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ORIGINAL ARTICLE

Factors associated with time to clinical remission in pediatric luminal Crohn's disease: A retrospective cohort study

Samuel Sassine,*,† Souhila Zekhnine,*,† Marwa Qaddouri,*,† Lisa Djani,*,† Christine Cambron-Asselin,*,† Mathieu Savoie-Robichaud,*,† Yi Fan Lin,*,† Kelly Grzywacz,*,†,‡ Véronique Groleau,*,†,‡ Martha Dirks,†,‡ Éric Drouin,*,†,‡ Ugur Halac,†,‡ Valérie Marchand,†,‡ Chloé Girard,*,†,‡ Olivier Courbette,*,†,‡ Natalie Patey,*,†,§ Dorothée Dal Soglio,*,†,§ Colette Deslandres*,†,‡ and Prévost Jantchou*,†,‡

*CHU Sainte-Justine Research Center, †Faculty of Medicine, Université de Montréal, ‡Division of Gastroenterology, Department of Pediatrics and §Department of Pathology, CHU Sainte-Justine, Montreal, Quebec, Canada

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Correspondence
Dr Prévost Jantchou, CHU Sainte-Justine, 3175 Côte Sainte-Catherine, H3T 1C5, Montreal, QC, Canada.
Email: prevost.jantchou@umontreal.ca

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Author contribution: Samuel Sassine conceptualized and designed the study, designed data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript, reviewed, and revised the manuscript. Mathieu Savoie-Robichaud, Lisa Djani, Yi Fan Lin, Christine Cambron-Asselin, Marwa Qaddouri, and Souhila Zekhnine collected data, carried out the initial analyses and drafted the initial manuscript. Kelly Grzywacz, Véronique Groleau, Martha Dirks, Éric Drouin, Ugur Halac, Valérie Marchand, Chloé Girard, Olivier Courbette, Dorothée Dal Soglio, and Colette Deslandres contributed to data collection, patients' follow-up, and critically reviewed the manuscript for important intellectual content. Natalie Patey conceptualized and designed the study, collected data, and critically reviewed the manuscript for important intellectual content. Prévost Jantchou conceptualized and designed the study, designed data collection instruments, coordinated, and supervised data collection, carried out the initial analyses, critically reviewed the manuscript for important intellectual content.

Abstract

Background and Aim: Data on factors influencing time to remission in pediatric Crohn's disease (CD) are very limited in the literature. The aim of this retrospective cohort study was to describe the trends of time to clinical remission over the past decade and to identify factors associated with time to clinical remission in children with luminal CD.

Methods: Patients under 18 years old diagnosed between 2009 and 2019 were included. All data were collected from the patients' medical records. Survival analyses and linear regression models were used to assess the impact of clinical, laboratory, endoscopic, histological, and therapeutic factors on time to clinical remission.

Results: A total of 654 patients were included in the study. There was no change in the time to clinical remission over the decade. Female sex in adolescents (adjusted bêta regression coefficient [$a\beta$] = 31.8 days, $P = 0.02$), upper digestive tract involvement ($a\beta = 46.4$ days, $P = 0.04$) perianal disease ($a\beta = 32.2$ days, $P = 0.04$), presence of active inflammation on biopsies at diagnosis ($a\beta = 46.7$ days, $P = 0.01$) and oral 5-aminosalicylates (5-ASA) exposure ($a\beta = 56.6$ days, $P = 0.002$) were associated with longer time to clinical remission. Antibiotic exposure ($a\beta = -29.3$ days, $P = 0.04$), increased eosinophils ($a\beta = -29.6$ days, $P = 0.008$) and combination of exclusive enteral nutrition with tumor-necrosis-factor-alpha (TNF-alpha) inhibitors as induction therapy ($a\beta = -36.8$ days, $P = 0.04$) were associated with shorter time to clinical remission.

Conclusion: In children with newly diagnosed Crohn's disease, time to clinical remission did not shorten during the decade. It was associated with baseline clinical and histological data and treatment strategies. Combination of enteral nutrition and TNF-alpha inhibitors was associated with faster clinical remission.

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Introduction

The incidence of Crohn's disease (CD) among the Northern American pediatric population is one of the highest in the world ranking at 13.9 per 100 000 children-years.[1] Recent studies have shown that inflammatory bowel disease (IBD) incidence has increased in recent years.[2] In adults, most patients will eventually develop a fistulizing or stenosing phenotype of the disease and one third will need surgery[3,4] The risk of CD complications and relapses increases in patients who have undergone bowel resections or those exposed to corticosteroids.[5–7]

Corticosteroid and exclusive enteral nutrition (EEN) are two common induction therapies in the treatment of pediatric CD. EEN is often the first choice for pediatric patient's due to its low incidence of side effect and the nutritional benefits such as correction of nutritional deficiencies and improved growth.[8] Many randomized clinical trials have demonstrated similar efficacy of EEN and corticosteroids to induce remission.[9–11] The initial response time to EEN is between 2 and 4 weeks of treatment for most patients.[11,12] The time to clinical response in most patients treated by IV corticosteroids is between 3 and 5 days while the time to response for patients on oral corticosteroids varies between 2 and 4 weeks.[11,12] Time to complete clinical remission is usually longer than time to clinical response.[11]

