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ORIGINAL ARTICLE

Lower Risk of B1-to-pB3-Stage Migration in Crohn's Disease Upon Immunosuppressive and Anti-TNF Treatment in the Swiss IBD Cohort Study

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Abstract

Background While the long-term evolution of disease behavior in Crohn's disease has been well described in the pre-anti-TNF era, our knowledge thereon remains scarce after the introduction of anti-TNF.

Aims Our investigation examined the long-term evolution of disease concerning Montreal classification's B-stages over time in patients enrolled into the Swiss IBD Cohort Study between 2006 and 2017.

Methods We analyzed prospectively collected SIBDCS data using a Markov model and multivariate testing for effects of treatment and other confounders on B-stage migration over time. The primary outcome was a transition in disease behavior from B1 to either B2 or pB3, or from B2 to pB3, respectively.

Results The 10- and 15-year probability of remaining in B1 was 0.61 and 0.48, as opposed to a probability to migrate to B2 or B3 of 0.25 or 0.14, and 0.32 or 0.2, after 10 and 15 years, respectively. In multivariate testing, the hazard ratio for migrating from B1 to pB3 (HR 0.27) and from B2 to pB3 (HR 0.12) was lower in patients > 40 years compared to patients < 17 years. We found that immunosuppression (HR 0.38) and treatment with anti-TNF for > 1 year (HR 0.30) were associated with a decreased likelihood of transitioning from stage B1 to pB3.

Conclusions While in the anti-TNF era most patients with Crohn's disease will eventually develop stricturing and/or penetrating complications, our data indicate that immunosuppressive and anti-TNF treatment for more than 1 year reduce the risk of transitioning from stage B1 to pB3 in the long-term run.

Keywords Crohn's disease · Tumor necrosis factor-alpha · Immunosuppressive agents · Montreal classification · Disease-modifying

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Introduction

In adults, Crohn's disease (CD) typically manifests in the second and third decade of life. Due to its primarily non-fatal character, the life expectancy of patients with CD is only minimally reduced compared to the general population [1–3]. However, due to the chronic relapsing nature of disease and disease-related complications, the disease exerts a substantial burden on patients [4]. Sachar et al. [5] defined three groups of clinical disease behavior and complications, i.e., stages: non-stricturing non-penetrating (inflammatory, B1), stricturing (stenosing, B2), and penetrating (fistulizing, pB3). These distinctive phenotypes are represented in the Montreal classification [6].

Little is known about the factors determining the risk of change in disease behavior over time and the onset of long-term complications. To date, known predictors of these include the initial location of CD lesions [7, 8] and the patients' age at diagnosis [9]. Further, smoking also promotes the disease's behavior change from an inflammatory stage to a stricturing or penetrating one [10–12].

A long-term observational study found that over a 5-year period the transition from inflammatory complications (B1) to B2, and pB3, happens in 10% and 26% of the patients, respectively [7]. However, some newer studies indicate that the fraction of CD patients with changes in disease behavior over time might be smaller [13–16]. Magro et al. [17] suggest that improved medical treatment options may have influenced the long-term evolution of disease and decreased the risk of B-stage migration. In contrast to the above-mentioned studies, the authors of a recently published study with data from the Dutch IBDSL cohort found that while hospitalization and surgery rates are decreasing, disease progression to complications is still common in CD patients and not affected by either immunosuppressive agents or biologicals [18].

Since 2005, antibodies targeting tumor necrosis factor (anti-TNF antibodies), including infliximab, adalimumab, and certolizumab pegol, have been used for the treatment of CD. Treatment with anti-TNF has beneficial effects on disease's severity in a large fraction of patients; however, it remains controversial whether anti-TNF agents reduce the likelihood of change in disease behavior according to the Montreal classification [19–22].

Therefore, we aimed to investigate the long-term evolution of Crohn's disease behavior over time in patients recruited for the Swiss IBD Cohort Study (SIBDCS) between 2006 and 2017.

Materials and Methods

The Swiss IBD cohort study (SIBDCS) is a prospective, multicenter cohort study that, starting in 2006, recruits patients with CD, ulcerative colitis, and colitis unclassified in entire Switzerland. It is a nation-wide study including tertiary referral centers, community hospitals, and private practices. Participating patients provide a written informed consent. This cohort has been approved by the respective ethics committees in Switzerland (Ethics Committee of the Canton Zuerich: EK-1316) and is funded by the Swiss National Science Foundation (N 3347CO-108792/1) [23]. Several publications with data from the SIBCS have been published over the last years [11, 24–27]. For the purposes of this study, we included all CD patients with enrollment and one or more follow-up visits between 2006 and 2017. We excluded patients with incomplete records, those whose diagnosis changed from CD to another IBD type during the observation period, and all the patients with stage pB3 at the time of enrollment. Our primary outcome was the change of B-stage (from B1 to B2, from B1 to B3, and from B2 to pB3, respectively).

