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Earlier Anti-Tumor Necrosis Factor Therapy of Crohn's Disease Correlates with Slower Progression of Bowel Damage

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Abstract

Introduction—Crohn's disease (CD) follows a relapsing and remitting course incurring cumulative bowel damage over time. The question of whether or not the timing of the initiating biologic therapy affects long-term disease progression remains unanswered. Herein, we calculated rates of change in the Lémann index—which quantifies accumulated bowel damage—as a function of the time between the disease onset and initiation of biologic therapy. We aimed to explore the impact of the earlier introduction of biologics on the rate of progression of long-term cumulative bowel damage.

Methods—Medical records of CD patients treated during 2009–2014 at The Mount Sinai Hospital were queried. Inclusion criteria were two comprehensive assessments allowing calculation of the index at t_1 and t_2 : two time-points 1 year apart. Patients with biologics introduced before or within 3 months at inclusion (t_1) were defined as Bio-pre- t_1 and those who did not as Bio-post- t_1 . The rate of disease progression was calculated as the change in the index per year during t_1 – t_2 .

Results—A total of 88 patients were studied: 58 Bio-pre- t_1 and 30 Bio-post- t_1 . Among the 58 Bio-pre- t_1 cases, damage progressed in 29 (50%), regressed in 20 (34.5%), and stabilized in 9 (15.5%). Median time to initiation of biologics among patients whose index improved was nominally shorter compared to that in patients whose index progressed (8 vs. 15 years). Earlier

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introduction of biologics tended to correlate with the slower rate of progression ($\rho = 0.241$; $p = 0.069$).

Conclusions—Earlier introduction of biologics tended to correlate with the slower progression of bowel damage in CD, reflected by the reduced rate of Lémann index progression.

Keywords

Crohn disease; Biological therapy; Infliximab; Adalimumab; Inflammatory bowel disease

Introduction

Crohn's disease (CD) follows a relapsing and remitting course that typically results in progressive bowel damage [1–3]. Although CD presents in several clinical patterns such as inflammatory, penetrating, and stricturing with or without perianal involvement, the disease behavior, in general, evolves as a result of cumulative bowel damage (CBD) [2, 4, 5]. Despite apparent symptom resolution, an active disease process often continues, accruing irreversible damage over time [6]. Advanced body-imaging techniques such as magnetic resonance enterography (MRE) and computed tomography enterography (CTE) allow detailed assessment of structural changes incurred as a result of the ongoing disease process (e.g., mucosal enhancement, bowel wall thickness) [7]. The Lémann index (Li) is a recently introduced objective quantitative measure of CBD based on small bowel imaging, upper endoscopy, perianal assessment, and colonoscopy [8, 9]. It has been used to identify risk factors for CBD and to assess the impact of various therapeutic strategies on the long-term outcome [10, 11]. The index has been used extensively for evaluating CBD at particular time points, but generally not with longitudinal follow-up [12].

Newer therapeutic goals for CD demand control of the disease process beyond symptomatic relief—to slow, arrest, or reverse the cumulating damage. For the use of biologics, “treat-to-target” and “top-down regimens” are increasingly favored [13, 14], in addition to the combination regimen comprising immunomodulators and biologics, proposed in the landmark SONIC study [15]. Studies have suggested advantages of biologic therapy and “treat-to-target”, which are reported to stabilize CBD [16] and promote mucosal healing [4, 15–17]. Moreover, the need to monitor CD using a dynamic model that incorporates *time* as a dimension in addition to the established three dimensions: age of onset, anatomic location, and disease behavior, has been proposed for over a decade [4, 17].

A pivotal question remaining is *when* in the course of CD is it optimal to initiate anti-TNF therapy. What is yet to be elucidated, for example, is whether or not the timing of starting biologics, tabulated on a continuous scale, affects the *rate* of progression of CBD over a measured time interval. In this study, using data from a tertiary IBD care center, we conducted a longitudinal study exploring the association between the *timing* of introducing anti-TNF therapy and the course of CD using a new quantitative metric—the *rate* of progression of CBD—by serial assessment of the Lémann index.

Methods

Patient Selection

This retrospective longitudinal study was conducted at a tertiary care Inflammatory Bowel Disease (IBD) Center, The Mount Sinai Hospital (MSH). The institutional database was queried to identify CD patients who underwent treatment during 2009–2014. Based on the selection criteria, electronic health records were used to extract clinical information. Inclusion criteria were: (1) age ≥ 18 years at time of inclusion; (2) a confirmed diagnosis of CD based on the ICD-9 codes, 555.0, 555.1, 555.2, and 555.9 and chart review; (3) availability of all required test results, including two MREs within 140 days of each Li assessments at least 1 year apart as recommended by the protocol [8]; and (4) first biologic treatment before or within 3 months of t_1 . Biologic treatment was defined as a full induction and at the least one maintenance dose of an anti-TNF drug with or without immunomodulators. The MSH institutional review boards approved the study protocol. No patient consent was required.