Tumor-necrosis-factor-alpha (TNF-alpha) inhibitors are efficient in inducing and maintaining CD remission, but approximately 10–40% of patients do not respond to TNF-alpha inhibitors.[13] The clinical time to remission for TNF-alpha inhibitors varies between 2 and 10 weeks for most patients.[11,12] A recent randomized clinical trial showed that at 10 weeks post induction, a higher proportion of patients treated with infliximab were in clinical remission compared to patients treated with corticosteroids or EEN.[14] In the last decade, there has been a change in TNF-alpha inhibitors use in patients with CD. The percentage of patients receiving early treatment with TNF-alpha inhibitors (<90 days after diagnosis) increased from 4.8% in 2009 to 53.5% in 2018.[15]

It is known that the clinical evolution of CD varies between patients.[16] The natural history of CD in the pediatric population remains poorly understood with a lack of reliable biomarkers to properly predict the clinical evolution of the disease in children[17,18] Very few studies have evaluated the factors associated with the time to remission in patients with CD and data are even more limited in pediatrics.[17–19] To our knowledge, no large-scale pediatric cohort has evaluated the impact and the interrelation of various risk factors (clinical, endoscopic, histological, therapeutic, and laboratory) on time to remission.

Therefore, the primary aim of this retrospective cohort study was to describe the time to clinical remission in children with CD and the trends over the past decade. The secondary aim was to determine the factors associated with time to clinical remission.

Materials and methods

Study design, participants, procedure. We conducted a retrospective cohort study including all patients diagnosed with luminal CD in a tertiary pediatric hospital (CHU Sainte-Justine, Montreal, Canada). The inclusion criteria in the cohort are as follows: (i) Age under 18 years old; (ii) CD diagnosis between 1 January 2009 and 31 December 2019 and (iii) diagnosis made at CHU Sainte-Justine. Patients had a diagnosis of CD according to the usual endoscopic and histological diagnostic criteria.[20] Patients with IBD unclassified at initial presentation, with subsequent confirmation of CD, were included. Patients with coexisting significant cardiac, respiratory, neurological or psychiatric disorders at the time of CD diagnosis as well as those with "Crohn's like disease" linked to other severe immune disorders were excluded. Patients with Very-Early-Onset IBD associated with specific genetic mutations and immune deficiencies were excluded. We also excluded patients with isolated orofacial or perianal disease and those with isolated proctitis due to their distinct phenotype and unique management compared to other patients in the cohort.

Eligible patients were identified from a password-protected prospective IBD database maintained in our center[21] Data collection was extracted from the clinical records. One fourth of the records were reviewed by an independent research assistant to ensure accuracy and consistency of data collection. The study was approved by the research ethics committee of the CHU Sainte-Justine (2021–2974).

Measures. The outcome variable in this study was clinical remission. We defined clinical remission as the resolution of clinical symptoms based on the short Pediatric Crohn's Disease Activity Index (sPCDAI). The sPCDAI is a validated score that includes abdominal pain, number of stools per day, general well-being, weight, abdominal examination, and extra-intestinal signs. The sPCDAI score varies between 0 and 90. Clinical remission is defined by a sPCDAI score <10.[11,22–24]

The independent variables were separated into five categories: (i) Clinical; (ii) Endoscopic; (iii) Histological, (iv) Laboratory, and (v) Treatment variables.

The clinical variables included age at diagnosis, patient's sex; weight, height and body mass index (BMI) *z*-scores at diagnosis; Pediatric Crohn's Disease Activity Index (PCDAI) at diagnosis[22]; Paris classification,[25] symptoms and extra-intestinal manifestations at diagnosis.

The endoscopic variables included the total score on the simple endoscopic score for CD (SES-CD).[26] The endoscopy reports were completed consistently over the decade and endoscopic photos were available in the medical records, which allowed for the retrospective calculation of the SES-CD. Histological variables included the presence of architectural distortions, moderate to severe lymphoplasmacytic infiltrates and

moderate to severe signs of active inflammation (cryptitis, foveolitis, crypt abscesses, ulcerations) on biopsies, as well as the presence of granulomas, eosinophils, and lymphoid follicles at diagnosis. Abnormal eosinophils count was considered as an increase in the number of eosinophils above normal values.[27,28] A team of three pathologists remained the same throughout the study period (2009–2019).

The laboratory variables included: hemoglobin, serum albumin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and fecal calprotectin (FC) levels at diagnosis, as well as the mean levels of those parameters between diagnosis and initial clinical remission.

Finally, the variables related to the treatment included induction treatments at diagnosis (EEN, corticosteroids, TNF-alpha inhibitor, oral 5-aminosalicylates (5-ASA)) or antibiotics (metronidazole, ciprofloxacin, vancomycin), and maintenance treatments initiated before clinical remission (TNF-alpha inhibitors, methotrexate, thiopurines, or oral 5-ASA). The use of oral 5ASA in CD is no longer recommended by several guidelines,[29] but some patients at the beginning of the study period were exposed to those treatments as well as those who were initially considered IBD unclassified at baseline then later confirmed to be CD.