Upon enrollment, the disease behavior of all patients was classified into one of the three stages as defined by Sachar et al. [5] and the Montreal classification. In the 2005 version of the Montreal classification, perianal fistulae and abscesses are no longer included in the definition of stage B3. Instead, perianal involvement can complicate any disease behavior form (pB1, pB2, and pB3, respectively) [6]. We accounted for that and used the pB3 definition in our analysis due to its clinical impact. Patients were subdivided into the following five groups based on different treatment regimens at or before the time of B-stage migration: (A) patients who never underwent treatment with immunosuppressive agents (IS) or anti-TNF (anti-TNF-naïve, IS-naïve); (B) patients with current or past treatment with IS but not anti-TNF (anti-TNF-naïve, past/current IS); (C) patients who underwent anti-TNF treatment for less than 1 year at the time of B-stage migration (anti-TNF current, less than 1 year); (D) patients who underwent anti-TNF treatment for more than 1 year at the time of B-stage migration (anti-TNF current, more than 1 year); and (E) patients with a history of anti-TNF treatment over the course of the observation period but not at the time of B-stage migration (anti-TNF past). In groups C–E, a combination with IS was possible. However, we deliberately decided to not include a specific group with anti-TNF/IS combination therapy in our analysis due to the fact that a combination is relatively infrequently used in Switzerland, specifically in patients with a pure inflammatory phenotype (i.e., B1). In addition, if a combination therapy is selected, in the vast majority of patients the combination will be continued for a limited duration of 6–12 months.

Distinguishing between groups with different anti-TNF treatment durations (less than one 1 year vs. more than 1 year) was necessary due to a potential selection bias caused by the severity and behavior of disease. In our clinical experience, patients presenting with a more severe and advanced state of disease or with higher risk of B-stage migration are more likely to be treated with anti-TNF. As such, for a subset of patients, treating physicians are more likely to prescribe anti-TNF at the time when patients are still considered to have stage B1 out of the concern that the disease is likely to undergo B-stage migration. At present, little is known about the minimal duration of anti-TNF treatment required for potential positive effects on the disease, if the indication of anti-TNF is present. As such, we defined one year of anti-TNF treatment as a cutoff in order to reduce the likelihood of including patients with unrecognized B-stage migration at the time of anti-TNF initiation. Therefore, we distinguished between patients with recent initiation of anti-TNF treatment (group C) and those with more than 1 year of anti-TNF treatment prior to a B-stage migration (group D).

Statistical Analyses

Statistical analyses were carried out using the Stata Software (v. 14.2, StataCorp, College Station, TX, USA) and the R software (v. 3.3.1, R Foundation for Statistical Computing, Vienna, Austria). Continuous data distribution was assessed using normal quantile–quantile (QQ) plots. Gaussian-distributed continuous data were summarized as mean, standard deviation, and range. Non-Gaussian continuous data were summarized as median, interquartile range (IQR), and range. Categorical data were summarized as raw frequencies and relative percentages.

In order to assess the evolution of patients' disease behavior, a multistate Markov model was applied using the msm package of R software [28]. The scheme of possible transitions between the B1/B2/pB3 stages is depicted in Fig. 1, with pB3 considered as the only absorbing state. Results of the Markov model fits are presented as transition probabilities (and 95% confidence intervals) after 1, 5, 10, and 15 years of follow-up. The effect of fixed and time-varying covariates on the transition intensities was reported as hazard ratios (HRs) and 95% confidence intervals. A log-likelihood ratio test was used to assess the statistical significance of adding each covariate into the multistate model. Time-to-event data were also analyzed using survival techniques appropriate for dealing with interval-censored data. Complication-free probabilities over time were computed using the Kaplan–Meier estimator. For the purpose of this study, a p value < 0.05 was considered as statistically significant.

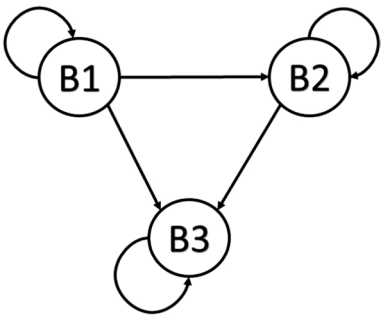

Fig. 1 Markov model with possibilities of B-stage migrations

Results

Recruitment

Of all the patients recruited for the SIBDCS, 1769 patients were identified as potentially suitable for this analysis. Twenty-one patients had to be excluded due to a change of diagnosis during follow-up, another 277 patients due to an insufficient number of required follow-up visits, and further 429 patients as they already were in stage pB3 at enrollment (therefore being unable to undergo stage migration by definition) (Fig. 2).

Demographics

Of the 1042 patients remaining for final analyses, 574 were female (55.1%). The median age at enrollment was 38 years (range 16–88 years), and the median disease duration at enrollment was 6 years (range 0–49 years). A vast majority of patients had a negative IBD family history at enrollment (78.8%). Six hundred and sixty-five patients (63.8%) were non-smokers at enrollment and 712 patients (68.3%) were considered non-smokers at their latest follow-up. Seven hundred and eighty-six patients (75.4%) have had a history of IS treatment at enrollment and 397 patients (38.1%) have had a history of anti-TNF treatment at enrollment (Table 1). Three hundred and sixty-one patients (34.6%) were treated, enrolled, and have received follow-up consultations in tertiary centers, 131 patients (12.6%) in regional hospitals, and 550 patients (52.8%) in private practices or private clinics.

