26, p=0.024). Bile acids observed are known to be products of gut bacterial oxidation.

Conclusions: Analysis of microbiome and metabolome reveals important pathways of anti-TNF response and species which might be responsible for response to anti-therapy with a relative stability of the microbiome despite treatment response.

P788

Microbiota related disease activity and distribution in subgroups of inflammatory bowel disease

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Background: Knowledge about a patients' microbiota profiles might give useful information in diagnosing, early relapse prediction and to distinguish responders from non-responders to treatment. Faecal calprotectin (FCal) is used as a marker in diagnosis and follow-up of patients with inflammatory bowel diseases (IBD). The IBD-Character project aims to analyse faecal microbiota profiles, microbial diversity and concentration of FCal in treatment naive newly diagnosed IBD patients, symptomatic non-IBD patients and healthy controls.

Methods: Patients were diagnosed according to international criteria, including endoscopic and histopathologic assessment. Patients with ulcerative colitis (UC) and Crohn's disease (CD) were classified based on anatomic distribution of inflammation according to the Montreal classification. Stool samples were stored at -80°C before microbiota 16S rRNA analysis (GA-map[™] Dysbiosis Test) (1) of dysbiosis defined as non, mild or severe, and analysis of specific microbial taxa. High FCal (fCAL[®] ELISA, Bühlmann laboratories AG) was defined as >100 µg/g. Stool samples collected within 369 days prior to and within 14 days after diagnosis (= onset of treatment), and with no antibiotic treatment last two months, were included.

Results: Data on dysbiosis, bacteria profiles and FCal were available in 41 CD, 58 UC, 8 IBD-U patients, and 129 symptomatic non-IBD and 45 healthy controls. There was a relationship between FCal and dysbiosis in UC patients (p=0.0249, ANCOVA), which was not the case for CD and the control groups. Univariate analysis of the bacterial profiles among the Montreal classified subgroups identified bacteria that could differentiate between one or more of the subgroups, see Table 1. Increasing UC severity consistently yielded lower bacteria abundance, e.g. Bifidobacterium. For CD patients no significant relationship was found, however the strongest nonsignificant bacte-

Table 1

	Bacteria	p-value	Adjusted p-value
UC	Bifidobacterium	<0.001	0.03
	Streptococcus	<0.01	0.03
	Alistipes	<0.01	0.03
	Eubacterium	<0.01	0.03
CD	Bifidobacterium	0.04	0.85

ria; Bifidobacterium showed increased abundance. (Kruskal-Wallis Rank Sum test, Benjamini & Hochberg p-value adjustment).

Conclusions: We have identified a relationship between gut microbiota profiles and UC diagnosed patients, and showed that specific bacteria profiles are able to stratify subgroups of UC. Relationship between FCal and dysbiosis was significant in the UC group only. The data demonstrate a diagnostic potential for a microbiota test in IBD [1].

References:

- [1] Casen et al. (2015), Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD, *Aliment Pharmacol Ther* 42: 71–83

P789

Microbiome composition is altered in patients with IBD independent of endoscopic activity

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Background: Genetic and microbial heterogeneity in inflammatory bowel disease (IBD) are likely important in pathogenesis and in determining phenotype classification into: Crohn's disease (CD), ulcerative colitis (UC) and IBD unclassified (IBDU). This study aims to characterise intestinal mucosal microbial profiles and potential association with IBD phenotypic characteristics.

Methods: IBD patients and healthy controls (HC) were recruited from a tertiary care IBD center on the day of colonoscopy performed for disease activity assessment. Clinical and demographic data were recorded. Quiescent IBD was defined as partial Mayo 0 or SES-CD 0–2. Amplicon sequencing of the V4 region of 16s rRNA bacterial DNA was completed on Illumina MiSeq platform and sequences processed using the QIIME pipeline. Alpha diversity was calculated using Chao1 index after rarefaction at 8,500 reads per sample and associations addressed using parametric t-test. Principle coordinate analysis was conducted using Bray-Curtis as the beta diversity metric and significance tested using Adonis test. Taxa analysis was completed with Kruskal Wallis test.

Results: 263 sigmoid colon biopsies (UC n=101, CD n=96, HC n=48) were analysed. HC showed separation of beta diversity ($p < 0.001$, $R < 0.15$) and greater alpha diversity ($0.001 < p < 0.04$) than quiescent CD (n=31), and quiescent UC (n=37) respectively. In HC, taxa analysis identified increased Firmicutes ($q = 0.001$), and reduced Fusobacteria relative abundance (RA) ($q = 0.04$) and at genus level, reduced Actinobacteria microbacteria RA ($q < 0.04$) relative to quiescent UC and CD. We also compared microbiome profiles between IBD phenotypes. In quiescent disease, patients with CD involving the colon clustered with UC patients on a PCoA plot with no significant differences in taxa, however alpha diversity was reduced in CD relative to UC. Patients with endoscopic activity and remission were subsequently combined. CD patients had persistent reduced alpha diversity ($p = 0.0004$), and also weak separation from UC patients by beta diversity metrics ($q < 0.02$, $R = 0.01$). Taxa analysis identified a trend of increased Fusobacteria and Proteobacteria RA ($q = 0.059$), and reduced Coriobacteriaceae adlercreutzia RA in colonic CD compared with UC ($q = 0.03$).

Conclusions: IBD patients have altered microbiome profiles relative to HC in active and quiescent disease, although histological activity was not captured here. Both UC and CD phenotypes had reduced Firmicutes and increased Actinobacteria abundance relative to HC,

indicating microbiome dysbiosis in the absence of endoscopic activity. We show reduced alpha diversity in CD phenotypes relative to UC despite no difference in taxa of quiescent patients.

P790

Microbiota profile in pediatric IBD: correlations with phenotype and disease activity

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Background: Many studies have shown that in active IBD there is a dysbiosis, which could be a cause for a disturbed epithelial barrier function. The pediatric IBD patient, especially at onset of disease, offers a unique opportunity to investigate pathogenetic and particularly microbiological aspects of the disease.

Methods: Children with IBD were enrolled in the period 2013–2014, both patients at diagnosis (treatment naïve) and during follow-up. Stool samples were collected and immediately frozen. The microbiota composition was analyzed through amplification of the V3-V4 regions of the 16S rRNA gene and subsequently sequencing on Illumina MiSeq using the 300 bp paired-end protocol. Microbiological data were correlated to clinical (disease type, phenotype, activity) and laboratory parameters (fecal calprotectin, inflammatory markers). In a subgroup of Crohn's disease (CD) patients microbiota was analyzed before and after a course of exclusive enteral nutrition (EEN).

Results: In the study period 16 IBD patients were enrolled (median age 12.5 years), 9 with Ulcerative Colitis (UC), 7 with CD. A total of 28 samples was collected and analyzed. The total number of sequences written was 348681 and the total number of input sequences was 94760274. After filtration the median sequence length was 318 bp (range: 214–29867 bp). Comparison between UC and CD samples revealed significance in phylum level diversity for the Firmicutes phylum ($p = 0.046$), more represented in CD than UC. No statistical difference was found comparing active UC versus inactive UC and active CD versus inactive CD at phylum level. At species level, *Faecalibacterium prausnitzii* was found to be increased in patients with active CD compared to patients in remission ($p = 0.02$). The relative abundance was compared between samples collected before starting EEN (group pre-EEN, 3 subjects, median age 10.9 years) and post EEN and with the relative abundance of another group of CD patients (4 subjects median age 14.2 years) that had completed an EEN course from at least one year. After 8 weeks of EEN an increase in the relative abundance of Firmicutes (65.9% versus 75%) and a decrease in Proteobacteria (11.8% versus 2.9%) was observed, although this did not reach the statistical significance at the Wilcoxon rank sum test.

Conclusions: The apparent increase in Firmicutes in CD subjects compared to UC subjects is an interesting result, worth of further exploration. The increased representation of *F. prausnitzii* in patients with active CD minimize the role of the decrease in the abundance of *F. prausnitzii* as a possible etiological factor in CD. EEN lead to a significant change in intestinal microbiota that seem to reverse in CD patients after some months from EEN discontinuation.

P791**Activation of the aryl hydrocarbon receptor after simvastatin and recombinant antagonist of receptors of interleukin-1 treatment in a rat model of inflammatory bowel disease**

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Background: The pathogenesis of inflammatory bowel disease is complex and multifactorial. Studies have led to the current concept that aryl hydrocarbon receptors have recently emerged as a critical physiological regulator of immune responses affecting both innate and adaptive systems. We studied the possibility of simvastatin and antagonist of receptors of interleukin-1 for pharmacological correction of colitis in rats with a focus on the expression intensity studies of AhR with lymphocytes of colon.

Methods: Experiments were carried out on male Wistar rats aged 8 months (body mass 260–285 g). Rats were divided into four experimental groups: group 1 – control; group 2 – rats with oxazolone-induced colitis; group 3 – rats given simvastatin (20 mg/kg, for 5 days, intraperitoneally); group 4 – rats given antagonist of receptors of interleukin-1 (3 mg/kg, for 5 days, subcutaneously). The AhR immunopositive lymphocytes were determined using an indirect immunofluorescence technique with using a monoclonal rat antibody.

Results: We established that development of colitis was not accompanied with the change of amount of AhR+ lymphocytes in immunopositive cells. Drug administration during the development of experimental pathology was accompanied by changes in the expression of AhR on lymphocytes.

Conclusions: Simvastatin and antagonist of receptors of interleukin-1 seemed to be beneficial in oxazolone -induced colitis rat model through modulate AhR expression with lymphocytes of colon.

P792**Modulation of the fecal metagenome in patients with Crohn's disease**

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Background: Patterns of gut microbiome dysbiosis in inflammatory bowel disease (IBD) patients are inconsistent among published studies. In this work, we explored associations between the gut microbiota and active IBD to analyze the potential of a convenient and early diagnosis of Crohn's disease (CD).

Methods: Fecal samples of new-onset CD patients and healthy controls were collected. Fecal samples were homogenized and DNA was extracted using QIAamp DNA Mini Kit (QIAGEN, Barcelona, Spain). DNA was then amplified by PCR using primers directed to targets flanking the variable regions 1 to 3 in the 16S bacterial rRNA gene.

A DNA pool with barcoded equimolar PCR products was used for clonal amplification and pyrosequencing in a GS Junior (Roche, Switzerland). For sequence analysis, MG-RAST server with the database ribosomal Project (RDP) was used, converting DNA sequences into relative abundances of microorganisms of different taxonomic levels. Statistical analysis were performed using the Graph-

PadPrism 7 and SPSS 20.0 software. Differences between means were performed with significance tests using an analysis of variance (ANOVA) and post-hoc test with less significance. Nonparametric data are expressed as median (range) and analyzed using the Mann-Whitney U test. Differences between proportions were analyzed by chi-square test. Significance was accepted at $p < 0.05$.

Results: Microbial community was characterized using 16S rRNA gene sequencing in 29 samples (n=13 CD patients, and n=16 healthy controls). The mean Shannon diversity was higher in the healthy control population compared to CD group (5.5 vs. 3.7). A decreased number of species was found in the CD group.

