

Changing Infliximab Prescription Patterns in Inflammatory Bowel Disease: A Population-Based Cohort Study, 1999–2014

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Background: Long-term data on real life use of infliximab (IFX) for inflammatory bowel disease (IBD) are lacking. We studied prescription patterns during the first 16 years following marketing authorization.

Methods: In a population-based cohort from the North Denmark Region, all IBD patients exposed to IFX during 1999 to 2014 were identified.

Results: A total of 623 patients (210 with ulcerative colitis [UC] and 413 with Crohn's disease [CD]) were exposed to IFX. In patients with UC, age at first exposure decreased by 10 months per calendar year ($P < 0.05$) during the study period. In patients with CD, disease duration at time of first IFX exposure decreased by 7 months per calendar year ($P < 0.001$). From 2005–2009 to 2010–2014, the proportion of IFX-exposed patients with pancolitis (40% vs 24%, $P = 0.04$) and the proportion of patients with extensive CD ($P = 0.002$) decreased. The mean time to discontinuation of IFX remained stable in patients with CD during the study period (2.5–3.0 years) and increased from 0.34 years (2005–2009) to 1.11 years (2010–2015) in patients with UC ($P = 0.04$).

Conclusion: During the first 16 years postmarketing, age at first exposure to IFX decreased in patients with UC, whereas disease duration at time of first exposure decreased in patients with CD. Also, a significant change toward less extensive disease in both UC and CD patients exposed to IFX was observed. Treatment duration in patients with UC increased during the study period, but did not reach the more constant and longer duration of treatment observed in patients with CD.

Key Words: indications, inflammatory bowel disease, infliximab, prescription patterns

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases (IBDs) mainly affecting the gastrointestinal tract. Patients are often diagnosed in young adulthood, and treatment has conventionally included topical and oral 5-aminosalicylates and corticosteroids, surgery, and, in more recent decades, also thiopurines and other immunosuppressants. Immunotherapy with biological agents was introduced by the end of the last millennium and has been used increasingly for treatment of IBD since then.^{1–6}

As the first biological agent, infliximab (IFX) was approved in 1998 for treatment of CD and in 2005 for UC. Knowledge of the use of IFX for IBD primarily comes from clinical trials. Few studies are based on observational data, and their main focus is safety of IFX.^{7–21} These studies have demonstrated that IFX is effective and safe. Additional studies have indicated that IFX may improve prognosis of the disease with decreasing surgery rates.²²

Few studies describe the patient population exposed to IFX in real life. Two studies suggest that IBD patients starting IFX therapy are younger than patients treated with conventional therapy,^{23, 24} but this may have changed with the gradually increasing use of IFX since its introduction to the market. The increasing use of IFX may also reflect treatment of a broader spectrum of patients with less extensive disease or treatment of the individual patient for a longer period of time.

We aimed to elucidate these hypotheses by assessing real-life use of IFX in a population-based IBD cohort followed from 1999 to 2014 in order to describe changes in prescription patterns with a focus on temporal changes in patient characteristics, treatment indications, and treatment duration.

MATERIALS AND METHODS

Study Population

We conducted a population-based cohort study of all IBD patients treated with IFX between 1999 and 2014 in the North

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Denmark Region (583,000 inhabitants). Patients were identified through GASTROBIO, a web-based registry of IBD patients established both for research purposes and to optimize clinical management.²⁵ All patients with a diagnosis of UC or CD who had been treated with IFX as their first biologic agent during 1999–2014 were included. The initial dosing of IFX was 5 mg/kg at weeks 0, 2, and 6, and then every 8 weeks. Hereafter the interval could vary from 6 to 10 weeks and the dose from 5 mg/kg to occasionally 10 mg/kg. No patients were on intermittent IFX dosing.

IFX has been administered to CD patients since 1999 and to UC patients since 2005 at Aalborg University Hospital as the only place in the North Denmark Region to offer biological therapy. This hospital is a primary center for the population living around the city of Aalborg, but a secondary center for patients living farther away who would require referral for evaluation and commencement of IFX. The region has a tradition for collecting data on all IBD patients dating back to 1978²⁶ and has since the introduction of IFX recorded all patient characteristics and treatments in the GASTROBIO database.²⁵ GASTROBIO delivers data to the Danish National Registry for Biological Therapy in Inflammatory Bowel Disease (BIO-IBD). Entering data into BIO-IBD is mandatory in all departments in Denmark prescribing biological therapy.²⁷

Definitions

Indications

Indications for treatment were entered by the treating physician into GASTROBIO and covered the following categories: “acute severe UC,” “chronically active UC,” “luminal CD,” and “fistulizing CD.” We defined “acute severe UC” according to Danish national guidelines, which are in accordance with the ECCO guidelines.^{28, 29}

Disease extent

Disease extent was determined based on endoscopic and radiological findings. For UC patients, disease location was divided into 2 groups: leftsided and pancolitis. According to the Montreal classification, upper gastrointestinal disease was used as a modifier for the rest of the locations (ileal, ileocolonic, and colonic disease) for CD.³⁰

Statistical Analyses

We used mean and standard deviation for descriptive statistics of continuous variables and provided total numbers and percentages for the categorical variables.

For all statistical analyses, 2-sided tests were applied with corresponding *P* values, using a significance level of 5%.

To assess changes over time, linear regression was performed on age at exposure and disease duration by year of first IFX exposure, and results were presented as a slope with 95% confidence intervals (CIs). A *P* value for the test of 0 slope was also presented. To evaluate early user bias, we conducted

sensitivity analyses removing the years 1999–2003. This did not apply to UC patients in whom IFX was first used from year 2005, when clinicians were experienced in using the drug for CD. For the categorical variables “indications” and “disease extent,” we assessed temporal changes by comparing the 2 time periods 2005–2009 and 2010–2014 for UC and 1999–2009 and 2010–2014 for CD using the χ^2 test.