Evolution of Disease

Over 30 years, a substantial fraction of patients progressed from stage B1 to B2 or pB3 (Fig. 3). The probability of B1 patients remaining in this stage after 10 years was 0.61; the probability of remaining in stage B1 after 15 years was 0.48. The probability to migrate from B1 to B2 or pB3 over 10 years was 0.25 or 0.14, respectively, and 0.32 or 0.20 over 15 years (Table 2, Fig. 4). At enrollment, 68 out of 1042 patients (6.5%) experienced upper gastrointestinal

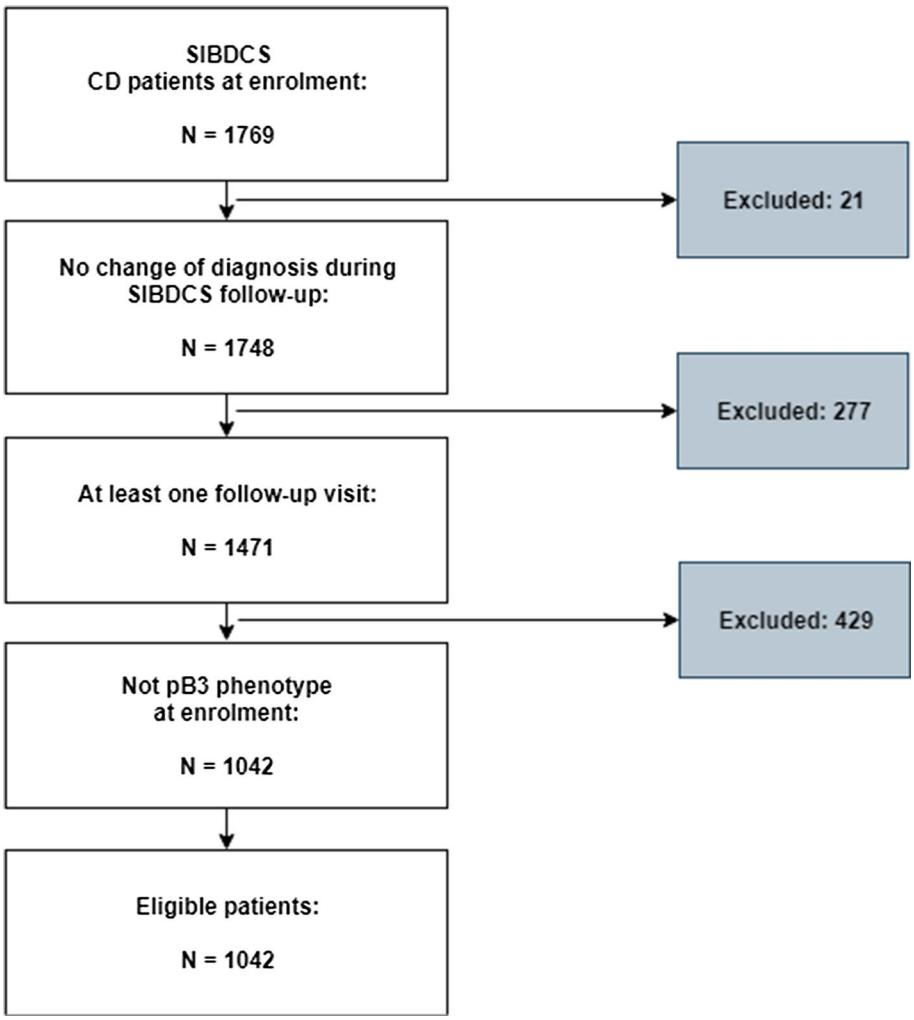

Fig. 2 Flowchart of the determination of suitable patients

complications; therefore, 974 patients out of 1042 (93.5%) were complication-free at enrollment. Thirty-five patients out of these 974 patients (3.6%) without upper gastrointestinal CD involvement at enrollment have had developed upper GI complications during our follow-up; therefore, 939 patients (96.4%) of all patients have had remained free of upper GI complications.

Concerning surgical interventions, a significant number of patients already have had been treated surgically at enrollment (675 patients, 64.7%), 27.9% of all the patients have had an intestinal resection, 6.0% have had a fistula/abscess surgery, and 30.9% have had any surgery. 51.4% of the patients with prior intestinal resection surgery were in group C (current anti-TNF less than 1 year). At the latest follow-up, 942 patients (90.4%) had a surgical intervention over the course of the disease. 70.3% of the patients in need of intestinal resection surgery were in group C, in which 52 out of 74 patients (70.2%) had underwent this procedure until the latest follow-up compared to approximately only a third of the patients in the other groups (Table 3).

Treatment Effect of IS and Anti-TNF

For the analyses of the treatment effect of IS and anti-TNF, the group naïve to both therapies was the reference group (group A). At enrollment, 325 (87.4%) of patients in group B (containing 372 patients of a total of 1042 patients, i.e., 35.7%) were under current or past treatment with azathioprine, 0 (0%) were under cyclosporine, 52 (14.0%) were under 6-mercaptopurine, 0 (0%) were under tacrolimus, and 36 (9.7%) were under methotrexate, respectively. In group E (containing 176 patients, i.e., 16.9%), at enrollment, 120 (68.2%) of patients have had been under infliximab, 32 (18.2%) under adalimumab, and 17 (9.7%) under certolizumab, respectively. In groups B and E, the mean duration of IS therapy was 3.8 and 4.4 years, respectively. Table 4 shows the mean clinical activity (CDAI) at enrollment and at the latest follow-up.