Data analysis. The date of diagnosis (defined as the date of endoscopy) was considered as the date of entry in the cohort. The time to clinical remission was defined as the time between the date of diagnosis and the date of initial clinical remission.

Remission was analyzed as a binary outcome in survival analyses and displayed for the whole cohort with Kaplan–Meier curves and descriptive statistics. Survival analyses were performed according to the explanatory variables with Kaplan–Meier curves and the log-rank test to compare time to remission between the different categories. For patients who did not achieve clinical remission, we considered in the survival analysis the date of last follow-up as the date of last medical contact with a pediatric gastroenterologist before transition to adult care.

Remission was also analyzed as a continuous outcome as time to clinical remission in bivariate and multivariate linear regression models. We determined a beta regression coefficient for each explanatory variable.

The year of diagnosis was dichotomized in two periods (2009–2014 and 2015–2019) according to the date of introduction of routine through therapeutic drug monitoring in our center and earlier introduction of biologics. Furthermore, the first ECCO-ESPGHAN guidelines on the management of pediatric CD were published in 2014.[8]

Results

The CHU Sainte-Justine CD cohort. Seven hundred and nine patients were diagnosed with CD between January 1st, 2009 and December 31st, 2019 and 654 eligible patients were included in the study. Figure 1 displays the flowchart of the

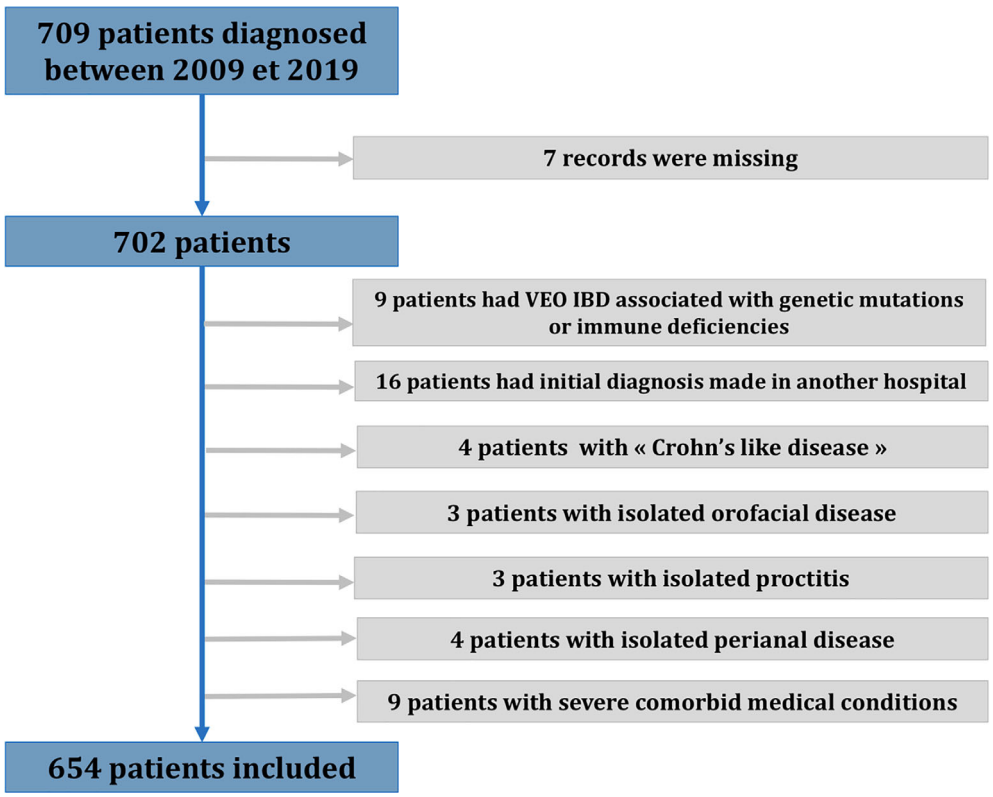

Figure 1 Flowchart of the cohort.