Dysbiosis was observed in CD group due to increased population of Firmicutes, presenting a Firmicutes/Bacteroidetes ratio of 1.71 versus 0.80 in controls. 77,143 readings were obtained in the case of control samples and 69,296 reads in CD group. A grouping pattern was identified for most of the subjects in both groups, showing a marked difference between control and CD groups. A permutational ANOVA calculated by FIRST showed statistically significant differences between groups. Significant differences were found in Entomoplasmataceae, Bacteriaceae, Lachnospiraceae, Ruminococcaceae and Rikenellaceae. When relative abundance of bacterial genera was analyzed, significant differences in Ruminococcus, Roseburia, Parabacteroides, Mesoplasma, Faecalibacterium, Eubacterium and Alistipes were observed, showing an increased distribution in the control group.

Conclusions: Less biodiversity and a significantly different pattern on microbiota distribution has been found in active CD patients compared to control group. Patients with CD may benefit from these findings in the early diagnosis and follow-up.

P793**Microbial composition in IBD may influence clinical symptoms independent of endoscopic activity**

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Background: Symptoms in inflammatory bowel disease (IBD) do not consistently mirror endoscopic activity. The aim of this study is to determine if there is a relationship between mucosal microbiome composition and clinical activity.

Methods: IBD patients and healthy controls (HC) were recruited from a tertiary IBD centre on the day of colonoscopy. Clinical and patient demographic data were recorded and mucosal biopsies obtained. Quiescent IBD was defined as Mayo 0 or SES-CD 0–2, mild as Mayo 1 or SES-CD 3–5, moderate to severe as Mayo >2 or SES-CD >6. Clinical activity was defined as partial Mayo score >3 or CDAI >220. Bacterial DNA from biopsies was extracted and the V4 region of 16s rRNA sequenced by Miseq and processed using the QIIME v1.9 pipeline. Alpha diversity was calculated using Chao1 index after rarefaction at 8,500 reads per sample prior to analysis and associations addressed using parametric t-test. Principle coordinate analysis was conducted using Bray-Curtis as the beta diversity metric and significance tested using an Adonis test after 1000 permutation on the first 3 PCoA axes. Taxa analysis was assessed using Kruskal Wallis test or Spearman correlation.

Results: 225 IBD patients and 48 HC were recruited. Sigmoid biopsies from patients with moderate to severe endoscopic disease were analysed initially. Measures of beta and alpha diversity were similar in clinically active patients (n=51) relative to clini-

cal remission (n=32). Taxa analysis showed reduced relative abundance (RA) of Gammaproteobacteria, Coriobacteria and Fusobacteriia ($0.01 < q < 0.04$) in asymptomatic relative to clinically active patients. Increasing RA of Actinobacteria micrococccaceae correlated with increasing CDAI and partial Mayo scores ($p=0.001$, coefficient=0.34). In contrast, microbiome composition in quiescent IBD was compared in patients with (n=12) and without clinical activity (n=65) and to HC (n=48). HC had greater Chao1 alpha diversity ($q=0.003$) when compared to IBD. Among IBD patients, Fusobacteriaceae RA was increased patients reporting symptoms despite endoscopic remission ($q=0.02$). Symptomatic patients have greater RA of Bacteroidaceae ($q=0.004$), Fusobacteriia ($q=0.004$) and Actinobacteriia ($q=0.01$) relative to clinical remission.

Conclusions: In IBD patients with and without mucosal healing, increasing clinical symptoms correlated with greater abundance of bacteria including Actinobacteriia and Fusobacteriia. The relationship between inflammation and intestinal dysbiosis remains unclear. These data suggest an association between specific taxa and clinical symptoms in active and quiescent IBD and may help to further explain why there may be poor correlation between clinical and endoscopic activity.

P794

Alterations of intestinal microbiota in ulcerative colitis

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Background: Changes in the composition of the intestinal microbiota are assumed to be associated with the onset and development of inflammatory bowel diseases (IBD).

The aim of our study was to identify the taxonomic features of the intestinal microbiota in patients with ulcerative colitis (UC).

Methods: The study included 46 patients with UC (25 men and 21 women, mean age 41.7 years). The disease duration ranged from 1 year to 36 years. All patients received 5-ASA as basic therapy. Whole genome sequencing was carried out on the SOLiD 5500 W platform (Life Technologies, Foster City, CA, USA). MetaPhlan2 was used for taxonomic profiling of analyzed metagenomes. Previously published metagenomes from 88 healthy subjects were used in the comparison control group.

Results: The proportion of reads on the human genome was strongly increased: $(14.61 \pm 18.62)\%$ vs $(0.47 \pm 0.91)\%$ in the control group, indicating the presence of inflammatory processes in the gut of the patients. The most predominant were Bacteroides, Prevotella and Faecalibacterium genera. Escherichia, Lactobacillus, Bifidobacterium and Streptococcus genera were predominant in some of the examined samples.

A significant decrease of commensal taxa of the following families: Lachnospiraceae, Rikenellaceae, Acidaminococ, Enterococcaceae, Desulfovibrionaceae, Verrucomicrobiaceae, Methanobacteriaceae was revealed, with the exception of Enterobacteriaceae, for which value was increased. Alpha-diversity index known to be associated with a healthy clinical status was used for assessment of the composition of microbiota. However, no significant difference was observed: for the control group it amounted to 3.32 ± 0.56 , for the experimental group it was 3.07 ± 0.65 .

Conclusions: The results of the analysis of metagenomic data from patients with UC, including assessment of the quality of the sequencing data, the assessment of taxonomic and functional composition of the microbiota showed significant changes compared to the samples of control group. The dysbiosis is characterized by the general decline of many commensal taxa. The lack of significantly increased taxa suggests the multi-directionality of the dysbiosis in UC patients.

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Nurses presentations

Nurses oral presentations

NO001

Clinical and psychological factors associated with erectile dysfunction in inflammatory bowel disease patients

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Background: Inflammatory Bowel Disease (IBD) can change patients' quality of life (QoL) and sexuality. The objectives were to evaluate the prevalence of sexual dysfunction and identify clinical and psychological factors associated with erectile dysfunction (ED) in men with IBD.

Methods: An observational study with 43 IBD outpatients and 48 controls was conducted. The Crohn's Disease Activity Index (CDAI) was used to assess the clinical activity of Crohn's Disease (CD) patients. Mayo score was used to assess the clinical activity of Ulcerative Colitis (UC) patients. The Inflammatory Bowel Disease Questionnaire (IBDQ) was used to measure QoL. The hospital anxiety and depression scale (HADS) was used to measure anxiety and depression. Erectile dysfunction was assessed with the International Index of Erectile Function (IIFE). Statistical analysis: descriptive statistics, Chi-square test (χ^2), Pearson correlation test and logistical regression. This study was approved by the Research Ethics Committee (CAAE: 27545914.2.0000.5411).

Results: We evaluated 25 CD patients and 18 UC patients. The mean age was 38.8y (± 13.5) for patients and 37.6y (± 9.9) for controls. Regarding CD patients, 28% presented with activity disease, 64% perianal disease; among UC patients, 17% presented activity disease. 33% patients anxiety and 11% depression. ED was found in 27.9% of patients and 12.5% of controls ($p=0.11$). The presence of ED in the IBD group was associated with weight loss ($p=0.0593$), fatigue ($p=0.0277$), weakness ($p=0.0445$), perianal disease ($p=0.0078$) and satisfaction with sex life ($p<0.0001$). Depression (OR: 1.501; 95% CI: 1.106–2.037, $p=0.0091$) ($R=-0.32180$; $p=0.0354$) and low self-esteem (OR: 0.817; 95% CI: 0.709–0.942, $p=0.0053$) ($R=0.43244$; $p=0.0038$) were associated with increased risk of ED. Patients with a better QoL (OR: 0.981; 95% CI: 0.963–0.999, $p=0.0379$) had a decreased risk of ED, which was not associated with the diagnosis of the disease ($p=0.67$) neither with the presence of disease activity.

Conclusions: Erectile dysfunction was a common finding in our study. Factors associated with ED were disease symptoms as weight loss, fatigue, weakness and presence of perianal disease. Psychological factors

NO002

Decision-making about emergency and planned stoma surgery for IBD: a qualitative exploration of patient and clinician perspectives

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Background: Many IBD patients worry about needing a stoma and may endure poor quality of life (QoL) and difficult bowel symptoms to avoid one. Stoma care advice abounds, but the emotional impact of anticipating and having stoma forming surgery (SFS), and whether expectations match the actual experience, is under-reported. This study explored patients' and clinicians' views of SFS and how pre-operative concerns compare to outcomes.

Methods: We purposively recruited UK participants from hospital outpatient and community sources, and clinicians from public hospitals. We conducted four focus groups and 29 semi-structured interviews with people with IBD and either: a current temporary, recently-reversed or permanent stoma, or stoma naïve and worried about the prospect, and individual interviews with 18 IBD clinicians. Interviews were audio recorded and transcribed. Data were analysed thematically.

Results: Four themes emerged:

Pre-operative concerns and expectations: patients and clinicians cite body image, stoma visibility, leakage and smell, and impact on relationships as concerns. Patients expect a stoma to disrupt preferred activities. Clinicians expect to avoid SFS in young adults.

Decision-making: patient decision-making about SFS is complex. Some clinicians, expecting patients to react negatively, avoid the topic. Others advocate early mention of surgery, with dialogue about SFS increasing when medication does not control IBD. The words "failure" and "last resort" transmit negativity about this therapeutic option to patients.

Surgery and recovery: disease status often forces consent for SFS, but age, gender, QoL, relationships, and prior contact with others with a stoma are influential. The immediate post-operative period is the most challenging.

Long-term outcomes: most patients' pre-operative concerns prove unfounded, with outcomes often better than expected. Patients' ability to accept a stoma may be influenced by duration and quality of information, preparation and support.

Conclusions: Patients need balanced information on benefits and challenges of all treatment options including surgery, from an early stage. Multi-disciplinary team dialogue about likely SFS should



begin when medication fails to control IBD. Using negative language and discussing SFS as a “last resort” are unhelpful. Patients and clinicians agree that support from similar others with a stoma is highly effective at reducing a patient’s concerns. For many, life with a stoma is better than anticipated, improving QoL and control. Ongoing IBD and stoma nurse support aids recovery and adjustment.

NO003

IBD nurses as integral part of a multidisciplinary IBD team: prospective study on view on patient outcomes

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Background: Inflammatory bowel diseases (IBD) are chronic gastrointestinal conditions with great impact on patient’s social and professional life. Information, education and empowerment will help to optimize and ameliorate disease outcomes. In this process IBD nurses play a key role. They support the patient and facilitate prompt recognition of symptoms. In this way, IBD nurses can accomplish better compliance, more early intervention during flares and as a consequence, improve patient outcomes. We prospectively investigated the effect of IBD nurses on improvement of quality of patient’s care.

Methods: In Sep 2016, a second IBD nurse joined the multidisciplinary IBD team in our tertiary referral center. In order to standardize assessments and measurements, all contacts (phone, e-mail and personal contacts) were prospectively collected and in detail by using a standard record. Patient characteristics, type of contact and interventions performed by the IBD nurse were categorized in the record and outcomes were reported.