The hazard ratio for migrating from stage B1 to pB3 and from B2 to pB3 was significantly lower in patients older than 40 years at diagnosis (HR 0.27, 0.08–0.91 and HR 0.12, 0.01–0.94, respectively). The hazard ratio for migrating from

Table 1 Demographic characteristics of patients included for analysis of B-stage migration

	Number of patients
Number of patients	1042
Gender	
Male	468 (44.9%)
Female	574 (55.1%)
Age at diagnosis (year) (median, IQR, range)	27, 20–37, 1–81
Age at enrollment (year) (median, IQR, range)	38, 27–51, 16–88
Age at the latest follow-up (year) (median, IQR, range)	43, 33–57, 18–94
Disease duration at enrollment (year) (median, IQR, range)	6, 2–13, 0–49
Disease duration at the latest follow-up (year) (median, IQR, range)	12, 8–21, 1–52
IBD family history	
None	821 (78.8%)
Yes	140 (13.4%)
Unknown	81 (7.8%)
Smoking status at diagnosis	
Non-smoker	524 (50.3%)
Smoker	483 (46.4%)
Unknown	35 (3.4%)
Smoking status at enrollment	
Non-smoker	665 (63.8%)
Smoker	354 (34.0%)
Unknown	23 (2.2%)
Smoking status at the latest follow-up	
Non-smoker	712 (68.3%)
Smoker	328 (31.5%)
Unknown	2 (0.2%)
Disease stage at enrollment	
B1	743 (76.1%)
B2	249 (23.9%)
pB3	0 (0.0%)
Disease stage at the latest follow-up	
B1	595 (57.1%)
B2	380 (36.5%)
pB3	67 (6.4%)
Therapy history at enrollment	
5-ASA	564 (54.1%)
Steroids	847 (81.3%)
IS	786 (75.4%)
Anti-TNF	397 (38.1%)
Therapy history at the latest follow-up	
5-ASA	628 (60.3%)
Steroids	912 (87.5%)
IS	865 (83.0%)
Anti-TNF	622 (59.7%)
Surgical history at enrollment	
Intestinal resection	291 (27.9%)
Fistula/abscess surgery	62 (6.0%)
Any surgery	322 (30.9%)
Surgical history at the latest follow-up	
Intestinal resection	380 (36.5%)
Fistula/abscess surgery	125 (12.0%)
Any surgery	437 (41.9%)

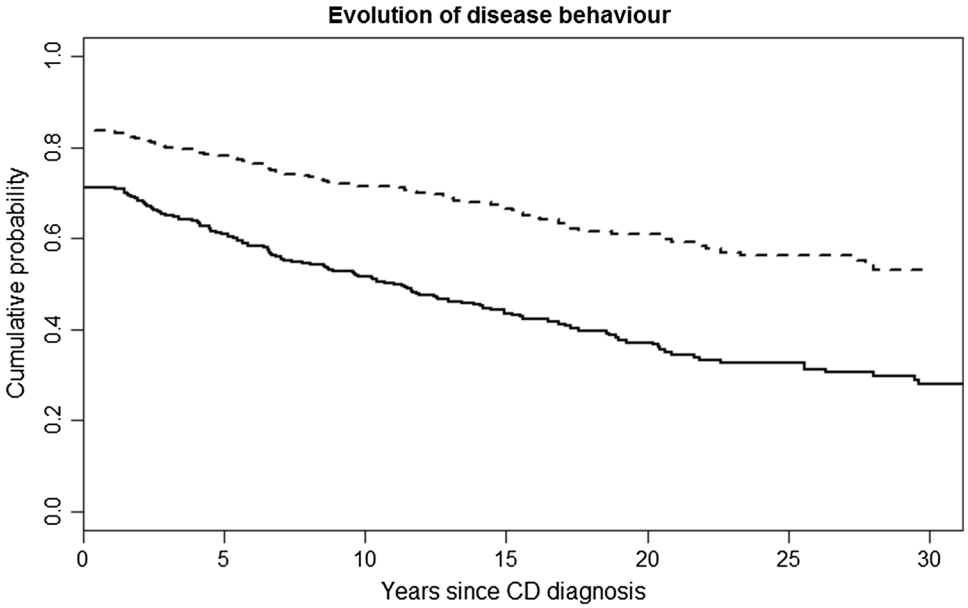

Fig. 3 Probability of remaining free of penetrating complications (upper dashed curve) and remaining free of stricturing and/or penetrating complications (lower solid curve) since the date of diagnosis in a Kaplan–Meier graph

Table 2 Transition probabilities and 95% confidence intervals for a given time interval