Table 1 Patients' characteristics at diagnosis

Total, Nb.	654
Clinical data	
Age, median (IQR), years	14.0 (11.5–15.6)
Sex, Nb. (%)[†]	
Male	360 (55.1)
Female	294 (45.0)
Weight *z*-score, median (IQR)	−0.6 (−1.5–0.2)
Height *z*-score, median (IQR)	−0.2 (−0.9–0.5)
BMI *z*-score, median (IQR)	−0.7 (−1.6–0.2)
PCDAI, median (IQR) ($n = 608$)[‡]	35.0 (25.0–45.0)
sPCDAI, median (IQR)	40.0 (30.0–50.0)
Symptoms at diagnosis, Nb. (%)	
Abdominal pain	590 (90.2)
Fatigue	296 (45.3)
Fever	131 (20.0)
Diarrhea	458 (70.0)
Rectal bleeding	293 (44.8)
Vomiting	128 (19.6)
Weight loss	413 (63.2)
Paris classification[§]	
Age at diagnosis, Nb. (%)	
A1a	78 (11.9)
A1b	534 (81.7)
A2	42 (6.4)
Location of digestive involvement, Nb. (%)	
L1	184 (28.1)
L2	149 (22.8)
L3	311 (47.6)
L4a isolated	1 (0.2)
L4b isolated	5 (0.8)
L4ab isolated	4 (0.6)
Upper digestive tract involvement, Nb. (%)	
None	228 (34.9)
L4a	289 (44.2)
L4b	46 (7.0)
L4ab	91 (13.9)
Disease phenotype, Nb. (%)	
B1	555 (85.0)
B2	52 (8.0)
B3	33 (5.1)
B2B3	13 (2.0)
Presence of inflammatory perianal involvement[¶], Nb. (%)	205 (31.4)
Presence of perianal abscesses/fistulas, Nb. (%)	123 (18.8)
Extra-intestinal manifestations, Nb. (%)	
Autoimmune hepatitis	4 (0.6)
Primary sclerosing cholangitis	11 (1.7)
Aphthous stomatitis	158 (24.2)
Arthralgia	122 (18.7)
Arthritis	37 (5.7)
Erythema nodosum	22 (3.4)
Pyoderma gangrenosum	0 (0.0)
Uveitis	4 (0.6)
Skin rash	37 (5.7)
Endoscopic and histological data[††]	
Coloscopy at diagnosis[‡‡], Nb. (%)	635 (97.1)
Upper digestive endoscopy at diagnosis, Nb. (%)	583 (89.1)
SES-CD[§§], median (IQR) ($n = 511$)	11.0 (7.0–18.0)
Presence of architectural distortions, Nb. (%)	487 (77.7)
Presence of moderate to severe lymphoplasmacytic infiltrate, Nb. (%)	523 (83.4)
Signs of moderate to severe active inflammation, Nb. (%)	395 (63.0)
Presence of granulomas, Nb. (%)	259 (41.3)
Increased eosinophils, Nb. (%)	357 (56.9)
Presence of lymphoid follicles, Nb (%)	377 (60.1)
Laboratory data[¶¶]	
Hemoglobin, median (IQR), g/L ($n = 626$)	117.0 (107.0–127.0)
Anemia at diagnosis, Nb (%)	374 (59.7)
Albumin, median (IQR), g/L ($n = 610$)	32.25 (28.0–37.0)
C-reactive-protein, median (IQR), mg/L ($n = 600$)	25.6 (6.7–57.5)
Erythrocyte sedimentation rate, median (IQR), mm/h ($n = 550$)	32.0 (20.0–44.0)
Fecal calprotectin, median (IQR), μg/g ($n = 186$)	1281.0 (515.0–2100.0)

[†]All percentages are column proportions.
[‡]Only continuous variables that are not available for all patients in the cohort have specified sample size.
[§]Crohn's disease localized to the distal one-third of the ileum ± limited caecal involvement is defined as L1, isolated colitis as L2, and ileocolonic disease as L3. Upper gastrointestinal tract involvement is designated L4a when proximal to the ligament of Treitz and L4b if distal to the ligament of Treitz but proximal to the distal one-third of the ileum. Disease behavior is classified as: inflammatory (B1), structuring (B2), penetrating (B3); or structuring and penetrating (B2B3). A1a CD includes patients aged less than 10 years old, A1b CD includes patients aged between 10 and 17 years old and A2 CD includes patients aged more than 17 years old.[25]
[¶]Inflammatory perianal involvement includes inflammatory fissures in addition to perianal fistulas and abscesses.
[††]Findings on histology including those on OGD and colonoscopy.
[‡‡]Nineteen patients did not undergo coloscopy at diagnosis, either because they refused the procedure or the procedure failed due to pain or inadequate colonic preparation. All of these patients had other bowel exploration imaging modalities.
[§§]Including only patients who had a complete successful colonoscopy at diagnosis (visualization of the rectum to the ileum), $n = 511$.
[¶¶]Measure of the laboratory parameter closest to the date of diagnosis within ±1 month.
OGD, Oesophago-gastro-duodenoscopy; PCDAI, Pediatric Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; sPCDAI, short Pediatric Crohn's Disease Activity Index.

cohort. Table 1 displays the patients clinical, endoscopic, histological, and laboratory characteristics at diagnosis. Tables S1 and S2, in Supplementary information display data on treatment exposure at and after diagnosis and the inflammatory markers levels during follow-up.

Time to clinical remission in CD patients and trends during the decade. The duration of follow-up for the whole cohort was 896.1 person-years. A total of 78.2% of patients achieved remission within 6 months of diagnosis.