Results: During Sep and Oct 2016, 703 patient contacts were recorded by the two IBD-nurses (43% male, median age 35 years, 77% Crohn’s disease; 65% of patients on biologicals). The vast majority of nurse-patient contacts were phone calls (64%), a minority involved personal contacts (28%) and e-mails (9%). Most of the contacts of the IBD nurse were assigned to providing disease information (24%), to the planning of procedures and consultations (21%), to administration (12%) and to the follow-up on medication (11%). In addition 11% of the patients contacted the IBD nurses for flare management, 9% for psychosocial support, 7% for the start of new therapy and 6% for education on therapy. Most of the interventions performed by the nurses involved comforting patients (22%), calling patients for follow-up (19%), for blood or stool sampling (15%) and planning an urgent outpatient visit (9%). Beside, information brochures were provided during 5% of the contacts, medication was initiated for 5% of the patients and 4% of the patients were referred to the general practitioner. By planning 75 urgent outpatient visits, the IBD nurses intervened earlier during a flare and as a result 17 emergency room visits could be avoided in this 2-month period only. Another 92 outpatient appointments could be avoided through counseling by phone and for 10 patients education and follow-up on therapy resulted in better compliance.

Conclusions: Standardized measurement of outcomes is a “hot topic” in today’s clinical practice. Prospective and standardized reporting of each nurse-patient contact allows us to measure important patient outcomes. In this way variability in reporting can be reduced, and the care can rapidly be monitored and improved.

Nurses poster presentations

N795

Fatigue in IBD must be to compared to the background population – generation of normative data for the IBD-F

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Background: The prevalence of fatigue in IBD has been revealed to be between 40–80% [1]. Furthermore, fatigue is a major concern among patients with IBD and some intervention studies have been accomplish. Fatigue is measured via self reported questionnaires.

Recently, the first IBD fatigue questionnaire: Inflammatory Bowel Disease Fatigue scale (IBD-F) was developed along with IBD patients in the UK [2]. The IBD-F comprises 35 questions. Five questions are measuring the severity of fatigue (score 0–20) and 30 questions are measuring the impact of fatigue (score 0–120).

All questions have a generic character and can be answered by everyone, regardless of IBD or not. If the IBD-F shall be used extensively in the field of IBD fatigue, normative values need to be available.

The aim of this study was to generate normative values for an electronic version of the IBD-F in a background population.

Methods: The IBD-F was translated and validated into Danish according to international guidelines.

An age- and gender-stratified random sample of 3460 Danes was drawn from the Danish Civil Registration System. The IBD-F was administered electronically to those from the sample who were registered to receive electronically correspondence with the authorities. Each participant received an individual link to the e-survey. In addition the participants were asked a few question concerning socio-demographics and morbidity.

Results: A total of 2990 (86%) citizens were contacted electronically. After a friendly reminder, 1925 (64%) citizens responded and 1905 had complete IBD-F data.

Both the severity of fatigue and the impact of fatigue was found significantly higher for females when compared to males (7.3 vs. 6.6; $p < 0.001$) & (17.0 vs. 13.5; $p < 0.001$).

Regardless of gender, most fatigue was found for citizens in the twenties and the thirties.

Mental co-morbidity increased the levels of fatigue more than physically co-morbidity. If both conditions were present the levels of were even higher.

Lower education was associated with higher levels of fatigue for both men and women.

Fatigue was significantly higher for those not being active on the labour market.

Conclusions: The levels of fatigue in the background population are higher for females and young citizens.

Furthermore co-morbidity, low education and being “out of the labour market” are factors that need to be considered when measuring fatigue in IBD.

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N796

Emotional en social functioning in patients with Crohn's disease needs more attention

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Background: Crohn's disease (CD) is a chronic inflammatory bowel disease with significant impact on the perceived quality of life (QoL). The treatment and support of patients with CD is mainly focused on somatic functioning inducing clinical remission. Emotional and social functioning receive less attention, but are important for the perceived QoL. The primary objective of this project was to study the QoL in our cohort of CD patients, with focus on emotional and social functioning. The secondary objectives were to identify patient characteristics associated with poor QoL and to identify if gastroenterologists and nurses discussed emotional and social functioning with their patients.

Methods: This was a retrospective cohort study in CD patients (N=348) treated at Rijnstate Hospital Arnhem. These patients were asked to fulfill the Inflammatory Bowel Disease Questionnaire (IBDQ) in 2014.

We selected patients with the highest (upper quartile, n=42) and lowest (lower quartile, n=59) scores on emotional and social functioning. These groups were compared on demographical and patient characteristics. All medical charts from the lowest scoring group were analyzed on descriptions of emotional and social functioning and whether interventions like referral to a psychologist were undertaken.

Results: Patients in the lowest scoring group had more disease activity, were more often hospitalized and used more anti-TNF medication compared to patients from the highest scoring group (Table 1). The lowest scoring group included more women. Signals of emotional and social (dis)functioning in this group were reported in

35/59 (60%) of the medical charts. Interventions were initiated by gastroenterologist or nurses in 17/59 patients (29%).

Conclusions: The QoL in our cohort of CD patients was comparable with other cohorts in the Netherlands. In this cohort we showed that patients with the lowest scores on emotional and social functioning have significant impaired QoL. The patients with the lowest perceived QoL on emotional en social scale, were characterized by female gender, disease activity, hospitalization and anti-TNF use. Although there is general attention to signals of emotional and social dysfunctioning; in 40% of patients this was not recognized. In the 60% of patients in which signals were recognized, interventions were undertaken in only 30%.

Further study is needed to identify if more attention for emotional and social functioning and more specific interventions in these domains will actually lead to a better perceived QoL in these patients.

N797

Therapeutic drug monitoring after thiopurine initiation improves drug efficacy

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Background: Thiopurines are effective in the maintenance treatment of inflammatory bowel disease (IBD). However, 20–30% of IBD patients discontinue the Thiopurine within 3 months after initiation due to adverse events or failure of therapy. Our aim was to evaluate the protocol of adjusting dose of Thiopurines, based on the level of metabolites (6-TGN and 6-MMP), on the percentage of patients continuing to use the drug.

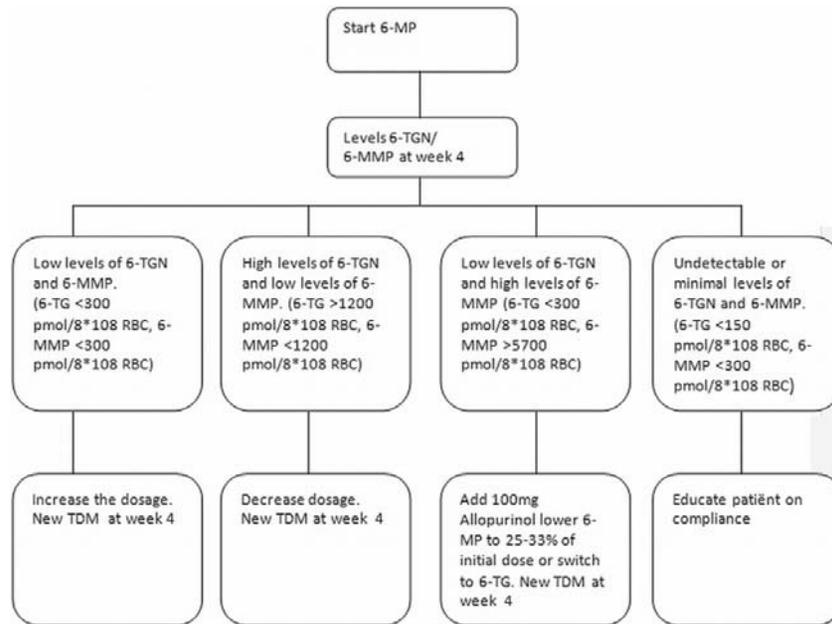
Methods: This is a retrospective cohort study in adult IBD patients. Two groups of 50 patients were compared. Weight based dosage of mercaptopurine (1–1.5 mg/kg) in the control group (2012–2013) was compared to metabolite level based dosage of mercaptopurine in the therapeutic drug monitoring (TDM) intervention group (2015–2016)

Abstract N796

Table 1. Demographic characteristics and disease-related characteristics of patients with Crohn's disease in domains of emotional and social functioning of the inflammatory bowel disease questionnaire

	Lowest scoring group N=59	Highest scoring group N=42	value
Patient characteristics			
Age in years, mean ± SD	46.0±13.5	49.3±16.9	ns
Female, n [%]	41 [69.5]	18 [42.9]	0.007*
Smoking, n [%]	16 [27.1]	10 [23.8]	ns
Disease characteristics			
Disease duration (years) Median, [min-max]	10.0 [0-36]	11.5 [0-61]	ns
Disease activity [‡] , n [%]	23 [39.0]	2 [4.8]	0.01*
Hospitalization [‡] , n [%]	6 [10.2]	0 [0.0]	0.03*
Medication			
Use of medication *, n [%]	52 [88.1]	34 [81.0]	ns
5-ASA	10 [16.9]	10 [23.8]	ns
Corticosteroids	13 [22.0]	4 [9.5]	0.09 ^{NS}
Thiopurines	33 [55.9]	20 [47.6]	ns
Anti-TNF	19 [32.2]	6 [14.3]	0.04*

* significant p<.05, NS non-significant, # at the moment of completion the Inflammatory Bowel Disease Questionnaire (IBDQ), ‡ max 3 months before completion of the IBDQ.



Abstract N797 – Figure 1. Therapeutic drug monitoring.

(Figure 1). Primary outcome was the percentage of patients still using mercaptopurine 3 months after starting the drug. Secondary outcomes were the number of adverse events and the number of IBD patients with a corticosteroid-free clinical remission at 3 months.

Results: Patients characteristics were similar in the two groups. The number of patients using a Thiopurine after 3 months was 92% in the intervention group and 76% in the control group. Adverse events were reported in 46% of patients in the intervention group and in 66% of patients in the control group. Corticosteroid-free after 3 months were 70% of patients in the intervention group and 56% patients in the control group.

Conclusions: We conclude that therapeutic drug monitoring based dosage is superior to weight based dosage at the initiation of Thiopurine therapy. 3 Months after starting treatment, in the therapeutic drug monitored group, more patients still use Thiopurines, less patients have adverse events and more patients are steroid free compared to weight based dosage group. Further evaluation is needed to study effect on long term remission of IBD.

N798 Kinship stigma in community-dwelling people with inflammatory bowel disease: family acknowledgement matters

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Abstract N797

Table 1. Results

	Intervention group N= 50	Control group N=50	Total N=100	P
Thiopurine continued 3 months after initiation, n (%)	46 (92%)	38 (76%)	84 (84%)	0.029* ^c
Patients with adverse events during the first 3 months, n (%)	23 (46%)	33 (66%)	56 (56%)	0.044* ^c
Corticosteroid-free 3 months after Thiopurine initiation, n (%)	35 (70%)	28 (56%)	63 (63%)	0.147 ^c

^aP≤0.05 = significant, clinical remission: normalisation of defecation and disappearance of blood in stool.

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Background: Stigma - feeling that you are being treated negatively because of a “mark” that you carry, is known to arise in people with inflammatory bowel disease (IBD). Public perceptions of disease, dirt and hygiene underpin the stigma experience. Goffman originally suggested that those who are “wise” to another’s mark will be supportive. Early evidence has indicated that in IBD, close family (or kin) who should be wise to their family member’s disease, may not be supportive. This study explored the experience of kinship stigma in people with IBD to reveal what it means when family are not “on your side” and the relevance of this for nurses caring for patients with IBD.

Methods: For this interpretive phenomenological study, participants were recruited from a UK IBD charity. Between July 2015 and April 2016, 18 unstructured interviews were captured, using a digital audio recorder. Participants were asked to describe their experiences of being stigmatized by those closest to them. Transcribed interviews were analysed by a research team using a hermeneutic method to uncover patterns and themes in the narrative data.