Transition probability	After 1 year	After 5 years	After 10 years	After 15 years
B1-to-B1	0.95 (0.84–0.96)	0.78 (0.75–0.81)	0.61 (0.57–0.66)	0.48 (0.42–0.53)
B1-to-B2	0.03 (0.03–0.04)	0.15 (0.12–0.17)	0.25 (0.21–0.29)	0.32 (0.27–0.37)
B1-to-pB3	0.01 (0.01–0.02)	0.07 (0.06–0.09)	0.14 (0.11–0.17)	0.20 (0.16–0.24)
B2-to-B2	0.98 (0.98–0.99)	0.92 (0.89–0.95)	0.85 (0.80–0.90)	0.79 (0.71–0.85)
B2-to-pB3	0.02 (0.01–0.02)	0.08 (0.08–0.11)	0.15 (0.10–0.20)	0.21 (0.15–0.29)

stage B1 to B2 was higher in patients that previously had treatment with an anti-TNF in the past but not currently (HR 2.07, 1.09–3.94). We found IS to be associated with a decreased likelihood of B1-to-pB3 progression (HR 0.38, 0.16–0.89). Furthermore, B1 patients undergoing the current treatment with anti-TNF for more than 1 year had a lower risk of migrating to pB3 (HR 0.30, 0.09–0.93) compared to IS-naïve and anti-TNF-naïve patients. However, such a decrease in risk was not seen for B1-to-B2 migration (HR 0.96, 0.54–1.67).

Covariates

Multiple covariates were considered in our analysis and are presented in Table 5. The probability of B-stage migration was not influenced by gender, IBD family history, or smoking status at diagnosis.

Discussion

Our study is the first of this kind demonstrating the prevalence and evolution of disease in Switzerland's CD patients registered in the SIBDCS. This study provides a comprehensive analysis of the evolution of CD behavior over a long observation period in the area of anti-TNF medication. Our data indicate that most patients with CD will eventually develop complications such as strictures or penetrating lesions. In this respect, we identified a comparable pattern of evolution of disease compared to preexisting data, such as by Cosnes et al. [7, 29] and Camus et al. [30]. Cosnes et al. [7] aimed to assess the long-term evolution of disease and to determine potential predictive factors in 2002 patients with CD studied retrospectively. In this study, 60% of patients initially in a B1 stage developed stricturing complications, equal to change their B-stage from B1 to B2, or penetrating complications, equal to a change from B1 to B3. However, in this investigation, Vienna classification of Crohn's disease instead of the Montreal classification was used. Treatment included aminosalicylate, azathioprine, methotrexate, systemic glucocorticoids, budesonide, enteral or parenteral nutrition (before 1999) and infliximab (after 1999). In 2012, the same investigators then aimed to assess predictable factors associated with a mild-to-moderate, long-term CD course and the evolution of disease in 600 patients. In mild-to-moderate CD, a change of B-stage was observed in 12% from B1 to B2, 12% from B1 to B3, and 7% from B2 to B3, respectively, over an observational time of 15 years, whereas

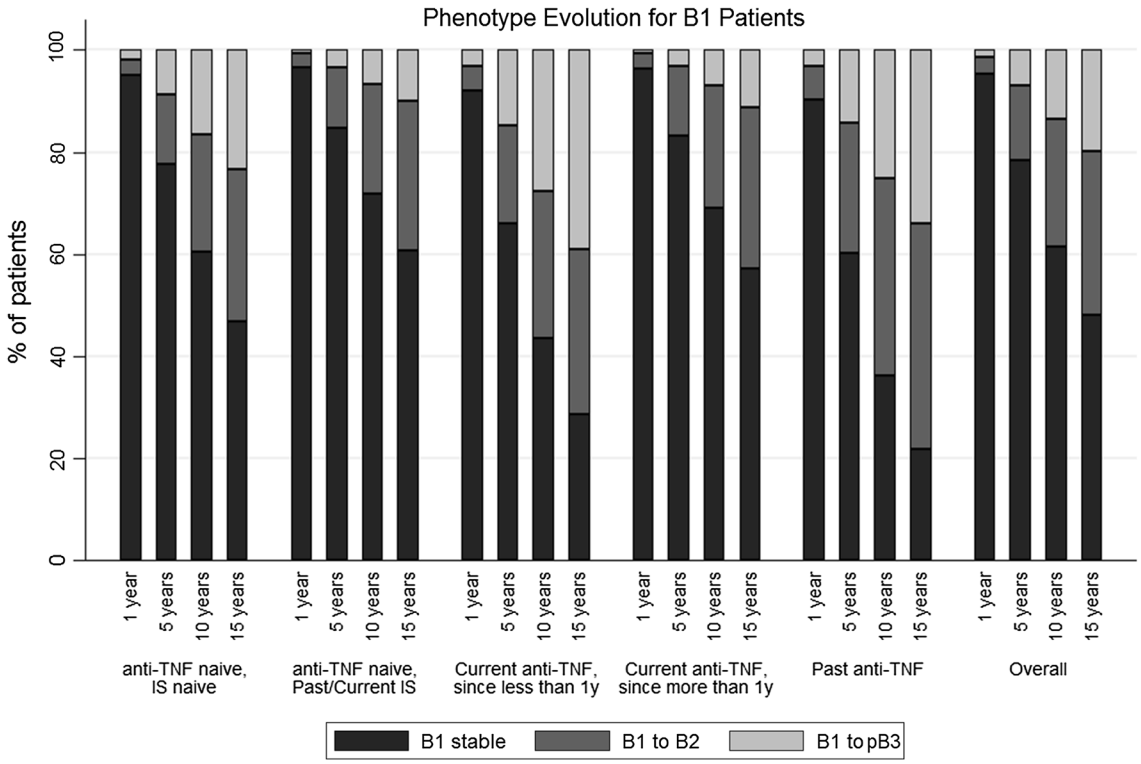

Fig. 4 Bar graph of the evolution of disease regarding B-stage migration over time in our five therapy groups