Data Collection

Using the electronic health records, we collected data on patient demographics including gender, age, and smoking status at onset (non-smoker, smoker, and ex-smoker); and clinical characteristics including diagnosis, Montreal classification for age of diagnosis; disease location; and behavior; endoscopy results; surgical history; disease characteristics; disease duration; and treatment history (Table S1).

Lémann Index of Cumulative Bowel Damage (Li) Calculation Protocol

The Lémann index was calculated for each patient at two different time points (t_1 and t_2) at least a year apart. At each of the two comprehensive assessments, surgical history, endoscopy data, and MRI enterography and/or pelvic MRI results were tabulated according to the standard published protocol required for calculation of Li [8]. Upper endoscopy was assessed for patients with upper tract (esophagus, stomach, and duodenum) involvement. Colonoscopy was also used to confirm the colorectal and perianal lesion reported on the MRE. Pelvic MRI or physical exam reports were used for pelvic involvement. All investigations were completed within 140 days for each time point.

Disease manifestations including fistulae (p_1 , p_2 , and p_3), strictures (s_1 , s_2 , and s_3), ulcers (p_1), abscesses (p_3), wall thickening and segmental enhancement (s_1 and s_2), mural stratification (s_2), and surgical resection (r) were graded according to the scale used to calculate computerized Lémann index. Li was calculated using Microsoft Excel-based macro published in Gastroenterology [8] (Figure-S1). The range of Li is 0–100; the higher the score, the greater the damage. The Li calculation protocol was established after multiple meetings, which included institutional radiologists and gastroenterologists. Two radiologists (MC and MW) were specifically trained to re-assess MRE for the Li scoring. Following these training sessions, interobserver concordance was assessed in 10 randomly selected patients using a two-way mixed-model method for absolute agreement. Inter-reader inter-class coefficient between the two radiologists was found to be excellent (97.7; 95% CI 91.2–99.4, $p < 0.001$). Two investigators together calculated the Lémann index (HP and JP). Intra-

rater reliability of calculating the Lémann index was done for another set of 10 randomly selected patients and was found to be excellent (inter-class coefficient 99.4; 95% CI 97.8–99.9; $p < 0.001$).

Delta Lémann Index (ΔLi)

The point change in the value of Li from t_1 to t_2 was defined as ΔLi [$\Delta Li = Li_{t_2} - Li_{t_1}$]. Patients whose index increased over time ($\Delta Li > 0$) were defined to have “damage progression”; those with unchanged Li ($\Delta Li = 0$) as “damage arrest or stabilization”; and those with index decreased ($\Delta Li < 0$), “damage regression.”

Rate of Progression of the Lémann Index

The rate of disease progression was defined as the change in the Li over time in years and was expressed as a continuous variable. It was calculated by dividing the point change in Li from t_1 to t_2 (ΔLi) by the time in years between t_1 and t_2 , i.e., rate = ΔLi /time in years. We plotted the rates of changes in Lémann index as a function of the elapsed time between onset of CD symptoms and initiation of biologic therapy.

Definitions

Biologic therapy—A full induction, i.e., 5 mg/kg IV infliximab at week 0, 2, and 6 or subcutaneous adalimumab 160 mg at week 0 and 80 mg at week 2 or subcutaneous certolizumab 400 mg at week 0, 2, and 4, plus 1 maintenance dose according to the standard protocol of each FDA-approved biologic therapy for CD including infliximab, adalimumab, and certolizumab with or without immunomodulators.

Time of disease onset (t_0)—Each patient chart was searched for the age of the earliest onset of CD-related symptoms signs including but not limited to abdominal pain, diarrhea, growth retardation, or other systemic symptoms: e.g., weight loss, anemia, extra-intestinal manifestations including joints (arthritis), eye (uveitis, iritis, episcleritis), skin (erythema nodosum, pyoderma gangrenosum), primary sclerosing cholangitis, or signs of malabsorption or malnutrition (e.g., vitamin B12 deficiency, hypocalcaemia, hypoalbuminemia), and then consequently received confirmed diagnosis of CD.

Time of diagnosis (t_d) was established as the time when the diagnosis of CD was confirmed based on at least two of the following: diagnostic ICD-9 codes, diagnostic tests, or patient chart notes recorded by care providers.

Time of initiating biologics (t_b) was noted as the time when a patient completed a full induction and the first maintenance dose.