The median time to clinical remission was 83.0 days after diagnosis (95% confidence interval [95% CI] [76.0–92.0]). Including the visit at the time of diagnosis, there was a median of 3 follow-up visits between the time of diagnosis and clinical remission [interquartile range (IQR): 2.0; 4.0]. The time to clinical remission was stable over the past decade. Patients diagnosed between 2009 and 2014 achieved clinical remission 81.0 days after diagnosis (95% CI [70.0; 96.0]) and patients diagnosed between 2015 and 2019 reached clinical remission 83.0 days after diagnosis (95% CI [72.0; 98.0]) ($P = 0.16$). Also, the number of follow-up visits between diagnosis and clinical remission remained constant over the decade: Median of 3 visits in the first half of de decade (IQR: 2.0; 5.0) and median of 3 visits in the second period (IQR: 2.0; 4.0) ($P = 0.61$). Fifteen patients did not achieve clinical remission before their transfer to adult care (2.3%). The median (interquartile range) follow-up for these patients was 95.0 (52.0–313.0) days after diagnosis.

Factors associated with time to clinical remission. The median time to initial clinical remission was different between males and females with, respectively, 76.0 days (95% CI [64.0; 87.0]), and 92.0 days (95% CI [79.0; 110.0]) ($P = 0.03$). In the subgroup of patients aged 13 years and older, the median time to clinical remission in males was significantly lower than in female, respectively 79.5 days (95% CI [63.0; 96.0]) and 97.0 days (95% CI [83.0; 116.0]) ($P = 0.002$) (Fig. 2). However, in children less than 13 years, there was no difference between males and females, respectively, 71.0 days (95% CI [61.0; 87.0]) and 78.0 days (95% CI [55.0; 129.0]).

The time to clinical remission was also different according to initial induction therapy (Fig. 3). Patients who were exposed to corticosteroids at induction had a longer median time to clinical remission than those not exposed: 92.0 days (95% CI [80.0; 104.0]) *versus* 64.0 days (95% CI [56.0; 80.0]) ($P = 0.0002$). Also, patients who were exposed to oral 5-ASA as induction therapy (75.5% for mild colitis and 27.5% were patients for mild ileitis) had the longest median time to clinical remission: 131.0 days (95% CI [109.0; 147.0]) *versus* 70.0 days (95% CI [62.0; 78.0]) ($P < 0.0001$) in patients not exposed (Figure S1). However, patients who were exposed to EEN at induction had the shortest median time to clinical remission: 64.0 days (95% CI [59.0; 81.0]) *versus* 90.0 days (95% CI [79.0; 99.0]) ($P = 0.04$) in the unexposed group (Figure S2).

Laboratory data between diagnosis and initial remission were associated with time to clinical remission. Indeed, patients with the most marked biochemical disorders achieved clinical remission more quickly: bêta regression coefficient (β, 95% CI) of the mean hemoglobin level (g/L): 1.24 (0.89; 1.59), $P = 0.0005$, β of the mean albumin level (g/L): 4.89 (4.05; 5.73), $P < 0.0001$, β of the mean CRP level (mg/L): −1.07 (−1.26; −0.88), $P < 0.0001$, β of the mean ESR level (mm/h): −1.74 (−2.18; −1.30), $P < 0.0001$ and β of the mean FC level (for each increase of 100 µg/g): −2.83 (−3.82; −1.84), $P = 0.004$. Also, in bivariate analysis, patients with higher PCDAI at diagnosis achieved clinical remission earlier: β (95% CI) = −0.80 (−1.18; −0.42), $P = 0.04$. Weight, height and BMI *z*-scores at diagnosis, extra-intestinal manifestations and endoscopic severity displayed by the SES-CD at diagnosis were not associated with time to clinical remission in bivariate analysis (β of SES-CD [95% CI] = −0.51 [−1.16; 0.14], $P = 0.44$).

A multivariate linear regression model of the association between time to clinical remission and patients' characteristics and treatments provided interesting results (Table 2). Adjusted on other variables, female sex was associated with a longer time to clinical remission. Stratified analysis demonstrated that the association was strongest in adolescents: $a\beta = 31.79$ (95% CI [18.60; 44.98], $P = 0.02$) but not in younger children: $a\beta = -20.79$ (95% CI [−38.35; −3.23], $P = 0.24$). Upper digestive tract involvement