Table 3 Surgical history at enrollment and at the latest follow-up concerning groups A to E

	Overall	Group A (143 (13.7%) patients)	Group B (372 (35.7%) patients)	Group C (74 (7.1%) patients)	Group D (277 (26.6%) patients)	Group E (176 (16.9%) patients)
Surgical history at enrollment						
Intestinal resection	291 (27.9%)	44 (30.8%)	113 (30.4%)	38 (51.4%)	52 (18.8%)	44 (25.0%)
Fistula/abscess surgery	62 (6.0%)	8 (5.6%)	14 (3.8%)	10 (13.5%)	18 (6.5%)	12 (6.8%)
Any surgery	322 (30.9%)	48 (33.6%)	120 (32.3%)	41 (55.4%)	64 (23.1%)	49 (27.8%)
Surgical history at the latest follow-up						
Intestinal resection	380 (36.5%)	50 (35.0%)	132 (35.5%)	52 (70.3%)	82 (29.6%)	64 (36.4%)
Fistula/abscess surgery	125 (12.0%)	11 (7.7%)	30 (8.1%)	16 (21.6%)	40 (14.4%)	28 (15.9%)
Any surgery	437 (41.9%)	54 (37.8%)	143 (38.4%)	56 (75.7%)	107 (38.6%)	77 (43.8%)

Table 4 Mean CDAI in groups B and E at enrollment and at the latest follow-up

	Mean CDAI at enrollment	Mean CDAI at the latest follow-up
Group B (372 patients)	44.7 (SD = 45.3)	27.7 (SD = 34.8)
Group E (176 patients)	71.5 (SD = 72.9)	45.7 (SD = 52.6)

in severe CD, B-stage migration occurred in 18% from B1 to B2, 25% from B1 to B3, and 11% from B2 to B3, respectively [31]. With regard to azathioprine, patients exposed to the drug were shown to require less often intestinal surgery (adjusted hazard ratio 0.69) or perianal surgery (adjusted hazard ratio 0.36) [30]. Furthermore, a recent French study [14] showed a similar pattern of evolution of disease in a comparison study of pediatric-onset versus elderly-onset patients leading the investigators to conclude that early-onset cases have a higher risk of migration into a more severe B-stage over time. However, these latter investigations from

Table 5 Effects of different covariates on transition probabilities (hazard ratios)

Covariate	HR for B1-to-B2 transition	HR for B1-to-pB3 transition	HR for B2-to-pB3 transition	Global likelihood ratio test *p* value
Disease duration before enrollment (duration < 2 years is ref)				
2–5 years	2.13 (1.21–3.73)	0.99 (0.98–2.55)	1.53 (0.46–5.08)	0.418
5–10 years	1.64 (0.94–2.84)	1.23 (0.55–2.75)	0.84 (0.21–3.35)	
10+ years	1.55 (0.91–2.63)	1.29 (0.61–2.71)	1.03 (0.34–3.16)	
Age at diagnosis (year) (age < 17 years is ref)				
17–40	0.90 (0.51–1.60)	0.95 (0.30–1.38)	0.60 (0.25–1.42)	0.048
40+	0.77 (0.38–1.54)	0.27 (0.08–0.91)	0.12 (0.01–0.94)	
Female gender (male is ref)	0.77 (0.53–1.12)	0.78 (0.44–1.39)	1.01 (0.49–2.10)	0.448
Anti-TNF treatment (anti-TNF-naïve and IS-naïve is ref)				
Anti-TNF-naïve and past or current IS	0.83 (0.49–1.39)	0.38 (0.16–0.89)	0.48 (0.13–1.74)	< 0.001
Current anti-TNF since less than 1 year	1.61 (0.90–2.89)	1.57 (0.73–3.38)	2.62 (0.91–7.55)	
Current anti-TNF since more than 1 year	0.96 (0.54–1.68)	0.30 (0.09–0.93)	1.30 (0.44–3.85)	
No current anti-TNF but past anti-TNF	2.07 (1.09–3.94)	1.78 (0.72–4.39)	1.34 (0.33–5.54)	
IBD family history (no occur is ref)	0.964 (0.57–1.64)	0.625 (0.23–1.68)	1.261 (0.44–3.62)	0.761
Smoking status (non-smokers is ref)				
Current smoker	1.17 (0.78–1.76)	0.99 (0.53–1.82)	0.80 (0.36–1.78)	0.067
Past smoker	1.41 (0.76–2.64)	NA	NA	

the pre-anti-TNF era could not take a potentially modifying effect of biologics into account.