Time of the first Li assessment (t_1) was recorded on the day of the first MRE. All other related investigations within 140 days of the tests were used to calculate the index according to the protocol.

Time of the follow-up Li assessment (t_2) was recorded as the day of the second MRE. All other related investigations within 140 days of the tests were used to calculate the index according to the Li protocol.

Bio-pre- t_1 cohort—Patients introduced to anti-TNF before or within 3 months at inclusion (t_1).

Bio-post- t_1 cohort—Patients introduced to anti-TNF never or after 3 months of inclusion time (t_1).

Study Design and Statistical Analyses

The *exposure* of interest was the time interval from earliest symptomatic onset of CD to initiation of biologic therapy. The primary *outcome* of interest was the *rate* of progression of Li over time. Our *analysis* of interest was the correlation, if any, between (a) the *time interval* to initiation of anti-TNF therapy (t_0 to t_b) and (b) the *rate* of progression of Li over the measured interval (t_1 – t_2). The time interval, t_1 – t_2 , was determined by the dates of the two Li assessments at least 1 year apart. We studied this relationship for both the Bio-pre- t_1 and the Bio-post- t_1 cohorts. Three months was used as a cutoff for Bio-pre- t_1 group, as this time interval is reasonably proximal to the beginning of t_1 to assume stability of Li during that time period. Time longer than that would allow too much change in Li from time t_1 to have occurred spontaneously or in response to other variables.

Continuous variables were compared using Student's t test for normally distributed variables. Nonparametric test Wilcoxon–Mann–Whitney (for two independent samples) or Kruskal–Wallis (three or more samples) was used for non-normally distributed variables. Categorical variables were compared using Chi-square or Fisher's exact test statistics. An intrinsic feature of the “rate of progression” of Li is the *direction* of the change in Li, over time. Therefore, we also performed univariate logistic regression to identify significant predictors of *increase* in Li. Next, multivariable analysis was performed using a priori determined variables and predictors with $p < 0.1$ in the univariate method. A priori variables included gender, age, and smoking status at diagnosis, and Li at t_1 . Correlation analysis was performed using Pearson for normally distributed and Spearman's rho test for skewed data. Sensitivity analysis was performed using inter-class coefficient (ICC) for inter-reader agreement in the MRE reports and intra-investigator agreement calculation of Li. All tests were two-sided and considered significant for a p -value less than 0.05. Statistical analyses were performed using IBM SPSS Statistical Software for Mac OS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 230 patient charts were queried, and 88 patients (38%) met the study inclusion criteria. Of them, 58 (66%) patients received biologics before or within 3 months of Li assessment, while 30 (34%) either did not receive biologics at all or received them later than 3 months of t_1 (Fig. 1).

Study Population

Patient and disease characteristics are described in Table 1. For the entire cohort, the median age of onset was 20 years: 32 years at t_1 and 35 years at t_2 . Describing the age at diagnosis according to the Montréal classification, the majority of patients were A2 (51%), followed

by A1 (41%) and A3 (8%). During the study period, the most advanced Montreal classification of disease behavior was B1 in 6% patients (non-stricturing and non-penetrating), B2 in 39% (stricturing only), and B3 in 56% (penetrating). Over one-third of the patients had perianal CD (p) (Table 1). At the time of diagnosis, 23% patients were active smokers, 8% ex-smokers, and 69% had never smoked tobacco.

At the baseline Li assessment (t_1), the median disease duration was 12 years (range 0–46), with 13% patients diagnosed within previous 2 years, 28% between 3 and 10 years, 22% for 11–20 years, 15% for 21–30 years, and 10% for over three decades. At the second Li assessment (t_2), median disease duration was 15 years. Half of the cohort had been treated with immunomodulators before t_1 , and 44% with systemic corticosteroids. After t_1 , 50% patients received immunomodulators, while only 19% received systemic corticosteroids.

Surgical Resections (Table 1)

Prior to the first Li assessment (t_1), over half of the patient cohort had already undergone at least one surgical resection. During the time between the first and the second Li assessment (t_1 – t_2), 20 patients underwent surgical resection. There were no significant difference in the proportions of patients undergoing surgery, both before t_1 and after t_1 , between the Bio-pre- t_1 and the Bio-post- t_1 cohorts.

Lémann Index of Cumulative Bowel Damage (Li) for the Entire Cohort

The median Li at t_1 was 11.1 (IQR 4.9–23.7), which increased to 14.2 (IQR 5.4–30.8) at t_2 (Table 2). During the time interval between t_1 and t_2 , Li increased (damage progressed) in 47 (53.4%), remained unchanged (damage arrested or stabilized) in 15 (17.0%), and decreased (suggesting damage regression) in 26 patients (29.5%).