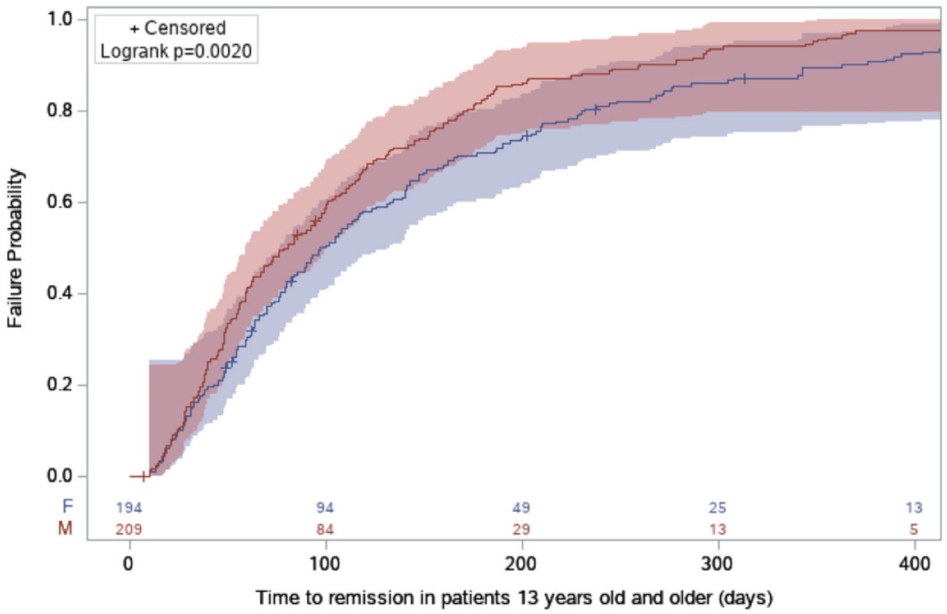

Figure 2 Kaplan–Meier curve representing time to clinical remission in patients 13 years old and older by sex. Sex: F, ——; M, ——.

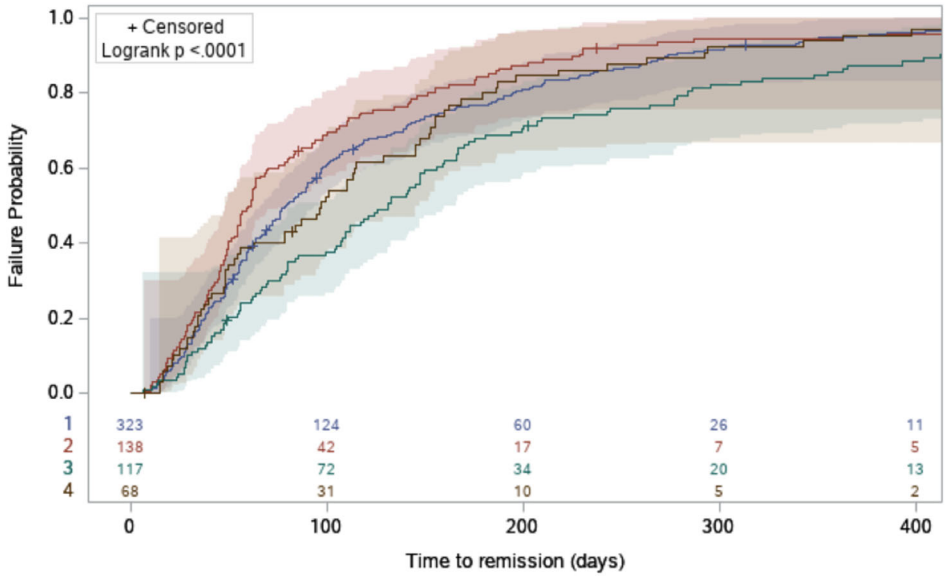

Figure 3 Kaplan–Meier curve representing the time to clinical remission of patients according to the first induction treatment administered. First induction treatment administered: 1. Corticosteroids, ——; 2. Exclusive enteral nutrition, ——; 3. Oral 5-ASA, ——; 4. TNF-alpha inhibitors, ——.

(L4b and L4ab), perianal disease and exposure to oral 5-ASA were independently associated with longer time to clinical remission. However, antibiotic use, high levels of inflammatory markers (ESR) and increased eosinophils on biopsies were associated with shorter time to clinical remission.

A subgroup analysis in patients who were exposed to TNF-alpha inhibitors (Table 3) before remission showed that, not only did early introduction of TNF-alpha inhibitors shortened time to clinical remission but a combotherapy of EEN and TNF-alpha inhibitors at induction hastened remission by 45 days. Also, in

Table 2 Multivariate linear regression model of time to clinical remission[†] ($n = 550$)

	Adjusted β regression coefficient (95% CI)	*P* value	R^2
			0.12
Intercept	125.91 (100.24; 151.58)	<0.0001	
Female sex	19.37 (8.74; 30.00)	0.06	
Upper digestive tract involvement[‡]			
No	0		
L4a	8.87 (−5.64; 23.38)	0.54	
L4b	46.36 (23.92; 68.80)	0.04	
L4ab	29.46 (13.68; 45.24)	0.07	
Presence of perianal fistulas/abscesses	32.22 (16.52; 48.92)	0.04	
Increased eosinophils in biopsies at diagnosis	−29.55 (−40.50; −18.60)	0.008	
First induction treatment			
EEN	0		
Corticosteroids (intravenous or oral)	10.63 (−3.14; 24.40)	0.44	
Oral 5-ASA	56.46 (38.59; 74.33)	0.002	
TNF-alpha inhibitors	28.64 (7.12; 50.16)	0.18	
Antibiotic exposure at diagnosis	−29.29 (−43.54; −15.04)	0.04	
Mean level of ESR (mm/h)	−1.69 (−2.19; −1.19)	0.008	

[†]Presentation of statistically significant results from a multivariate linear regression model including: year of diagnosis, age at diagnosis, sex, PCDAI at diagnosis, disease location, disease phenotype, presence of perianal involvement, treatments administered before remission, histological features at diagnosis and mean ESR levels. SES-CD at diagnosis was not included in the model, since it was not associated with time to clinical remission in bivariate analysis.