Results: One constitutive pattern: Family Acknowledgement As Support, and three themes: Visible/Invisible; I am the disease/I have the disease, and Amplification and Loss were revealed. Failure of family

to acknowledge the impact of disease on the patient, including required adjustments to daily routine, family life, diet and activity conveys a lack of understanding and validation of the person with IBD. Household social rules about toilets, meals and bowel control influence the family's support of the person with IBD and whether home is seen as an emotionally safe or unsafe place. The challenges of living with a changeably visible and invisible disease are compounded by an expectation that family should not need "evidence" to prove the presence and impact of IBD. IBD can widen pre-existing cracks in the family structure, amplifying the loss of support and of relationships already being experienced. Inadequate family support may impact on the individual's ability to cope with his/her illness on a broader social scale.

Conclusions: There is no guarantee that family members will be supportive towards the person with IBD. IBD is a family affair, impacting all family members. Lack of support may follow a family history of unsupportive behaviours which become intensified by illness. Kinship stigma appears to be more difficult to experience than other forms of stigma and may have wide-ranging implications for nurses and families caring for someone with a chronic illness. Assessing family response and attitude towards chronic illness may be fundamental for providing appropriate supportive nursing care to the patient and family.

N799

Inflammatory bowel disease affects sexual female desire and sexual female excitement

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Background: Sexual Dysfunction (SD) is a multidimensional problem, characterized by lack, excess, discomfort and/or pain during sexual intercourse, affecting one or more phases of sexual response (desire, excitement, orgasm and resolution). A specialized nurse for the assistance of Inflammatory Bowel Disease patients must recognize, identify possible dysfunctions and intervene in problems and act with sense of social responsibility and commitment to citizenship as a promoter of health. Objectives: The aims of this study were to evaluate the prevalence of female sexual dysfunction in IBD patients and identify clinical and psychological factors associated with it.

Methods: It was an observational study with 56 IBD outpatients and 70 controls paired by age. The control group consisted of healthy individuals who were companions of the patients, not spouses. The Short Medical Outcomes Study Questionnaire (SF 36) was used to measure the healthy related quality of life. The women's sexual response assessment was done through the Female Sexual Function Index (FSFI). Statistical analysis: descriptive statistics, Chi-square test (χ^2).

Results: The mean age was 38.8y (± 10.19) in IBD group and 38.4y (± 10.15) in control group. Among the IBD group 55% had Crohn's Disease (CD), 45% with perianal disease, 42% in disease activity and 3% had stoma. Twenty-five women had Ulcerative Colitis (UC), 72% presented pancolitis and 16% were in disease activity. SD was prevalent among the IBD group, although without difference when compared to the control group (45.6% vs 32.8%; $p=0.14$). Impairment was observed in all evaluated domain, with statistical difference between the domain desire (3.17 ± 1.21 vs 3.79 ± 1.11 ; $p=0.003$) and excitement (2.76 ± 2.09 vs 3.5 ± 1.94 ; $p=0.04$) between patients and controls. There was no statistical difference in the domain lubrication (3.27 ± 2.37 vs 3.96 ± 2.23 ; $p=0.19$), orgasm (3.1 ± 2.32

vs 3.82 ± 2.2 ; $p=0.16$), satisfaction (3.3 ± 2.46 vs 4.04 ± 2.25 ; $p=0.15$) and pain (8.3 ± 6.17 vs 9.57 ± 5.91 , $p=0.65$). Alcoholism ($p=0.05$) was associated with SD in the women with IBD. In the control group the associated variables were dyspareunia ($p=0.001$), low self-esteem ($p=0.001$), sex life satisfaction ($p=0.037$) and sexual abstinence ($p \leq 0.001$). There were no association among quality of life, presence of anxiety or depression and SD in IBD group. On the other hand, there was correlation among SF-36 physical aspects ($p=0.009$) and SF-36 emotional aspects ($p=0.006$) and the presence of SD.

Conclusions: Female sexual dysfunction was a common finding in our study. Impairment in desire and sexual female excitement domains were more prevalent in IBD patients when compared to control group.

N800

Statistical comparison of predictors of quality of life in inflammatory bowel disease

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Background: Impairment of the quality of life in IBD is multifactorial, but primarily has been attributed to clinical variables. The study of the predictors of this impairment has become a priority for nurses. Currently a large variety of socio-demographic, clinical, psychological, social and functional predictors have been detected that could be used to improve the quality of life. It would be very useful to know which are the most influential to prioritize our performance.

Methods: A descriptive study to identify predictors of quality of life in a population of 181 patients diagnosed with IBD. IBDQ-36 was used to measure the quality of life and 8 questionnaires to measure socio-demographic variables, clinical activity, self-care, family support, social support and psychological variables (depression, coping, ... Simple linear regressions between 18 predictors significantly associated ($p < 0.05$) were performed with quality of life. Finally, the coefficients of determination (R²), that indicate quantitatively the influence on the quality of life, were compared.

Results: The top 10 predictors, with a higher coefficients of determination (R²: 0.465–0.077, $p < 0.05$), were: trouble performing daily activities, depression, pain, clinical activity, walking problems, ineffective emotional coping, problems for self-care, relapses, corticosteroids and low perception of self-control. Knowledge of self-care, family support and social support are next. The predictor with lower influence was the type of Inflammatory Disease (Crohn vs colitis), R²:0.019. TABLE01

Conclusions: Functional requirements, related to the person's autonomy, and psychological disorders influence the impairment of quality of life more than clinical variables such as pain or clinical activity. Nursing consultation should focus on the functional and psychological assessment of the patient, enhancing autonomy and emotional coping. That way we can improve the quality of life parallel to clinical treatment.

N801

Patient opinion assessment of a comprehensive clinical tool to improve health-care in inflammatory bowel disease. The Implica-2 project

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Background: Patient personal opinions should be taken into account as they can be useful in the design of future clinical tools. We aim to provide information about the opinions of Inflammatory Bowel Disease (IBD) patients about a clinical tool designed by IBD nurses to improve health-care.

Methods: The clinical tool is compounded by three elements: an i-pad size folder to keep copies of medical appointments and reports, a notebook to list symptoms that worry patient about or concerns and questions before each medical visit and some IBD medication information leaflets. After 6 month an anonymous questionnaire was administered to assess the usefulness of this tool.

Results: 77 IBD patients were enrolled in this study: 43 ulcerative colitis (56%), 34 Crohn's disease (44%). The patients were 39 male (51%), mean age 46.4 (13) years, time since diagnosis 13.5 (9.5) years and 27 (36%) were on combination therapy. Finally 61 patients (79.2%) answered the questionnaire. Altogether, 87.7% used the folder and 12.3% did not employ it. The i-pad size folder was valued as useful by 90.2% of patients who had used it. Regarding the medication information leaflets, 44 patients (72%) read all the information and 11 (18%) the most part of it. 84% patients said they were given sufficient information, 4 patients demanded more information on side effects of medicines and 1 subject considered that a less technical language in medication leaflets should be used. The notebook was not used by 39 patients (64%).

The overall assessment of this tool reached a value of 8 (2) points in a visual analogue scale VAS (1–10 range).

Conclusions: Our clinical tool designed to improve health care for IBD patients achieved a very positive assessment by users, specially the folder and the medication information leaflets. Exploring the opinion of the ultimate users of the clinical tools is worth, because it allows us to identify strengths and weaknesses of it.

N802

Improving care for patients with perianal Crohn's disease; review of a perianal virtual clinic

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Background: Effective communication within the inflammatory bowel disease (IBD) team is essential to the management of perianal Crohn's disease (PCD). We identified that medical, nursing and surgical care could be fragmented for patients with complex PCD. To address this we developed the perianal virtual clinic (PVC); a quorum of gastroenterologists, surgeons, and clinical nurse specialists who meet once weekly for 2 hours. Virtual review of patients with complex PCD is combined with up to 2 patients face to face.

Methods: PVC review includes evaluation of clinical symptoms, radiological investigations and biochemical markers. Medical management is optimised using drug levels and anti-drug antibodies and further radiological assessment or clinic review is arranged as appropriate. Patients reporting acute PCD activity are invited to attend the clinic where we offer a seamless one-stop service from assessment to surgery. This includes examination, discussion of treatment options,

relevant screening, consent and surgical pre-assessment. PVC activity and outcomes have been reviewed between January and June 2016.

Results: During this period we reviewed 69 virtual patients and 31 acute cases face to face.

Virtual: 31/69 were booked for a EUA directly from PVC; 45% of these were approved to commence a biologic following this. 14 were booked a routine outpatient appointment. 5 had their MRI reviewed without need for treatment alteration and 7 booked face to face for assessment and optimisation of medical treatment. 5 patients had an MRI prior to commencing biologics and approved to start without further surgical drainage. 7 had their future MRI scans planned for on-going monitoring.

Face to face: 16/31 were scheduled straight to EUA following surgical assessment and biologics were optimised soon after. Medical therapies were optimised in a further 5 patients utilising antibiotics and biologics. 3 were booked for perianal MRI with subsequent EUA. 1 had their luminal reassessment with colonoscopy and small bowel MRI. 2 were booked for luminal surgery.

A further 4 were assessed following EUA to review response and plan future care.

Conclusions: PVC is an effective way of managing PCD ensuring an efficient interface between surgical, medical and nursing teams. This has led to more timely surgical interventions and early appropriate initiation of biological therapies. Those patients who attend the urgent face to face clinic have a one-stop service from assessment to consent and surgical pre-assessment.

N803

Accelerated infusions of biosimilar infliximab are safe and well tolerated and monitoring post-infusion is not required

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Background: Infliximab is an anti TNF α antibody widely used in the treatment of inflammatory bowel disease. Accelerated infusion durations over 30–60 minutes, with reduced post infusion monitoring of 30–60 minutes have been shown to be safe and well tolerated in the originator molecule Remicade [1]. We previously audited 310 Remicade infusions in 103 patients and found that accelerated infusions were safe and that monitoring patients post-infusion was not necessary. Our unit started prescribing biosimilar infliximab Remsima in new starters in April 2016, and switched patients from Remicade from June 2016. The aim of this audit was to evaluate the safety of accelerated infusions of Remsima and the need for post-infusion monitoring.

Methods: 276 Remsima infusions were administered to 154 patients during April to October 2016 (6 months). Data was recorded on completion of the infusion and post-infusion monitoring (PIM). Infusions were administered over 30, 60 or 120 minutes (Table 1). In patients switching from Remicade the first infusion was administered over at least 60 minutes. Patients receiving doses of 10mg/kg had their infusions administered over at least 60 minutes. In order to assess the need for PIM all patients were observed for 30 minutes following completion of the infusion. Blood pressure, pulse, respiratory rate, oxygen saturations were recorded every 30 minutes during the infusion and 30 minutes after completion of the infusion. Adverse reactions were classified as:

- Mild: no action required
- Severe: immediate action or treatment withdrawal

A systolic drop in BP of ≥ 20 mm/Hg was documented with details of action taken. Treatment of reaction and outcomes were recorded, including occurrence during infusion or post-infusion period. Details of any delayed reactions following discharge were obtained from patient notes.