In our long-term observation within the anti-TNF age, we found that patients with an initial purely inflammatory phenotype (B1) are less likely to develop stricturing and especially penetrating complications over time when treated with IS or anti-TNF for more than 1 year. Regarding anti-TNF administration, this beneficial effect was neither seen in patients with a less-than-one-year treatment duration nor in those who discontinued anti-TNF treatment. Similar to our findings in adults, a recent pediatric study demonstrated a decreased likelihood (HR 0.3) of developing penetrating complications (defined as Montreal classification stage B3) when receiving early anti-TNF therapy with infliximab or adalimumab in children [32], indicating that the potential benefit of early anti-TNF might be unrelated to age.

CD patients receiving IS (and not anti-TNF) may represent a collective with mild-to-moderate disease severity. Nevertheless, these patients are much more likely to experience a more severe course of disease than CD patients without IS or anti-TNF treatment. In this respect, Targownik et al. [33] could show that 65% of patients will either be in need of resective surgery or the start of anti-TNF within 5 years of initiation of IS therapy, due to ineffectiveness. Therefore, our results regarding reduced risk of B-stage migration in patients receiving IS are noteworthy. Two recent trials demonstrate only very limited benefits of thiopurine treatment regarding disease control early after CD diagnosis and give rise to doubts on the benefits of thiopurines in CD in general [34, 35]. While the role of IS in delaying the disease progression remains unclear, our findings suggest that IS in early stages of the disease (i.e., stage B1) may delay the transition to a more severe state, especially for the transition to the penetrating pB3 stage. Thus, patients with CD in the inflammatory stage B1 may benefit from an immunosuppressive treatment. While the risk reduction appears to be similar to the one achieved by sustained anti-TNF treatment (HR between 0.3 and 0.4 for B1-to-B3 migration in our multivariate analysis), the patient collective across these two groups is not the same.

Our study has several limitations. In early years of data collection, only a limited number of cases were available and the number of patients with a follow-up time of more than 10 years is therefore limited. Also, nowadays the well-established agents such as ustekinumab and vedolizumab were approved in Switzerland in 2010 and 2015, respectively, and therefore did not match the criteria for our long-term follow-up. We therefore focused solely on the anti-TNF available in Switzerland for the whole observational period of time. Furthermore, the non-randomized prospective observational design of our cohort is invariably linked to a remaining risk of bias. Due to the non-interventional,

non-randomized design of our real-life cohort study, patients with more severe disease were more likely to be treated with anti-TNF, potentially leading to an underestimation of the overall net benefit of treatment. Above all, patients under the current anti-TNF treatment are collective with a higher risk of disease-related complications than those under IS treatment, and according to our clinical experience, a fraction of patients with imminent or present but clinically unrecognized complications may be initiated on anti-TNF. On the other hand, a potential beneficial effect of anti-TNF administration on B-stage migration would not be plausibly expected to occur within weeks to a few months after induction. Therefore, we decided to separately analyze patients with a short interval between induction and B-stage migration. Our analysis could not investigate whether a combination of anti-TNF and IS would have a beneficial effect on the risk of B-stage migration, taking into account the infrequent and—if at all in B1 stage prescribed—temporally limited administration within the SIBDCS (6 in most, not more than 12 months in the vast majority of instances as mentioned in the methods section), and that a protective effect of pharmacotherapy on the long-term risk of B-stage migration presumably necessitates a prolonged duration.

Even though selection bias remains a concern in our study, investigating the question whether anti-TNF has the potential to modify the evolution of CD in a prospective, double-blind, and randomized trial over an observational period of several years is virtually impossible. Accordingly, we feel that our study with prospective, highly standardized, long-term, and real-life data represents an important piece of information regarding the potentials and limitations of currently available standard medical treatment options in CD. These results may also contribute to a more pro-active therapeutic concept in the treatment of early CD patients with a limited current extension of disease or limited clinical disease activity but adverse prognostic feature in concert with other recent evidence, indicating decreasing surgery rates in the last decades, but at the same time pointing to continuously high overall 10-year surgery rates in CD of close to 50% [36].

In conclusion, we demonstrate a high likelihood of B-stage progression in CD patients over a long follow-up period, similar to that observed in previous seminal investigations on this issue. Both treatment with IS and with anti-TNF longer than 1 year appear to reduce the risk of B1-to-pB3-stage migration and hence overall disease progression in CD.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ekbom A, Helmick CG, Zack M, Holmberg L, Adami HO. Survival and causes of death in patients with inflammatory bowel disease: a population-based study. *Gastroenterology*. 1992;103:954–960.
2. Hovde O, Kempski-Monstad I, Smastuen MC, et al. Mortality and causes of death in Crohn's disease: results from 20 years of follow-up in the IBSEN study. *Gut*. 2014;63:771–775.
3. Jess T, Winther KV, Munkholm P, Langholz E, Binder V. Mortality and causes of death in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. *Gastroenterology*. 2002;122:1808–1814.