Older age at introducing biologics tended to correlate with the higher score of Li at t_1 ($r = 0.249$, $p = 0.059$), but not at t_2 ($r = 0.161$, $p = 0.83$). Disease duration correlated with Li at both time assessments: t_1 ($r = 0.442$, $p = 0.001$) and t_2 ($r = 0.426$; $p < 0.001$). Box-plots depicting increase in the Li correlating with disease duration are presented in Figs. 2 and 3 for t_1 and t_2 , respectively.

Lémann Index by the Time of Initiating Biologics

In the 58 patients in the Bio-pre- t_1 cohort that received biologics before or within 3 months of t_1 , damage progressed in 29 (50%), stabilized in 9 (15.5%), and regressed in 20 (34.5%). In the Bio-post- t_1 group, the damage progressed in 18 (60%), arrested in 6 (20%), and reversed in 6 (20%).

Delta Lémann Index (Li) and Time to Initiation of Anti-TNF

The median time from disease onset to the introduction of biologics was 9.5 years (range 0–42 years). Of the total patients, 31% received biologics within 5 years of disease onset, 19.0% between 6 and 10 years, 25.9% between 11 and 20 years, and 24.1% after two decades of the disease onset.

Of the 58 patients in the Bio-pre- t_1 group, half ($n = 29$) experienced a *decrease* in Li, i.e. $Li \leq 0$, during the follow-up time. Median time to initiation of biologics in patients with $Li \leq 0$ was almost half of that in patients with $Li > 0$ ($p = 0.058$; Fig. 4).

Univariate logistic regression analysis showed earlier introduction of biologics was associated with damage regression or arrest ($Li \leq 0$) ($p = 0.043$; Table 3). Multivariable analysis adjusting for potential confounders including age of onset, gender, and Li at t_1 confirmed that earlier initiation of biologic therapy remained a significant predictor of bowel damage stabilization or regression ($p = 0.03$; Table 3).

Rate of Progression of Li and Time of Initiating Anti-TNF Therapy

The overall rate of change of Li ($Li/t_2 - t_1$ years) ranged from -3 to $+37.8$ Li per year. On a continuous scale, earlier introduction of biologics was associated with either the decreased rate of progression or increased rate of improvement as reflected by the rate of change in Li ($p = 0.069$; Fig. 5). By contrast, in the Bio-post- t_1 group that either received biologics after 3 months of t_1 or never, no association was observed between the rate of change of Li and time from disease onset (t_0) to either t_1 or t_2 . ($p = 0.934$; Fig. 6).

Outlier analysis was performed as a sub-analysis. The outlier in this series with the rate of progression greater than 35 Li per year (Fig. 5) had undergone two resections culminating in short bowel syndrome and also developed perianal disease, all within 14 months of follow-up between t_1 and t_2 . The association between the timing of introduction and the rate of progression became significant after excluding the outlier (correlation coefficient, $\rho = 0.297$; $p = 0.025$).

Discussion

The use of the Lémann index of cumulative bowel damage in CD has become increasingly common in recent years [10, 18–21]. Moreover, we are not the first investigators to note that Li decreases with anti-TNF therapy [16], but our study has incorporated two innovations. First, we quantified the disease trajectory as the *rate* of progression of Li and utilized this measure as the primary outcome of interest. Second, we correlated this outcome measure with the *time* from presumed disease onset to the first introduction of anti-TNF therapy, measuring this interval as a continuous variable. Using this onset-to-treatment interval as the independent variable, and *rate* of progression of Li as the outcome measure, we found that the earlier initiation of biologics was tended to correlate with a slower rate of progression of Li ($p = 0.069$; Fig. 5). The association of worsening Li with the longer time interval between the disease onset and initiation of biologics remained significant after application of a multivariable logistic regression analysis, which showed that later introduction of anti-TNF by 10 years decreased the odds of disease regression or stabilization by 91% (Table 3).

In the EXTEND trial, Rutgeerts et al. [22] reported that adalimumab induces and maintains remission. Our study furthermore indicates the impact of earlier anti-TNF treatment on the rate of CD progression. While association is not the same as causation, this observation would be consistent with the hypothesis that early introduction of anti-TNF therapy could have an ameliorative effect on structural damage over the long term. These results are

specifically important in the context of the newer therapeutic goals of CD shifting from symptomatic remission to transmural healing. An experimental animal study demonstrated improved outcomes with early introduction of anti-TNF [23]. Other clinical studies have demonstrated that introducing biologics within 2 years of disease onset contributes to improved disease control, but they used outcome measure as clinical indices [24, 25]. Our findings are in support of the emerging treatment paradigm that using the “therapeutic window of opportunity” in early CD may promote healing more effectively, thus preventing further irreversible bowel damage progression culminating into the natural disease course.