Results: During the infusion: 1 patient (0.36%) had a severe adverse reaction during the first Remsima infusion following a switch from Remicade. BP dropped ≥ 20 mm/Hg during 19 infusions in 16 patients (range 22–50mm/Hg, median 24mm/Hg). No action was taken, all patients discharged following 30 minute post-infusion observation.

Post-infusion monitoring: No adverse reactions were recorded during the PIM.

- 1 patient had a drop in systolic BP of 24mm/Hg. No action was taken.
- There were no patient self-reported adverse events post-discharge.

Conclusions:

- Observed infusion reaction rate was 0.36% (2.91% infusion reaction in previous Remicade infusion audit).
- No adverse reactions occurred in the post-infusion monitoring period
- This audit suggests that accelerated infusions of Remsima are safe and well tolerated and post-infusion monitoring is unnecessary.

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N804

An evaluation of patient satisfaction with IBDoc calprotectin home test system

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Background: Faecal Calprotectin is a well-established biomarker to measure the level of inflammation in the gut. Assessment of calprotectin is important to measure disease activity, effectiveness of treatments as well as predicting relapses in Inflammatory Bowel Disease (IBD). Until now stool samples have been sent for laboratory analysis, leading to long delays between sample collection and test result. New technology (IBDoc) allows reliable testing of faecal calprotectin using a smartphone at home. The IBD centre at Mercy university Hospital (MUH) was one of just three IBDoc pilot sites in Europe in 2015. Since its launch little is known about the patient experience of using IBDoc. The objective of this study was to evaluate the patient satisfaction with IBDoc calprotectin home test system.

Methods: 100 patients with IBD (age 18–45 years) naïve to the IBDoc system were trained to perform the test and asked to carry out a calprotectin stool test independently at home. The users then filled in a questionnaire to determine ease of use, importance of patients being able to view results, reassurance that treatment is working, satisfaction with remote monitoring and its contribution to quality of care.

Results: 98 of 100 users were able to generate a calprotectin test result independently. All 100 respondents agreed that it was very important to them that they could view the result on their phone. 86% of respondents felt that IBDoc made them feel more confident and reassured that their treatment was working. 100% preferred doing the test at home as opposed to bringing the sample to the hospital. Reasons cited for this included: convenience, privacy and not having to travel to the hospital with a sample. 97% of respondents felt that

remote monitoring (such as IBDoc) is a positive progression in IBD services. Overall satisfaction with IBDoc showed that 91% were very satisfied while the remaining 9% were satisfied.

Conclusions: This study shows that calprotectin home testing using a smartphone as measuring system was very well received among the tested users (100% satisfaction). Similar to the self testing available in chronic conditions such as diabetes and hypertension, it is now also possible for sufferers of IBD to self test and monitor their condition from home with a simple test. IBDoc offers patient empowerment for IBD patients who can remotely monitor their disease from the convenience of their own home.

N805

Do we need to monitor patients after vedolizumab infusion?

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Background: Vedolizumab is a humanised IgG monoclonal antibody that is licensed for use in moderate to severe ulcerative colitis and Crohn's disease. The manufacturer advises that vedolizumab is administered over thirty minutes, and that patients are observed for 2 hours after the first 2 infusions and for 1 hour after subsequent infusions for signs and symptoms of acute infusion related reactions. The aim of this audit was to establish whether monitoring following completion of the infusion is required.

Methods: 179 Vedolizumab infusions were administered to 55 patients from November 2015 to July 2016 (9 months). Data was recorded on completion of the infusion and post infusion monitoring (PIM) period. Infusions were administered over 30 minutes. Patients were observed post infusion for 120 minutes following the first 2 doses, and 60 minutes after subsequent doses. Blood pressure, pulse, respiratory rate, oxygen saturations were recorded at the start and on completion of the infusion and hourly during post infusion monitoring. A systolic drop in BP of ≥ 20 mm/Hg and details of action taken were documented. Adverse reactions, their treatment and outcomes were recorded, including occurrence during infusion or post infusion period. Adverse reactions were classified as:

- mild: no action required
- moderate: action required but treatment continued
- Severe: immediate action or treatment withdrawal.

Results: During the infusion: 1 patient had an adverse reaction during each of 3 infusions (1 moderate, 2 mild).

Systolic BP dropped ≥ 20 mm/Hg in 3 patients (25–30mm/Hg). All patients were asymptomatic and infusions were completed as plan.

During PIM:

- 1 patient did not comply with the PIM regime after their first infusion with no self-reported adverse events.
- 1 patient had a drop in systolic BP of 21mm/Hg following infusion 4 requiring no action.
- No adverse reactions were recorded in 55 patients following 178 infusions.
- 1 patient reported joint aches post discharge which settled spontaneously.

Conclusions:

- Observed infusion reaction rate was 1.67%
- No adverse reactions occurred during post infusion monitoring.
- BP drops > 20 mm/Hg were observed in 1.67% infusions and 0.56% during post infusion monitoring. All patients were asymptomatic and no action was taken.

- We suggest post-vedolizumab infusion monitoring is unnecessary.
- In this Teaching Hospital setting, 347 hours of patient and nurse time could be saved per annum based on current infusion numbers.

N806

Comparison of patient satisfaction between regular care and clinical trial care for IBD patients treated with biologicals

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Background: Patients with Inflammatory Bowel Disease (IBD) can be treated with biologicals in a regular care or clinical trial setting. Nurse specialists play an important role in the regular care of patients receiving biologicals, whereas clinical trial nurses coordinate the care of patients who receive treatment in clinical trials. The aim of our study was to analyze and compare patient satisfaction in these two patient groups.

Methods: We conducted a cross-sectional comparative study in adult IBD patients (Crohn's disease and ulcerative colitis) receiving biological treatment as regular care (infliximab, adalimumab, golimumab, vedolizumab) or in a clinical trial (infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, etrolizumab, IL-23 p19 monoclonal antibody, and an antibody against MAdCAM-1) at the Academic Medical Center in Amsterdam. Patients were invited to participate by email. Patient satisfaction and experience was registered using a validated online questionnaire focusing on outpatient care that consisted of 55 multiple choice questions and two open questions.

Results: In total 79 patients responded to the invitation (33 regular care patients and 46 trial patients). Response rate was 50%. Between the two groups no significant differences were found with regard to patients characteristics (proportion CD/UC, age, sex, co-morbidity,

perceived state of health, ethnic background, etc.). Patient satisfaction about treatment, communication and how information was provided by health care providers was high. Regular care and clinical trial patients appreciated the care on average with an 8.0 and 8.17 (on a scale from 0–10), resp. (p=0.34). Highly educated patients scored on average significantly lower on patient satisfaction compared to low to average educated participants (mean patient satisfaction 3.5 (min 1.3 – max 4; N=24) vs. 3.8 (min 2.9 – max 4; N=42), resp. (p=0.02). Clinical trial patients experienced significantly more autonomy compared to regular care patients: 3.20 vs. 2.75, resp. (p=0.03).

Twenty-nine patients did not have suggestions how to improve their care, 29 patients gave suggestions how to improve the care they received, and 12 patients did not have an opinion.

Conclusions: IBD out-patients who receive treatment with biologicals as regular care are equally satisfied as compared to patients that receive biologicals in a clinical trial. Patients who participated in a clinical trial experienced significantly more autonomy. Patients in both groups wanted more personal advice on lifestyle and how to cope with IBD.

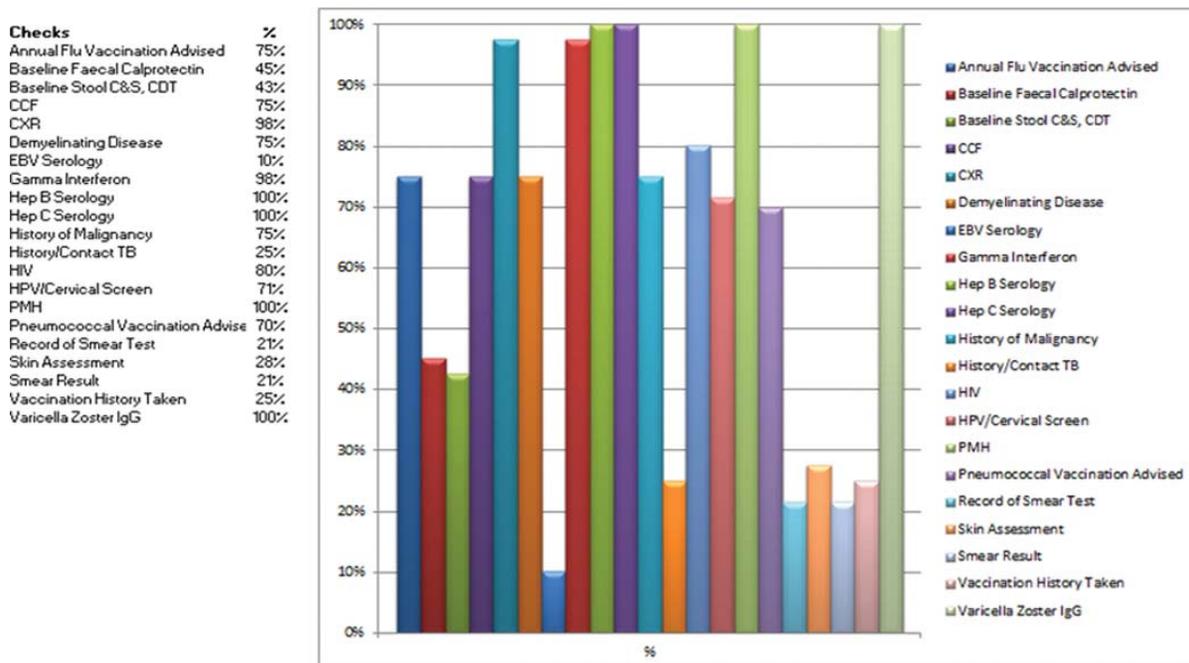
N807

The use of a pre-screening tool for anti-TNFs in IBD in four North West NHS trusts: a study

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Background: Inflammatory Bowel disease therapies have continued to evolve following the introduction of anti TNF agents. It is recog-



Abstract N807 – Figure 1. Results.

nised that pre-screening for these therapies varies nationwide, with no standardised requirements evident [1].

The aim of this study is to identify if current pre-screening practice within four independent North West England NHS trusts are in line with the European Crohns and Colitis Organisation (ECCO) consensus [2,3].

Methods: A retrospective multicentre cohort study was conducted examining the aspects of the existing pre-screening tools to determine utilisation in each of the four participating NHS trusts.

Results: Ten patients from each NHS trust (N=40) were included, three out of the four trusts had a pre-existing tool for screening. 62% of patients had Crohns disease with the remaining 38% having ulcerative colitis, there were a greater number of males and the age group 18–35 being the most prevalent. 50% of patients were starting Adalimumab, 40% a biosimilar with the remaining 10% Vedolizumab. Assessing the screening outcomes the study identified, EBV Serology, smear testing and results, vaccination history and skin assessment as areas that were not consistently reviewed (10–28%). Not all trusts had access to faecal calprotectin but Gamma Interferon with Hepatitis and virology screening were done in 98–100% of cases. The majority of the pre-screening was done by the IBD Nurse Specialist (27/40) with the time to treatment showing that 50% of the patients waited over 14 days to commence therapy although 25% of these patients chose to wait over the 14 days [4].