4. Floyd DN, Langham S, Séverac HC, Levesque BG. The economic and quality-of-life burden of Crohn's disease in Europe and the United States, 2000 to 2013: a systematic review. *Dig Dis Sci*. 2015;60:299–312. https://doi.org/10.1007/s10620-014-3368-z.
5. Sachar D, Andrews H, Farmer R, et al. Proposed classification of patient subgroups in Crohn's disease. *Gastroenterol Int*. 1992;5:141–154.
6. Van Assche G, Dignass A, Panes J, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *J Crohns Colitis*. 2010;4:7–27.
7. 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.
8. Louis E, Collard A, Oger AF, Degroote E, Aboul NasrElYafi FA, Belaiche J. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut*. 2001;49:777–782.
9. Polito JM 2nd, Childs B, Mellits ED, Tokayer AZ, Harris ML, Bayless TM. Crohn's disease: influence of age at diagnosis on site and clinical type of disease. *Gastroenterology*. 1996;111:580–586.
10. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology*. 2006;130:650–656.
11. Biedermann L, Fournier N, Misselwitz B, et al. High rates of smoking especially in female Crohn's disease patients and low use of supportive measures to achieve smoking cessation-data from the Swiss IBD Cohort Study. *J Crohns Colitis*. 2015;9:819–829.
12. Lang BM, Biedermann L, van Haaften WT, et al. Genetic polymorphisms associated with smoking behaviour predict the risk of surgery in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2018;47:55–66.
13. Annese V, Duricova D, Gower-Rousseau C, Jess T, Langholz E. Impact of new treatments on hospitalisation, surgery, infection, and mortality in IBD: a focus paper by the Epidemiology Committee of ECCO. *J Crohns Colitis*. 2016;10:216–225.
14. Gower-Rousseau C, Vasseur F, Fumery M, et al. Epidemiology of inflammatory bowel diseases: new insights from a French population-based registry (EPIMAD). *Dig Liver Dis*. 2013;45:89–94.
15. Gower-Rousseau C, Savoye G, Colombel JF, Peyrin-Biroulet L. Are we improving disease outcomes in IBD? A view from the epidemiology side. *Gut*. 2014;63:1529–1530.
16. Nguyen GC, Nugent Z, Shaw S, Bernstein CN. Outcomes of patients with Crohn's disease improved from 1988 to 2008 and were associated with increased specialist care. *Gastroenterology*. 2011;141:90–97.
17. Magro F, Rodrigues-Pinto E, Coelho R, et al. Is it possible to change phenotype progression in Crohn's disease in the era of immunomodulators? Predictive factors of phenotype progression. *Am J Gastroenterol*. 2014;109:1026–1036.
18. Jeuring SF, van den Heuvel TR, Liu LY, et al. Improvements in the long-term outcome of Crohn's Disease over the past two decades and the relation to changes in medical management: results from the population-based IBDSL Cohort. *Am J Gastroenterol*. 2017;112:325–336.
19. Magro F, Portela F. Management of inflammatory bowel disease with infliximab and other anti-tumor necrosis factor alpha therapies. *BioDrugs*. 2010;24:3–14.
20. Ferges W, Rampertab SD, Shafqet M, et al. Experience with anti-TNF-α biologic agents in succession in patients with Crohn's disease: a retrospective analysis of a single center. *J Clin Gastroenterol*. 2016;50:326–330.
21. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology*. 2008;135:1493–1499.
22. Jeuring S, Van den Heuvel T, Zeegers M, et al. 79 Disease behavior in Crohn's disease patients diagnosed in the biological era: a Dutch population-based IBD-SL Cohort Study. *Gastroenterology*. 2015;148:S-22.
23. Pittet V, Juillerat P, Mottet C, et al. Cohort profile: the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). *Int J Epidemiol*. 2009;38:922–931.
24. Herzog D, Fournier N, Buehr P, et al. Prevalence of intestinal complications in inflammatory bowel disease: a comparison between paediatric-onset and adult-onset patients. *Eur J Gastroenterol Hepatol*. 2017;29:926–931.
25. Manser CN, Frei P, Grandinetti T, et al. Risk factors for repetitive ileocolic resection in patients with Crohn's disease: results of an observational cohort study. *Inflamm Bowel Dis*. 2014;20:1548–1554.
26. Safroneeva E, Vavricka SR, Fournier N, et al. Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. *Aliment Pharmacol Ther*. 2015;42:977–989.
27. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol*. 2011;106:110–119.
28. Jackson C. Multi-state models for panel data: the MSM package for R. *J Stat Softw*. 2011;2011:28.
29. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*. 2011;140:1785–1794.
30. Camus M, Seksik P, Bourrier A, et al. Long-term outcome of patients with Crohn's disease who respond to azathioprine. *Clin Gastroenterol Hepatol*. 2013;11:389–394.
31. Cosnes J, Bourrier A, Nion-Larmurier I, Sokol H, Beaugerie L, Seksik P. Factors affecting outcomes in Crohn's disease over 15 years. *Gut*. 2012;61:1140–1145.
32. Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. *Lancet*. 2017;389:1710–1718.
33. Targownik LE, Leung S, Lix LM, Singh H, Bernstein CN. Persistence with immunomodulator monotherapy use and incidence of therapeutic ineffectiveness among users of immunomodulator monotherapy in IBD. *Am J Gastroenterol*. 2018;113:1206–1216.
34. Cosnes J, Bourrier A, Laharie D, et al. Early administration of azathioprine vs conventional management of Crohn's Disease: a randomized controlled trial. *Gastroenterology*. 2013;145:758–765.
35. Panés J, López-Sanromán A, Bermejo F, et al. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. *Gastroenterology*. 2013;145:e761.
36. Frolkis AD, Dykeman J, Negrón ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology*. 2013;145:996–1006.