[‡]Upper gastrointestinal tract involvement is designated L4a when proximal to the ligament of Treitz and L4b if distal to the ligament of Treitz but proximal to the distal one-third of the ileum.

5-ASA, 5-aminosalicylates; CI, confidence interval; EEN, exclusive enteral nutrition; PCDAI, Pediatric Crohn's Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease.

Table 3 Multivariate linear regression model of time to clinical remission in the subset of patients exposed to TNF-alpha inhibitors before remission[†] ($n = 205$)

	Adjusted β regression coefficient (95% confidence interval)	*P* value	R^2
			0.42
Intercept	258.05 (222.15; 293.95)	<0.0001	
Oral 5-ASA exposition at induction	48.81 (21.36; 76.26)	0.07	
EEN exposition at induction	−36.80 (−54.70; −18.90)	0.04	
Increased eosinophils in biopsies at diagnosis	−34.25 (−50.64.; −17.86)	0.04	
Signs of moderate to severe active inflammation in biopsies at diagnosis	46.71 (28.27; 65.15)	0.01	
Antibiotic exposure at diagnosis	−51.92 (−71.52; −32.32)	0.01	
TNF-alpha inhibitors initiation less than a month after diagnosis	−80.51 (−99.3; −61.71)	<0.0001	
Mean level of ESR (mm/h)	−2.56 (−3.39; −1.73)	0.001	

[†]Presentation of statistically significant results from a multivariate linear regression model including only the patients who received TNF-alpha inhibitors, including the same variables as the first model, adding the variable of the time to TNF-alpha inhibitors exposure.
5-ASA, 5-aminosalicylates; EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate.

these patients, moderate to severe signs of active inflammation on biopsies was associated with longer time to clinical remission.

Discussion

Over the past decade, there has been no improvement in the time to clinical remission. In this study, since one of the predictor variables of time to clinical remission was corticosteroids exposure in the induction phase, first clinical remission was not defined as the initial corticosteroid free remission.

The median time to clinical remission was 83 days between 2015 and 2019, similar to the previous years: 81 days between 2009 and 2014. This finding is surprising because over the last decade there has been an increase in early use of TNF-alpha inhibitors[15] and more frequent monitoring of blood TNF-alpha inhibitors levels in pediatric CD. Indeed, the median time to initiation of TNF-alpha inhibitors was 279.0 days (IQR: 111.0–736.0) after diagnosis between 2009 and 2014 as compared to 55.0 days (IQR: 11.0–147.0) between 2015 and 2019.[15] The rate of TNF-alpha inhibitors as first-line treatment was 22.2% in the first period and 53.6% between 2015 and 2019. Also, twice as many patients treated with infliximab had therapeutic drug monitoring before initial remission in the second half of the decade (26.6% in patients diagnosed between 2009 and 2014 *versus* 46.3% in the 2015–2019 cohort). Therefore, we hypothesize that the earlier and more frequent use of biological therapies is not sufficient alone to shorten the time to clinical remission, but early therapeutic drug monitoring may play a role. Turner et al. published a recent meta-analysis showing that the clinical response to TNF-alpha inhibitors was even slower than that of corticosteroids and EEN.[11] Time to clinical remission was ascertained from the medical record and in our clinical practice there is no short-term protocolized follow-up in the induction phase. It is therefore impossible to determine the exact first day of clinical remission in this retrospective cohort study. Nonetheless, the frequency of follow-ups remained constant over the decade and similar between groups (telephone and out-patient clinic).

A strong association between female sex and longer time to clinical remission was found in adolescents. The severity of CD cases might be associated with higher levels of estrogen. A study has identified the occurrence of an overexpression of RNA coding for estrogen nuclear receptors and G-protein coupled estrogen receptors within the gastrointestinal tract of CD patients.[30] A retrospective cohort study has also shown that pediatrics CD girls had more severe forms of the disease.[31] In our cohort, however, the severity of disease at baseline was similar between girls and boys but the outcome was different while they were treated similarly.

Patients with small bowel disease (L4b and L4ab) achieved clinical remission later. This corroborates other past studies that have shown that upper GI tract involvement was associated with more complications during follow-up.[5–7,19,32] The results highlight the importance of prompt assessment of small bowel involvement in child with CD with appropriate imaging such as small bowel magnetic resonance imaging (MRI) or capsule endoscopy to provide optimal disease management. Although recommended by pediatric guidelines, the small bowel imaging, in this cohort, was performed within 3 months of CD diagnosis in only 73.7% of the patients (small bowel magnetic imaging or small bowel follow-through). Overall, 75.5% of patients had a diagnostic MRI within 3 months after diagnosis between 2015 and 2019, as compared to 34.2% of patients diagnosed between 2009 and 2014. Nonetheless, the time to first small bowel imaging remains too long since 32.0% of patients underwent MRI more than 1 month after diagnosis. Of notice, 10.9% of patients underwent capsule endoscopy at baseline. We believe that more extensive use of capsule endoscopy and more rapid evaluation of the small bowel by MRI in children with CD may impact therapeutic choices, such as the more rapid use of biologics and EEN, that would allow for optimal disease management and shorter time to remission.