In our study, the overall Li, as expected, tended to increase with longer disease duration, an observation that is similar to what was conceptualized at the inception of the Lémann index [8, 9]. Similarly, other authors have shown the association between the longer duration and the higher Lémann index [26]. What came to us as a surprise, however, was our finding that the Li decreased or remained stable in about half of the cohort, representing arrest or even regression of structural damage. Nonetheless, these findings are like many others [2, 11, 18, 27]. For example, Cosnes et al. [2] followed an inception cohort of patients over 5–10 years and found that Li increased in 57%, remained unchanged in 10%, and decreased in 33%, data not unlike our own.

When adjusted for the Li at t_1 , gender, smoking status at diagnosis, and disease duration, the multivariable analyses showed no significant impact of age at disease diagnosis on disease progression. These findings differ from a recent study in Korean patients that showed a favorable effect of older age of diagnosis on disease prognosis. However, the outcome measures in this study were remission at the last follow-up and number of surgeries, rather than a quantitative indicator measuring cumulative bowel damage [28].

The retrospective design of this study carries certain limitations. The p value for our primary outcome was only borderline significant, which may be attributed to the smaller sample size. There may be a risk of confounding by indication, as treating physicians may tend to treat more severe disease more aggressively earlier than later. One might expect this confounding, however, to militate against rather than in favor of the apparent benefit of early biologic therapy. There is also a potential for referral bias, since all patients were seen at a tertiary care center. Moreover, on account of the colinearity of disease duration and time interval between the disease onset and introduction of biologic, we did not include the disease duration in our multivariable model; instead, in order to control for preexisting cumulative disease damage, our model used the Li at t_1 . Finally, our analysis did not include information on the type of payer, which might have influenced decision making for the use of biologics. Nonetheless, our study reflects a long and nearly complete follow-up of confirmed cases with mostly long-standing disease starting from the time of onset.

Conclusion

This study uses the *rate* of progression (or regression) of cumulative bowel damage as the primary outcome measure to assess an association with the *timing* of initiating anti-TNF therapy in the course of Crohn’s disease. We found that earlier introduction of biologics tended to correlate with a slower rate of progression (or with stabilization or even regression

of cumulative bowel damage. Besides the therapeutic implications of this finding, we suggest that the *rate of progression* of the Lémann index of cumulative bowel damage may be a useful outcome measure for future studies of the clinical course of Crohn's disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Compliance with ethical standards

Conflict of interest No industrial support was received for the work presented in this article. Dr. Dubinsky serves as a consultant for Janssen, Abbvie, and UCB. Dr. Taouli reports research grant support from Guerbet and Bayer. None of the other authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

References

1. Wagtmans MJ, van Hogezaand RA, Griffioen G, Verspaget HW, Lamers CB. Crohn's disease of the upper gastrointestinal tract. *Neth J Med.* 1997;50:S2–S7. [PubMed: 9050325]
2. Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis.* 2002;8:244–250. [PubMed: 12131607]
3. Thia KT, Sandborn WJ, Harmsen WS, Zinsmeister AR, Loftus EV Jr. Risk factors associated with progression to intestinal complications of Crohn's disease in a population-based cohort. *Gastroenterology.* 2010;139:1147–1155. [PubMed: 20637205]
4. Papi C, Festa V, Fagnani C, et al. Evolution of clinical behaviour in Crohn's disease: predictive factors of penetrating complications. *Dig Liver Dis.* 2005;37:247–253. [PubMed: 15788208]
5. Rinawi F, Assa A, Hartman C, et al. Evolution of disease phenotype in pediatric-onset Crohn's disease after more than 10 years follow up-Cohort study. *Dig Liver Dis.* 2016;48:1444–1450. [PubMed: 27637153]
6. Bhattacharya A, Rao BB, Koutroubakis IE, et al. Silent Crohn's disease predicts increased bowel damage during multiyear followup: the consequences of under-reporting active inflammation. *Inflamm Bowel Dis.* 2016;22:2665–2671. [PubMed: 27753691]
7. Eder P, Michalak M, Katulska K, et al. Magnetic resonance enterographic predictors of one-year outcome in ileal and ileocolonic Crohn's disease treated with anti-tumor necrosis factor antibodies. *Sci Rep.* 2015;5:10223. [PubMed: 25993615]
8. Pariente B, Mary J-Y, Danese S, et al. Development of the Lémann index to assess digestive tract damage in patients with Crohn's disease. *Gastroenterology.* 2015;148:52–63.e3. [PubMed: 25241327]
9. Pariente B, Mary JY, Colombel JF, Cosnes J. Development of the Crohn's disease (CD) digestive damage score: the Lémann score. *J Crohn's Colitis.* 2013;7:S3.
10. Amitai MM, Zarchin M, Lahat A, et al. Structural bowel damage in quiescent Crohn's disease. *Dig Liver Dis.* 2017;49:490–494. [PubMed: 28233685]
11. Fiorino G, Bonifacio C, Allocca M, et al. Bowel damage as assessed by the Lémann index is reversible on anti-TNF therapy for Crohn's disease. *J Crohn's Colitis.* 2015;9:633–639. [PubMed: 25958059]