Conclusions: The four participating North West NHS Trusts identified the need for a standardised pre-screening tool for Inflammatory bowel disease patients requiring anti TNF therapy. This is necessary to ensure conformation and uniformity locally and nationally. Following the introduction of a standard pre-screening tool across the four sites a further audit in 6 months is anticipated.

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N808

Cooking workshops as strategy of health promotion of patients with inflammatory bowel diseases

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Background: Diet can be a successful part of treatment plan to improve the quality of life of patients with inflammatory bowel dis-

eases (IBD). An important aspect that affects food choices is household member's skills in food acquisition, transportation, storage, and preparation. Practical cooking workshops are effective in improving cooking skills and in increasing healthier food choices. In this patient's group, this type of activity can also contribute to reduce the sensation of being excluded or being different at times pleasurable of the family meal. The aim of the study was to analyze the perception of IBD patients in cooking workshops as a strategy for developing cooking skills, promote healthy eating and improve quality of life

Methods: Eight cooking workshops, with five hours each, with participation of students and teachers of gastronomy and IBD patients were conducted from May 2015 to January 2016 to individuals with IBD. Patients were recruited at the IBD outpatient clinic of the Gastroenterology Unit from the Federal University Hospital of Rio de Janeiro, Brazil. The workshops' planning took into account the characteristics of the diseases, nutritional needs and cultural/ socio-economic aspects of the patients. A qualitative pilot study was developed in May 2016, that included IBD patients of both gender who attended to five or more cooking workshops. The following topics were discussed in the focus group: influence of diet in IBD symptoms; methodology adopted in the workshops; impact of workshops on cooking skills; life implementation of the acquired knowledge, quality of diet and quality of life.

Results: Among twelve focus group participants (8 CD and 4 UC), aged from 47 to 66 yrs, 67% were female, 25% works out, 83% cook regularly and live with family. Participants reported that some foods interfere in IBD symptoms such as soda, alcoholic beverages, processed foods, high fat foods, leafy vegetables, peels and seeds. They emphasized that the interaction between patients, students and teachers is important to the success of activities, with no recommendation of changes in the methodology. The recipes learned are used daily by patients and disseminated to friends, family and neighbors. The patients perception is that these cooking workshops contributed to the improvement of cooking skills allowing the introduction of new foods and preparation techniques in their menu.

Conclusions: Cooking workshops are well accepted among IBD patients. These activities allow improve of their quality of life with an increasing cooking skills, learning to cook healthy, fitting foods to their symptoms and socializing with other people with/without IBD.

N809

IBD control questionnaire: validation and evaluation as part of a virtual biologic clinic in Galway University Hospital, Ireland

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Background: Patient-reported outcome measures in clinical practice are increasingly advocated as a means of supporting patient-centred care. The IBD-Control Questionnaire measures overall disease control (in the previous 2 weeks) from the patient's perspective. As part of a new consultant led virtual biologic clinic (VBC) we aimed to validate the IBD Control Questionnaire in our VBC, specifically the IBD Control-8 and VAS subscales.

Methods: In a single-centre retrospective study 60 randomly selected questionnaires were reviewed of patients receiving biologics. The questionnaire consisted of the IBD-Control questionnaire and Mayo score or Harvey Bradshaw Index. CRP levels were also recorded. In IBD-Control8, ≥ 13 points and IBD-Control VAS ≥ 85 points identified patients with inactive IBD.

Results: Mean age was 41, diagnosis UC = 26, Crohn's = 34 receiving

biologics. Disease activity was categorised as per Mayo, HBI and IBD Control. There was a strong correlation between the IBD Control-8 and VAS, $p \leq 0.001$. A negative correlation was identified between CRP and VAS, $p < 0.001$. A one way between groups ANOVA of the Mayo and VAS scores revealed a statistically significant difference between two groups (remission, moderate/severe). Analysis for the Crohn's cohort revealed a statistically significant difference between all three groups, $p < 0.001$. Standard multiple regression was used to assess the IBD 8 and CRP levels to predict overall control in the past two weeks. Both independent variables made a statistically significant contribution. However the IBD8 variable recorded a higher beta value (0.69) than CRP levels (0.3)

Conclusions: A strong correlation was shown between the IBD Control measure with both the Mayo and HBI. With a moderate correlation with VAS and CRP levels. While both CRP and VAS contributed to the regression model, VAS scores were revealed as the stronger predictor of IBD control. IBD Control has strong measurement properties and is easily administered. Its introduction in our VBC has been very positive from both patient and staff perspectives. The findings illuminate the importance of incorporating clinical and patient reported measures in terms of patient management.

N810

Audit of patient satisfaction with telephone reviews for inflammatory bowel disease

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Background: Patients with inflammatory bowel disease (IBD) require long term follow up. However, many patients attending routine clinic appointments are in remission and require only verbal assessment of their condition. It was noted that the nurse led IBD clinics were often overbooked and access to appointments when required was difficult. Telephone reviews for those with Coeliac disease were already being carried out successfully and it was felt that this may also be a suitable alternative to traditional face to face clinic appointments for patients with stable IBD.

Methods: Over a three month period 50 patients scheduled to attend the nurse-led IBD clinic were invited to receive a telephone review rather than face to face consultation. Blood request forms were sent to patients along with the appointment letter notifying them of the time and telephone number they would be contacted on. They were asked to have the blood tests done 1–2 weeks prior to their review. Following the 3 month trial period all patients who had been invited to participate in the telephone clinic were sent a questionnaire to evaluate their satisfaction with the telephone reviews.

Results: Of the 50 patients invited to have a telephone review, two had requested to be seen in clinic, of the remaining patients the Clinical Nurse Specialist (CNS) had been unable to contact 3 patients. Two had normal blood results and returned answer phone messages to notify the CNS that they were symptomatically well.

32 questionnaires were returned (64%). There was a fairly even spread of patients in terms of duration of the disease with 16 having IBD for <10 years and 17 patients >10 years. Male and female ratio was also even with 16 male and 14 female (2 had not answered). Two patients who returned the questionnaire had not completed all sections as they had requested to be seen in clinic.

Of the 30/32 patients who had received a telephone review general satisfaction was high and the majority would be happy to continue with this method of follow-up. 26 (87%) were happy to continue

telephone reviews, 1 (3%) was undecided and 3 (10%) preferred to come in to clinic.

In an overall rating for the telephone review 1–10 (1 being very poor) 24 (80%) rated it as 8 or above.

Conclusions: The telephone reviews were well received by patients and offer an acceptable alternative to the traditional clinic follow up appointments for those with stable IBD. The level of satisfaction with all aspects of the telephone review was high. Offering telephone reviews meets the recommendations of the IBD Standards in terms of providing choice to patients and maintaining patient-centred care.

N811

Infliximab versus adalimumab: clinical and endoscopy response in ulcerative colitis patients. A prospective study

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Background: The anti-TNF agents are a new therapeutic strategy on Ulcerative Colitis (UC). Infliximab (IFX) and adalimumab (ADA) are effective in inducing and maintaining clinical remission and in reduction of hospitalizations and surgeries rates. The aim of this study was to compare the efficacy of IFX versus ADA in clinical response and endoscopic response in UC patients.

Methods: A prospective and longitudinal study was carried out in UC patients. Patients were randomized to receive IFX or ADA and were evaluated at baseline and weeks 14, 30 and 54 of treatment. Mayo score ≤ 2 points was considered clinical remission and a decrease of ≥ 3 points was defined as clinical response. Endoscopic Mayo sub score of 1 or 0 was defined as endoscopic response. Statistical analysis: ANOVA and Tukey's multiple comparison test.

Results: Thirty-one patients were included, the mean age was 42.06y (± 15.70) and the mean duration of the disease was 4.84y (± 4.00). Left colitis was found in 6 (19.35%) patients and pancolitis in 25 (80.65%) patients. Ten patients received ADA and 21 IFX, and no statistically significant difference between the groups in gender, mean age, disease duration and location, and Mayo score and Endoscopic Mayo sub score was found at baseline.

Clinical response was observed in 6 (60%) patients from ADA group and in 12 (57.14%) patients from IFX group ($p=1.0$). Endoscopic response occurred in 3 (37.50%) patients in ADA group and in 9 (47.37%) patients from IFX group ($p=0.70$). The rate of hospitalization in the ADA group was 3 (30%) and 7 (33.33%) in IFX group ($p=1.00$).

Conclusions: There were clinical and endoscopic response in patients with UC treated with anti-TNF agents. There was no difference between IFX and ADA group.

N812

Re-designing the IBD nurse service for children and families in Glasgow using digital working – a tertiary centre experience

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Background: In June 2015 the Children's Hospital in Glasgow moved site. This process involved a move to "paper lite" and agile working practices including the use of "hot desks". Historically the Glasgow IBD Nurse Service ran a telephone advice-line which was

recorded and triaged using a paper template. Calls were answered in an ad hoc fashion (usually between clinics or other patient related contact) and paper documentation was used.

Prior to the move, parent and patient email contact had increased. Many parents and young people had expressed a preference for email contact as being more flexible and easier to refer back to than telephone contact. We introduced a combination of email and telephone clinics documented digitally to produce a more robust process for dealing with patient contact in the paper lite era.

Methods: A generic IBD Nurse email account was created using a secure server to re-direct all patient related contact. All patients are given the IBD Nurse email address at diagnosis and offered this as a means of access for the service. A generic template email is sent to all new contacts. Implied consent is obtained when the parent or young person replies to the mail. The email signature gives clear advice on IBD nurse service access including rapid access and all contact details. Emails are answered daily between 1pm and 4pm and all communication is "cut and pasted" into the patients electronic record. Advice-line messages are picked up at 11am and 3pm daily and sent to the generic IBD Nurse email by admin staff. These messages are "cut and pasted" into the electronic shared calendar and triaged using a colour coded system. Red: not dealt with. Amber: in progress. Green: completed and outcome documented. All adviceline calls are responded to by email or in the IBD Nurse telephone clinic.

Results: We compared our processes before digital working was implemented to those now used. We also audited the number of emails sent from March to August 2016.

Table 1

Before move	After move
IBD Nurse advice line calls transcribed onto paper for triage.	Advice line calls now collated electronically and stored in shared electronic clinical calendar. Calls are colour coded to illustrate when they are complete – 'Traffic light' system used.
Adviceline calls responded to in ad hoc manner.	Telephone clinics now used to respond to clinical calls and emails when necessary. 2 clinics per week. 6x30 min slots at each clinic. Allows time to complete full patient episode including documentation, dictation and co-ordination of any other events.
Patient emails received in ad hoc manner direct to IBD nurse personal account. Reactive management.	Patient specific contact now directed to generic IBD nurse email account and responded to in daily email clinic. All communication 'cut and pasted' into electronic patient record.

Table 2

Month	Number of patient emails sent
March	345
April	347
May	223
June	285
July	275
August	335

Conclusions: Moving to the new Children's Hospital required a review of working practices. We present our experience of implementing digital working into the Glasgow IBD Nurse service. This required significant service redesign but has resulted in a more proactive and organised approach to dealing with patient contact. Our expectation is that it will also produce more robust data for future audit.

N813

Reaction rates in patients transferred from biologic to bio-similar treatment for IBD

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Background: Biologic medication, (Infliximab) for patients with inflammatory bowel disease has been available in the UK since the late 1990's. The cost implications for health authorities for patients receiving biologic medicines is high, however the enhanced quality of life for patients is described by many as priceless. In recent years, a cost effective alternative drug called a bio-similar has become available in the form of Inflectra. A bio-similar is drug designed to have active properties similar to one that has previously been licensed. The clinical data shows that the effects of the bio-similar family of medication should be on par with that of the biologic group – however do patients react to the bio-similar medication when changing from a biologic to bio-similar.