Perianal fistulas and abscesses at diagnosis were very common (18.8% patients) and associated with a significantly longer time to remission independently of treatments and baseline disease severity. Even if the infliximab target trough levels were higher than 10 μg/mL in these patients,[8] they required a longer time to achieve clinical remission. The pathophysiological mechanism of fistula formation is still not well understood but the

extracellular matrix remodeling associated with deep transmural inflammation seems to be an explanation, which could account for the slower response to treatments.[33]

Increased eosinophils were associated with a shorter time to clinical remission whereas patients with moderate to severe acute disease activity achieved clinical remission later. We hypothesize that baseline histological characteristics could be linked to particular CD phenotypes. Patients with increased intestinal eosinophils could possibly express specific cytokines associated with a faster response to induction treatments. It is well known that interleukins 5 and 3 play an important role in the physiopathology of eosinophilic esophagitis.[34] It would be interesting to investigate if those cytokines are more readily expressed in patients with CD presenting increased eosinophils. The most recent literature reviews clearly detail the involvement of T lymphocytes, plasma cells, macrophages, and dendritic cells in the pathophysiology of IBD, but the involvement of eosinophils is largely absent.[35] Also, Lampinen et al. have shown that the number of eosinophils, their viability, and their activity are increased in the inflammatory mucosa in active CD compared to control subjects.[36] The absence of eosinophils has also been shown to worsen colitis in mice, since these leukocytes secrete TGF-beta, an anti-inflammatory cytokine.[37]

Experts do not recommend the use of oral 5ASA to induce remission in CD due to lack of efficacy.[29] This treatment is sometimes administered to patients with mild forms of CD.[8] The current study demonstrated that the use of oral 5ASA as induction therapy is strongly associated with longer time to clinical remission compared to steroids, EEN or TNF-alpha inhibitors. Therefore, as advised by recent pediatric guidelines, the use of 5ASA should not be recommended for the treatment of luminal CD in children. Despite the decrease in clinical use in recent years, 11.3% of patients newly diagnosed with CD in 2019 were exposed to oral 5ASA at induction (mono or combotherapy). Among the patients recently exposed to 5ASA in 2019, 62.5% had mild colitis (the majority of whom classified as IBD unclassified at baseline) and 37.5% had mild ileitis.

EEN was associated with an accelerated time to remission as compared to corticosteroids, especially in patients who were concomitantly or subsequently treated with TNF-alpha inhibitors. It is the first therapy suggested to treat pediatric patients with CD during the induction phase by several guidelines.[8] In children who received TNF-alpha inhibitors before achieving remission, exposure to EEN as induction therapy was associated with earlier time to clinical remission (45 days less). However, by the end of the decade in 2019, only 21.1% of patients received EEN as the first induction therapy while 39.4% of patients received corticosteroids.

Experts do not agree on the efficacy of antibiotics as an induction treatment of CD.[29] However, the results of the current study showed that the concomitant exposition to antibiotics may be beneficial since it significantly reduces time to clinical remission in children with luminal CD. However, this must be weighed against the risk associated with *Clostridium difficile* infection.

Patients with high levels of inflammatory markers (CRP, FC, ESR) reached clinical remission faster. We hypothesize that inflammatory phenotypes have a better response to anti-inflammatory treatments independent of the treatment regimen. Also, it is possible that inflammatory patients had a shorter time to diagnosis compared to patients with a more quiescent and longer evolving disease. Multiple studies have shown that a longer time to diagnosis is a risk factor for complications.[38–40] However, several studies have shown that persistent elevated biomarkers (CRP, ESR, FC) were associated with more relapses and hospitalizations.[5,41] A recent meta-analysis showed that the achievement of clinical remission preceded by 1 to 3 weeks the normalization of serum inflammatory markers and time to FC normalization and mucosal healing was even longer. Clinicians should therefore be watchful after clinical remission is achieved since it is only an intermediate therapeutic target.[11]

The study is based on the analysis of a very large cohort of children with CD. The size of our cohort was large enough to identify several factors associated with clinical remission. Nonetheless, several limitations must be underlined associated with the retrospective nature of the study. Firstly, the clinical and biological follow-up was not standardized. Secondly, most of the disease activity scores (PCDAI, sPCDAI, SES-CD) were retrospectively calculated. Thirdly, even though the team of three pathologists has remained constant throughout the decade, there may be inter-observer variability that could not be quantified. In addition, the pathology reports did not include the numeric value of eosinophilic count per digestive segment. Therefore, the increase in the number of eosinophils was left to the pathologist's interpretation. Lastly, due to the study design, we could not investigate other factors such as the time between the onset of symptoms and diagnosis as well as genetic markers or microbiota composition. More prospective studies with close post-induction follow-ups evaluating time to remission are needed.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1. Induction and maintenance treatments.
Table S2. Laboratory data during patient's follow-up before clinical remission.
Figure S1. Kaplan-Meier curve representing the time to clinical remission of patients according to the intake of oral 5-ASA before remission.
Figure S2. Kaplan-Meier curve representing the time to clinical remission of patients according to the intake of EEN before remission.