12. Fiorino G, Morin M, Bonovas S, et al. Prevalence of bowel damage assessed by cross-sectional imaging in early Crohn's disease and its impact on disease outcome. *J Crohn's Colitis*. 2016;11:274–280.
13. Kirchesner J, Lemaitre M, Rudnichi A, et al. Therapeutic management of inflammatory bowel disease in real-life practice in the current era of anti-TNF agents: analysis of the French administrative health databases 2009–2014. *Aliment Pharmacol Ther*. 2017;45:37–49. [PubMed: 27781286]
14. Bouguen G, Levesque BG, Pola S, Evans E, Sandborn WJ. Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2014;12:978–985. [PubMed: 24246770]
15. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362:1383–1395. [PubMed: 20393175]
16. Bodini G, Giannini EG, De Maria C, et al. Anti-TNF therapy is able to stabilize bowel damage progression in patients with Crohn's disease. A study performed using the Lémann index. *Dig Liver Dis*. 2017;49:175–180. [PubMed: 27864028]
17. Sachar DB. Einstein, Darwin and conventional wisdom about Crohn's disease. *Dig Liver Dis*. 2005;37:227–229. [PubMed: 15788204]
18. Bhagya Rao B, Koutroubakis IE, Ramos Rivers C, et al. Delineation of Crohn's disease trajectories using change in Lémann index: a natural history study. *J Clin Gastroenterol*. 2016;50:476–482. [PubMed: 26646805]
19. Bhagya Rao B, Koutroubakis IE, Rivers CR, et al. Correlation of anemia status with worsening bowel damage as measured by Lémann index in patients with Crohn's disease. *Dig Liver Dis*. 2016;48:626–631. [PubMed: 27005859]
20. Pellegatta G, Bodini G, Giannini EG, et al. Tu2009 does Lémann index reflect the quality of life in Crohn disease patients on treatment with biological therapy? *Gastroenterology*. 2016;150:S1004–S1005.
21. Rao BB, Click BH, Koutroubakis IE, et al. The cost of Crohn's disease: varied health care expenditure patterns across distinct disease trajectories. *Inflamm Bowel Dis*. 2017;23:107–115. [PubMed: 27930405]
22. Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology*. 2012;142:1102–1111.e2. [PubMed: 22326435]
23. Schmidlin-Ren P, Reingold LJ, Broxson CS, et al. Anti-TNF α alters the natural history of experimental Crohn's disease in rats when begun early, but not late, in disease. *Am J Physiol Gastrointest Liver Physiol*. 2016;311:G688–G698.
24. Oh EH, Oh K, Han M, et al. Early anti-TNF/immunomodulator therapy is associated with better long-term clinical outcomes in Asian patients with Crohn's disease with poor prognostic factors. *PLOS ONE*. 2017;12:e0177479. [PubMed: 28542298]
25. Ma C, Beilman CL, Huang VW, et al. Anti-TNF therapy within 2 years of Crohn's disease diagnosis improves patient outcomes: a retrospective cohort study. *Inflamm Bowel Dis*. 2016;22:870–879. [PubMed: 26818419]
26. Ruel J, Ruane D, Mehendru S, Gower-Rousseau C, Colombel JF. IBD across the age spectrum: is it the same disease? *Nat Rev Gastroenterol Hepatol*. 2014;11:88–98. [PubMed: 24345891]
27. Fiorino G, Bonifacio C, Peyrin-Biroulet L, Danese S. Preventing collateral damage in Crohn's disease: the Lémann index. *J Crohn's Colitis*. 2016;10:495–500. [PubMed: 26744441]
28. Choi JH, Kim ES, Cho KB, et al. Old age at diagnosis is associated with favorable outcomes in Korean patients with inflammatory bowel disease. *Intest Res*. 2015;13:60–67. [PubMed: 25691844]

Fig. 1. CONSORT diagram depicting patient selection for the study. MRE MRI enterography; t_1 time point 1 when Li was assessed at inclusion; Bio-pre- t_1 : biologics before or within 3 months of inclusion, i.e., t_1 Bio-post- t_1 no biologics or initiating biologics after 3 months of inclusion, i.e., t_1

Fig. 2.
The Lémann index by disease duration at t_1 ; $N=88$; coefficient, Kruskal–Wallis statistic = 13.79, $p=0.008$)

Fig. 3.
The Lémann index by disease duration at t_2 ; $n = 88$; Kruskal–Wallis test statistic = 15.99; $p = 0.003$

Fig. 4.