Methods: A retrospective review was carried out of all IBD biologic patients within the Royal Gwent Hospital who were transferred to bio-similar. The patients were looked after in the gastroenterology day-case unit by the same infusion nurse who had administered the biologic therapy. Medication was administered and patients were monitored in accordance with local policies for biologic and now bio-similar administration. In total 70 patients were transferred from biologic to bio-similar.

Results: During the retrospective review of the above patient group it was found that of the 70 patients, 22% of patients (n=15) suffered a reaction. Most were minor with patients suffering hives, a mild wheeze or a feeling of being unwell, whilst the patient's observations remained stable. 6% of the 70 (n=4), had more severe reactions such as respiratory distress, widespread wheeze and tachycardia. In all cases symptoms resolved with stopping the infusion, Hydrocortisone and Chlorphenamine. Of the 70, 12% (n=8) had the bio-similar discontinued. Of the 70 patients transferred to bio-similar therapy, only 3% (n=2) had experienced reactions to biologic previously.

Conclusions: It is unclear as to why these patients reacted to the bio-similar. It could be suggested that the revisiting of symptoms of reaction prior to administration of the bio-similar produced a subconscious response. This could be linked to those who showed some anxiety towards the change in medication. One could suggest that further investigation into the responses noted would be appropriate

N814

Improvement in the treatment and management of patients affected by inflammatory bowel disease: hepatitis B and vaccination status

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Background: The prevalence of HBV infection in patients with inflammatory bowel disease (IBD) is similar to that found in the general population. However, in patients with IBD several conditions such as malnutrition, surgery and immunosuppressive therapies, particularly anti-TNF α agents, may lead to a recurrence of HBV infection. International guidelines suggest HBV vaccination for all HBV anti-HBcAb seronegative patients already at diagnosis or before starting treatments with immunosuppressant. However, studies have shown that the percentage of vaccination of HBV patients affected by IBD is still low.

The objective is to assess the prevalence of HBV and the rate of HBV vaccination in a population of IBD patients

Methods: Monocenter observational study. Collection of data was carried out in the first trimester of 2016 in the day hospital of Gastroenterology Unit at Brotzu Hospital, for a total amount of 130 patients. Data were collected on a nursing questionnaire which was created for the study.

Results: 130 patients were studied. Of these, 57 (44%) were treated with biological agents (adalimumab, golimumab, infliximab). The majority of these patients were women (56%). The percentage of patients with ulcerative colitis (UC) was 72% overall, while in the sub-group of patients treated with anti-TNF α agents those with UC and Crohn's disease (CD) were 48% and 52% respectively. The study has shown a vaccination rate of 60%, reaching 70% in the sub-group of patients receiving biological treatments (36 out of 54).

Conclusions: Vaccination against HBV in patients with IBD is important because of the risk of recurrence of the infection during treatment with immunosuppressive drugs, especially anti-TNF α biologic therapy. These data suggest that more effort is needed to increase vaccination rates among IBD patients, as soon as possible, at least before beginning treatments with immunosuppressants.

N815 IBD Team Climate Inventory: finding solutions to team challenges

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Background: Effective teamwork is associated with a range of positive outcomes such as a reduction in medical errors, increased patient safety, reducing work-related stress for staff and improving local team relationships [1]. It is suggested that the best care for IBD patients is provided by a multidisciplinary team, offering an effective model for long-term care of patients and reflect the need to be adaptable and responsive to patients with changeable and progressive disease who have both complex medical and psychosocial care needs [2], The IBD Team Climate Inventory (TCI) measures team function and can help to "diagnose where teams need help to be more effective" [3]. The aim of this project was to assess team function using the TCI to identify any challenging teamwork factors and implement change to progress team function and enhance supportive working environments for IBD team members to improve the effectiveness of the team in terms of care delivery and staff working experience.

Methods: A postal questionnaire was sent to the IBD team (n=29). TCI was first measured across the team in April 2016 and re-assessed in a sub group (nursing) in October 2016 after a Consultant-led Virtual Biologic Clinic was in place 4 months. Team characteristics were collected using both closed and open ended questions.

Results: Overall the TCI team score was 3.5. There was no statistically significant difference in scores by professional group within three of the subscales. However there was a statistically significant difference in the participatory safety (PS) sub scale scores across the professional groups $F(3,19)=7.5$, $p=0.001$, size effect was moderate (0.6). Posthoc analysis indicated that the mean score in the nursing group was significantly difference from the other groups (Nursing, $M=2.78$, $SD=0.455$). While the mean PS team score was 3.5, the nursing group mean score was significantly lower (2.8) with the infusion unit nursing staff reporting an even lower score average of 2.4. Open ended questions revealed that the nursing staff in the infusion unit reported a level of isolation from the other IBD team members. Communication with and access to the medical profession

was perceived to be limited in terms of managing patients, which was seen as a barrier to teamworking and building working relationships. This qualitative data is reflective of the participatory safety scores reported.

Conclusions: This research suggests that the TCI can be used to identify challenges for the multidisciplinary IBD team. The consultant led Virtual Biologic Clinic model employed enhanced levels of access to and communication between team members, contributed positively to patient management and created a more supportive working environments for staff.

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N816 Anti-TNF therapy improves the quality of life in patients with ulcerative colitis

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Background: Inflammatory bowel disease (IBD) is characterized by a chronic relapsing inflammation of the gastrointestinal tract. The major subtypes are Crohn's disease (CD) and ulcerative colitis (UC). The symptoms can have significant psychosocial implications that can affect the health-related quality of life (HRQoL). Anti-TNF agents are not only effective at inducing remission but have also been shown to improve HRQoL. Given the importance of restoration of health and improvement of HRQoL in UC patients, the purpose of the present study was to determine the impact of the treatment with anti-TNF agents on the improvement of patient's quality of life.

Methods: A prospective, longitudinal study was performed on patients with UC treated with anti-TNF agents. Biological treatment was indicated for patients with moderate and severe colitis refractory to immunosuppressants or steroids refractory or steroids dependent, and those admitted to the hospital with severe colitis, when they were steroid refractory or dependent. The inflammatory bowel disease questionnaire (IBDQ) was used to measure the HRQoL at baseline and at weeks 14, 30 and 54. The Mayo score was used to assess the clinical response of UC patients. Statistical Analysis: variables were analyzed at four time points using variance analysis of repeated measurements (ANOVA) with the Tukey post-test. This study was approved by the Research Ethics Committee (CAAE: 57721515.7.0000.5411).

Results: Thirty-one patients were included in this study. Eighteen (58.06%) were male, 96.77% Caucasian race, mean age was 46.02y (± 15.7) and disease duration was 4.84y (± 4.0). Location data included 80.65% with pancolitis, 19.35% with left colitis, and no patients with distal colitis. The mean of Mayo score at baseline was 7.33 (± 3.25) points and the endoscopy sub score was 2.71 (± 0.55) points. Anti-TNF therapy included adalimumab in 10 patients and infliximab in 21 patients. Clinical response was achieved in 18 patients (58.06%) in total, and the endoscopy response was achieved

in 44.44% of the patients. Patients improved their HRQoL, without differences between groups ($p=0.99$). In ADA group, the IBDQ score ranges from 115.71 (± 51.98) at baseline to 134.14 (± 46.03) at week 14 ($p=0.99$), 165.33 (± 61.91) at week 30 ($p=0.63$) and to 166.00 (± 62.56) at week 54 ($p=0.60$). In IFX group, the IBDQ score ranges from 116.20 (± 45.47) at baseline to 154.83 (± 50.79) at week 14 ($p=0.26$), 170.75 (± 49.93) at week 30 ($p=0.04$) and 176.62 (± 42.27) at week 54 ($p=0.02$).

Conclusions: UC patients treated with anti-TNF agents presented an improvement in HRQoL.

N817

Epidemiological profile of Crohn's disease and ulcerative colitis in a Brazilian single centre

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Background: Epidemiological studies of Inflammatory Bowel Disease (IBD) are scarce in Latin America. The purpose of this study was to evaluate the demographic characteristics and clinical aspects of Crohn's Disease (CD) and Ulcerative Colitis (UC) in a single centre in Brazil.

Methods: Retrospective study. Epidemiological and clinical data were extracted from the hospital database containing 136 patients with IBD that live on the Midwestern of Sao Paulo state. The data were collected between January and November 2016 and included all patients with 15 years old or over with CD or UC confirmed. This study was approved by the Research Ethics Committee (CAAE: 50640915.2.0000.5411).

Results: Sixty-two patients with CD and 74 patients with UC were evaluated. Among patients with CD, 54.83% female, 90.32% declared Caucasian ethnicity and mean age was 44.58 years (± 15.7). Seven patients were smokers (11.29%). The average disease duration was 13.8y (± 8.9). By Montreal Classification, the patients were classified as A1 (≤ 16 years): 8.06%, A2 (17–40 years): 67.74% and A3 (> 40 years): 19.35%; L1 (Terminal ileum): 25.80%, L2 (Colonic): 11.29%, L3 (Ileocolonic): 58.06% and L4 (Isolated upper GI disease): 3.22%; B1 (Nonstricturing, nonpenetrating): 11.29%, B2 (Stricturing): 46.77% and B3 (Penetrating): 35.48%. Any stage of perianal disease was found in 50% of patients. Presence of complications was frequently found in the sample, specially intestinal stenosis (33.87%), fistulae (29.03%) and abscess (12.90%). The most frequent extra-intestinal manifestations were arthralgia (19.35%) and erythema nodosum (9.67%). Primary sclerosing cholangitis (PSC) was described in 3.22% of the patients. About treatment, 74.19% use Azathioprine; 19.35% Mesalazine; 32.25% Infliximab and 24.19% Adalimumab. The use of corticosteroids has been reported in 37.09%. With UC, 74 patients were reported, totalizing 64.86% female, the mean age was 50.1y (± 17.7), 9.45% smokers. The average of disease duration was 14.4y (± 10.1). Location data included 50.05% of the patients with pancolitis, 16.21% with left colitis, and 20.27% with distal colitis. Arthralgia was presented in 23%, sacroileitis in 4.05% and PSC in 2.70%. One patient developed colorectal cancer. The treatment consisted in oral Mesalazine in 55.40%, Sulfasalazine in 28.37% and Mesalazine suppository in 21.62%. Azathioprine has been used in 35.13% and 3 patients used biological therapy (2 with Infliximab and 1 with Adalimumab).

Conclusions: In this study, there was a small predominance of patients with UC. Females were more prevalent in both diseases. Steno-

sis, fistulae and abscess were the most common complications on CD patients. For UC, pancolitis was the principal disease location.

N818

A specialized IBD unit infusion center is preferred by patients

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Background: An increasing amount of inflammatory bowel disease (IBD) patients are receiving therapies given by intravenous (IV) infusion. Infusion centers administer a large range of IV therapies to a broad variety of medical conditions. An infusion center located in the IBD unit is specialized both for IBD patients and for their specific treatments. The aim of the study was to determine satisfaction of IBD patients treated in the IBD unit compared to their experience in a generalized infusion center.