Box-plots depicting distribution of the timing of initiating biologics among patients who received the treatment before or within 3 months of t_1 ($n = 58$) stratified by outcome of interest: damage arrest/regression; Wilcoxon–Mann–Whitney U test, $p = 0.058$

Fig. 5.

Correlation between the rate of progression of the Lémann index of cumulative bowel damage on the *Y*-axis and the timing of initiating anti-TNF Therapy on *X*-axis among patients who received biologics prior of within 3 months of t_1 : Bio-pre- t_1 , $n = 58$; correlation coefficient Spearman's $\rho = 0.241$; $p = 0.069$

Fig. 6.

Correlation between the rate of progression of the Lémann index of cumulative bowel damage on the *Y*-axis and the timing of initiating anti-TNF Therapy on *X*-axis among patients who received biologics either after 3 months of t_1 or did not receive any biologics during the study period: Bio-post- t_1 , $n = 30$; correlation coefficient Spearman's $\rho = -0.024$; $p = 0.934$

Table 1

Demographic, clinical, and disease characteristics

Characteristics	Total $N = 88$ N (%)	Bio-pre- t_1 $n = 58$ n (%) ^a	Bio-post- t_1 $n = 30$ n (%) ^a	p Value
Age, years, median (min–max)				
Age at diagnosis	20 (2–60)	19 (2–60)	21 (2–42)	0.982
Age at t_1	32 (10–72)	35 (19–72)	31 (10–64)	0.315
Age at t_2	35 (19–74)	38 (20–74)	34 (19–68)	0.451
Gender				0.472
Female	43 (48.9)	29 (50.0)	14 (46.7)	
Male	45 (51.1)	29 (50.0)	16 (53.3)	
Smoking status				0.305
Never	61 (69.3)	37 (63.8)	24 (80.0)	
Current	20 (22.7)	15 (25.99)	5 (16.7)	
Former	7 (8.0)	6 (10.3)	1 (3.3)	
Montréal classification: age of onset				0.836
A1 [< 17 years]	36 (40.9)	25 (43.2)	11 (36.7)	
A2 [18–40 years]	45 (51.1)	28 (48.3)	17 (56.7)	
A3 [> 40 years]	7 (8.0)	5 (8.6)	2 (6.7)	
Montréal classification: behavior ^b				0.246
B1 [inflammatory]	5 (5.7)	5 (8.6)	0	
B2 [stricturing]	34 (38.6)	23 (39.7)	11 (36.7)	
B3 [penetrating]	49 (55.7)	30 (51.7)	19 (63.3)	
P [perianal/anal]	21 (35.2)	19 (32.8)	12 (40.0)	0.500
Montréal classification: location ^b				0.433
L1 [ileal]	26 (29.5)	15 (25.9)	11 (36.7)	
L2 [colonic]	10 (11.4)	6 (10.3)	4 (13.3)	
L3 [ileocolonic]	52 (59.1)	37 (63.8)	15 (50.0)	
L4 [upper GI tract]	14 (15.9)	12 (20.7)	2 (6.7)	0.077
Disease duration at t_1				0.952
[< 2 years]	13 (13.8)	8 (13.8)	5 (16.7)	