Methods: A prospective longitudinal study was conducted over a 3-month period in one new specialized IBD unit infusion center at Shaare-Zedek Medical Center. 28 patients fulfilled the inclusion criteria. All participants were treated prior to inclusion in a general infusion center. They all had to reply to a questionnaire. The questions related to their general satisfaction, preference of infusion center and the reasons for this preference.

Results: 18 (64%) of patients were men, 20 (71%) had Ulcerative Colitis, and Infliximab and Vedolizumab were given evenly to 50% each. 27 (96%) patients preferred the IBD unit, when the main reasons included: Medical staff more available (68%), Medical staff is familiar with my condition (61%), and familiar location (64%). Other reasons, including shorter infusion time, professional staff, better knowledge of medical situation and medication side effects were all mentioned for this preference. 22 (79%) patients mentioned the location to be an extremely important factor. 26 (93%) of participants said that this location had a positive effect on their disease, and 25 (89%) also emphasized the specialized IBD nurse to have a great deal impact on their feeling. 16 (57%) of patients rated very positively the interaction with other patients with IBD.

Conclusions: A specialized IBD unit infusion center is highly rated by IBD patients. This model offers many advantages over the conventional generalized infusion centers

N819

Analysis of the role of nursing in a IBD unit

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Background: Our IBD unit (Hospital Virgen de la Victoria) currently attends more than 900 IBD patients. Since 2014, april we've been holding a nursing consultation following N-ECCO recommendations.

Developed activities:

- Phone assistance.
- Education of IBD after diagnosis.
- Education health biological treatment.
- Pediatric Transition.
- Analytical monitoring of stable patients on treatment with azathioprine.

The main objective of the study has been focused on the analysis of the activity developed by IBD nurse during its initial stage.

Methods: Descriptive and observational study of Activities of nursing consultation of our IBD unit Since 2014 April to 2016 November. **Results:** There have been a total of 374 calls from 161 patients. 186 (49.7%) calls were answered by the nurse and 188 (50.3%) together with the doctor.

295 (78.9%) calls were resolved by phone, 55 (14.7%) were referred to medical consulting preferentially, 15 (4.0%) were referred to emergency room and 9 (2.4%) to other specialist.

IBD nurse has attended 25 first visits after diagnosis of the disease, 28 Blood tests monitoring of patients under treatment with azathioprine, 23 follow-up blood tests for monitoring the adverse effects of treatments, 29 health education visits of patients with biological treatments and 8 pediatric transition visits.

Conclusions:

- Telephone attention is the most demanded, improving accessibility and communication with patients by providing a bypass circuit when necessary, guiding the patient in the most appropriate way.
- The presence in our unit of an advanced nurse has allowed the realization of different activities aimed at the education and management of IBD allowing the continuity of care in the follow-up of patients with IBD.

N820

The value and perception of IBD patients on electronic news letter as a mode of patient-medical team communication

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Background: There is importance for enhancing communication and sharing between IBD patients and the medical team. Disease-related knowledge can positively affect the acceptance of the disease, enhance patient's engagement in his care, facilitate adherence and improve patient-related outcomes. A periodic e-news' letter can be a part of such patient engagement strategy; however its value for the patient has not been evaluated.

Methods: An electronic newsletter was developed and delivered to patients being cared for in the specialized IBD clinic of a tertiary medical center (July 2015 –November 2016). The letter included short description of all the various team personal including doctors, IBD clinic nurses, clinic secretaries and supporting staff. The letter also included information about several aspects of IBD. Six months after the newsletter was sent, a questionnaire was distributed to patients assessing their perception on the newsletter and the knowledge they gained from it.

Results: Five hundred and eighty seven questionnaires were distributed and 178 (30.3%) returned, of whom 87 (48.8%) reported receiving the electronic newsletter. All patients stated that the letter content was sufficiently clear; 95.5% considered the content to be relevant for them and the presentation- reader-friendly; 40.3% required additional clarifications from the team regarding the newsletter content. Seventy six percent confirmed that the newsletter help them to recognize and get acquainted with the members of the IBD team. 98.5% considered the newsletter to be valuable to them and expressed their willingness to continue receiving it regularly.

Conclusions: An electronic newsletter is highly appreciated by the IBD patients, and can provide them with valuable education on IBD and improve their familiarity with the medical team of the IBD clinic.

N821

Communication with IBD nurse is associated with disease severity but not with better adherence to treatment

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Background: Inflammatory bowel diseases usually have an unpredictable course, often with sudden exacerbations. It is therefore of vital importance that patients should have rapid access to medical services to enable early intervention when necessary. Nowadays, many centers have a dedicated IBD nurse to ensure easy communication with patients. The aim of the study was to evaluate association of use of IBD nurse with disease parameters and adherence to treatment.

Methods: IBD patients from Meir Medical Center, serving a population of 600,000 people in Israel were recruited for this analysis. All participants filled questionnaires which included demographic, clinical and socioeconomic data and accessibility to GI services, as well as use of IBD nurse services. Severity of disease was calculated according to the GETAID system, and adherence was estimated by the Morisky score.

Results: Questionnaires were answered by 93 patients. Mean age was 41±15, 50 females, mean disease duration 13 months (range 1–192), 68 (73%) had Crohn's disease, 47 (50.5%) of patients used IBD nurse frequently and 46 (49.5%) rarely. Good adherence was reported in 33/47 (70%) patients using IBD nurse services and in 28/46 (61%) of patients not using IBD nurse services. However, using IBD nurse services was not associated with good adherence (p=0.34). Interestingly, use of IBD nurse services was significantly more common among patients with a higher severity disease score (77%, p=0.028). **Conclusions:** The service of IBD nurse is more important in severely ill patients. Larger cohort studies are needed to evaluate the impact of IBD nurse on adherence.

N822

Non-programmed assistance of IBD patients in our institution. Ratios of activity and effectiveness of IBD-nurse role

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Background: Growing complexity and increasing volume of patients with inflammatory bowel disease (IBD) make necessary multidisciplinary units. IBD nurses should be part of these units and have specific documents to register their assistential activity. Further than programmed activity, non programmed activity represents an important part of the assistential activity since patients attend to the unit without an arranged date or contact via telephone or e-mail.

Methods: A register sheet of assistential activity for nursery in our unit was developed. The document was designed with three main topics: demographic data and clinical data of the patient, reason of consultation, symptoms with Mayo partial or Harvey-Brandshaw scale as suitable and the response/solution given. This solution could be given by either an IBD nurse, a doctor and/or administrative staff. **Results:** During 7 consecutive months, 465 non-programmed appoint-

ments to our unit were registered. 95.91% of the contacts were solved via phone call and or mail. Main contact topics were problems with medical treatment (24.3%), doubts solution (32.0%), change or new appointment date (11.4%), change or appointment for complementary studies (4%), clinical reports or results (24%). Only 4.08% needed face-to-face consultation, 3.44% in IBD-unit and 0.65% in emergency service.

Conclusions: The register of non-programmed clinical assistance by means of a specific document allows to improve the registry of activity in our IBD unit, improves communication between members of the unit, leaves a documentary report of a non-scheduled activity and focus assistance on patients needs in order to perform a better distribution of resources. Furthermore, IBD nursery can attend >95% of non-programmed appointments without being present the patient, strengthening the efficiency of the role of IBD nursery.

N823

The linked project, creating network

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Background: In Spain we have approximately 100 nurses who work with patients with Inflammatory Bowel Disease (IBD). Based on the definitions of the N-ECCO (Nurse - European Crohn & Colitis Organization), only 20 of them are advanced IBD Nurses. There is currently no consensus on the level of education that such nurses should be achieve, although the level of care is “clearly beyond the first level of qualification” and would normally be achieved following a combination of broad clinical practice, professional development and formal education. There is no academic regulation in our country, and educational programs are carried out today through initiatives promoted from GETEII (Working Group on Inflammatory Bowel Disease) and different partners.

Methods: In order to promote continuous training and generate a stable network among nurses, in 2016, the Linked Project was set up. This project consists of having a minimum of sessions in each territory with 3 workshops, one of them being taught by a nurse specialised in the field of IBD. All of them utilise a participative and dynamics methodology.

Results: 10 meetings with 92 participating nurses. Topics covered: Initial visit, telephone follow-up, treatment and vaccines, communication techniques, adherence, ostomies, psychological aspects, time management tools.

The assessment of the scientific level: 20% far exceeds their expectations and 74% above their expectations 6% met their expectations. The interest of the topics treated: 53% Excellent interest, 36% Very good and 11% Good. The workshop has met expectations: 47% Fully agree 39%, Strongly agree 14% Neither agree nor disagree. I would attend the workshop again: 77% Strongly agree, 23% Quite agree. I would recommend attendance to a partner: 85% Strongly agree, 15% Strongly agree. 20% It intends to change its clinical practice after attending the workshop, 67% think it has strengthened its clinical practice and finally 13% Need more information or resources.

Conclusions: The Project has been very well-received by all participants, reaching, to a great extent, the desired expectations. In

several areas of the country, the meeting served as a starting point for establishing a network among nurses in order to continue training, share their daily clinical practice and in some cases initiate research projects. From GETEII, we intend to continue working to achieve formal academic training and will continue to be actively involved in the ongoing training necessary to achieve quality care for our patients.

N824

Impact of educational intervention on inflammatory bowel disease nurse specialist

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Background: Nursing care must be systematized and individualized to promote integral care to the Inflammatory Bowel Disease (IBD) patients, in order to cope with all the patients needs. All the health careers must be aware of the specificities of the disease in order to obtain satisfactory results such as acceptance of the disease, medical therapy adherence, maintenance of clinical remission as well as reduction of complications like hospitalization, surgical interventions and mortality. Therefore, all these actions could improve the quality of life of these patients. The health education process has as its main goal contribute with the improvement of services for general population and the IBD nurse specialist has a key role in this complex process of patient education and patient care. Objectives: To assess disease-related knowledge among general hospital nurses before and after the educational intervention and to evaluate the effects of this action on the studied population.

Methods: A transversal, descriptive and comparative study was conducted. The sample was composed of 32 general hospital nurses from the Hospital das Clínicas da Faculdade de Medicina de Botucatu, São Paulo/Brasil. A IBD specific test was applied in two moments: before and after the educational intervention. The test was consisted of 3 topics: concept of IBD, nursing care and use of biological therapy. Each topic was ranked from 0 to 100 points. The educational intervention was composed by a theoretical and practical IBD course ministered by a multidisciplinary team (physicians, nurses, dieticians and psychologist) with duration of 20 hours. Statistical analysis: descriptive.

Results: Twenty-nine nurses and 3 nursing technician were included in the study. The mean time of experience in nursing practice was 9.6y (±4.8y). Most part of the subjects (66%) was in contact with IBD patients and 56% reported to have knowledge about biological therapy. It was observed a rise of knowledge after the educational intervention about the concept of the disease (60.71±28.95 vs 75.93±22.45), nursing care (28.57±32.31 vs 42.59±38.49) and biological therapy (58.93±30.39 vs 75±20.8). The personal security in administering biological therapy increased from 40% to 83% after the educational intervention. The assessment of the impact of the course regarding the participants' knowledge was effective, with mean 8.79 (±1.11), being zero the absence of impact and ten high impact.

Conclusions: The knowledge about IBD was considered average among these professionals assessed and the educational intervention was effective in the increase of this disease-related knowledge.

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