Characteristics	Total N = 88 N (%)	Bio-pre- t_1 n = 58 n (%) ^a	Bio-post- t_1 n = 30 n (%) ^a	p Value
[3–10 years]	28 (31.8)	19 (32.8)	9 (30.0)	
[11–20 years]	22 (15.0)	14 (24.1)	8 (26.7)	
[21–30 years]	15 (17.0)	11 (19.0)	4 (13.3)	
[> 30 years]	10 (11.4)	6 (10.3)	4 (13.3)	
Duration between t_1 – t_2 , years	2.1 (1–6.6)	2.0 (1–5.5)	2.3 (1–6.6)	0.829
Disease duration at t_2 , years	16.0 (1–49)	16.0 (3–49)	14.0 (1–41)	0.498
Pre- t_1 medications				
Immunomodulators	43 (48.9)	27 (46.6)	16 (53.3)	0.546
Systemic corticosteroids	39 (44.3)	25 (43.1)	14 (46.7)	0.750
Post- t_1 medications				
Immunomodulators	44 (50.0)	30 (51.7)	14 (46.7)	0.653
Systemic corticosteroids	21 (23.9)	15 (25.9)	6 (20.0)	0.541
Pre- t_1 surgery				
No	33 (37.5)	19 (32.6)	14 (46.7)	0.201
Yes	55 (62.5)	39 (67.2)	16 (53.3)	
Upper GI tract	2 (2.3)	2 (3.5)	0	0.546
Small bowel/ileocolic	35 (39.8)	23 (39.7)	12 (40.0)	0.826
Colo-rectal	18 (20.5)	14 (24.1)	4 (13.3)	0.366
Post- t_1 surgery				
None	68 (77.3)	46 (79.3)	22 (73.3)	0.526
Yes	20 (22.7)	12 (20.7)	8 (26.7)	
Upper GI tract	0	0	0	NA
Small bowel/ileocolic	11 (12.5)	5 (8.6)	6 (20.0)	
Colorectal	9 (10.2)	7 (12.1)	2 (6.7)	0.712

Continuous variables are presented as median (range) and categorical as n (%)

t_1 – t_2 : Time duration between the two assessments, onset– t_1 : time from onset to the first assessment

^aTotal percentage may not add up to 100 because of rounding the decimals

^bNumbers may not add up to 100, as the disease presentation classification is not mutually exclusive for behavior and location

Table 2

Lémann index and disease progression trajectories

Lémann index (Li) Parameter	Total N = 88	Bio-pre- t_1 n = 58	Bio-post- t_1 n = 30
At t_1			
Mean (SD)	15.1 (13.5)	16.06 (14.0)	13.2 (12.6)
Median (min-max)	11.1 (0-73.3)	13.5 (0.3-73.3)	10.0 (0-51.5)
At t_2			
Mean (SD)	19.1 (14.2)	20.1 (16.6)	17.3 (16.8)
Median (min-max)	14.2 (0-73.8)	14.5 (0-73.8)	12.5 (0-67.5)
Li [Lit_2-Lit_1]			
Mean (SD)	4.0 (8.6)	4.0 (9.2)	4.0 (7.6)
Median (min-max)	0.6 (-13.9 to 37.8)	0.3 (-13.9 to 37.8)	0.7 (-9.6 to 22.6)
The rate of Li [Li/time in years from t_1 to t_2]			
Mean (SD)	2.7 (6.1)	2.5 (6.3)	3.2 (5.7)
Median (min-max)	0.2 (-3.0 to 37.8)	0.1 (-3.0 to 37.8)	0.3 (-2.9 to 22.6)

Li, the Lémann index; t_1 , time point one of the Lémann index assessment; t_2 , time point two when the Lémann index was assessed; Li change in the Li over the two time points t_1 and t_2 ; rate of Li: the change in Li per year for the proposed duration of study, i.e., t_1-t_2

Logistic regression analyses for bowel damage regression or arrest among patients introduced to anti-TNF before or within 3 months of t_1 , $n = 58$

Table 3

Characteristics	OR (95% CI)	p Value	AOR (95% CI)	p Value
Delay initiating biologics, each 10 years from onset	0.09 (0.09–0.10)	0.043	0.09 (0.09–0.10)	0.026
Montréal age, years				
A1 [17]	Reference		Reference	
A2 [18–40]	0.94 (0.32–2.77)	0.909	0.47 (0.12–1.79)	0.266
A3 [> 40]	4.33 (0.42–44.43)	0.217	2.42 (0.19–31.1)	0.497
Gender				
Female	Reference		Reference	
Male	1.52 (0.54–4.26)	0.432	1.94 (0.54–6.90)	0.308
Smoking at diagnosis				
Never smoker	Reference		Reference	
Active smoker	0.20 (0.04–1.03)	0.054	1.45 (0.32–6.49)	0.631
Former smoker	0.66 (0.11–4.04)	0.650	0.49 (0.05–4.77)	0.538
CD duration, years				
From diagnosis to t_1	0.97 (0.92–1.01)	0.965	–	–
Time from anti-TNF to t_1 , years	0.87 (0.73–1.03)	0.101	0.86 (0.69–1.06)	0.151
Time from t_1 to t_2 , years	1.03 (0.98–1.09)	0.204		
Lémann index at t_1	1.00 (0.96–1.04)	0.868	1.04 (0.99–1.09)	0.173

t_1 Time point 1 of the Lémann index assessment, OR odds ratio, AOR adjusted odds ratio, CI confidence interval, Bio initiation of biologics