Likewise, time to discontinuation was analyzed using Kaplan-Meier curves, and the differences between the periods 2005–2009 and 2010–2014 for UC and 1999–2009 and 2010–2014 for CD were compared using the log rank test. In order to further qualify the time to discontinuation analyses, we performed Cox regression analysis. Results were expressed as hazard ratios (HRs) with 95% CIs.

Analyses were performed using Stata (Stata/IC 12.1 for Windows, www.stata.com).

ETHICAL CONSIDERATIONS

The study was approved by the Danish Board of Health (3-3013-720/1) and the Danish Data Protection Agency (2008-58-0028).

RESULTS

Patient Characteristics

From 1999 to 2014, 717 IBD patients received biological therapy. Of these, 94 patients (13.1%) were excluded: 8 (1.1%) due to a diagnosis of “IBD unclassified,” 2 (0.3%) did not have IBD, 37 (5.2%) were treated with a different biological agent as their first biological treatment, and 47 (6.6%) had started treatment at a hospital outside the region. This left 623 patients (210 with UC and 413 with CD) exposed to IFX as their first biological agent available for analyses. Ninety-five (15%) of these patients (33 UC and 62 CD) were referred from a different hospital in the region for biological treatment. Of these, 35 patients (5 UC and 30 CD) were referred during years 1999–2009, and 60 patients (28 UC and 32 CD) during the years 2010–2014. Baseline characteristics are shown in [Table 1](#). Age distribution at time of diagnosis is shown in [Fig. 1](#).

Patient Age and Disease Duration

Age at exposure

Overall, the mean age at first exposure to IFX was 37.0 years for UC patients and 34.5 years for CD patients. During years 2005–2014, the age at first IFX exposure decreased by approximately 10 months or 0.8 years per calendar year (95% CI, -1.58 to -0.03 ; $P < 0.05$) in patients with UC. In the overall period (1999–2014), age at first exposure to IFX in patients with CD did not change significantly (-0.12 years/calendar year; 95% CI, -0.49 to 0.26 ; $P = 0.53$). The sensitivity analysis for CD (2004–2014 only) was insignificant as well (-0.17 years/calendar year; 95% CI, -0.67 to 0.34 ; $P = 0.52$).

TABLE 1. Baseline Characteristics of a Population-Based Cohort of Patients With Inflammatory Bowel Disease Exposed to Infliximab (1999–2014)

	Ulcerative Colitis	Crohn's Disease	Total
Patients, No. (%)	210	413	623
Male	108 (51)	170 (41)	278 (45)
Female	102 (49)	243 (59)	345 (55)
Age at diagnosis, No. (%)	210	413	623
Mean (SD), y	30.5 (14.9)	28.1 (12.9)	28.9 (13.6)
Age at IFX, No. (%)	209	412	621
Mean (SD), y	37.0 (15.8)	34.5 (14.3)	35.4 (14.8)
BMI, No. (%)	150	315	465
Mean (SD), kg/m ²	25.9 (5.5)	24.3 (5.4)	24.8 (5.5)
Smoker, No. (%)	207	397	604
Yes	20 (9.7)	141 (35.5)	161 (26.7)
Previous	65 (31.4)	80 (20.2)	145 (24.0)
Never	104 (50.2)	160 (40.3)	264 (43.7)
Unknown	18 (8.7)	16 (4.0)	34 (5.6)
IBD family history, No. (%)	181	372	553
Yes	28 (15.5)	64 (17.2)	92 (16.6)
No	153 (84.5)	308 (82.8)	461 (83.4)
Indication for IFX, No. (%)	182	257	439
Severe acute UC	58 (31.9)		
Chronically active UC	124 (68.1)		
Fistulizing CD		58 (22.6)	
Luminal CD		199 (77.4)	

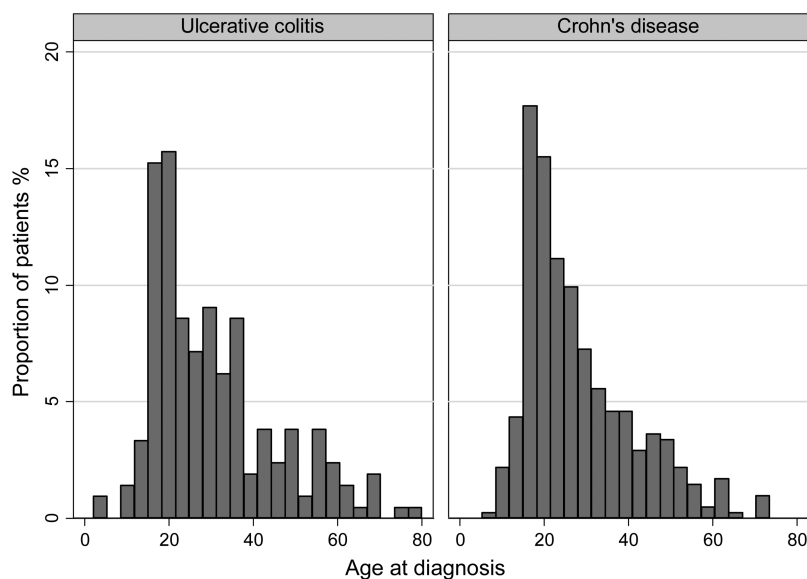


FIGURE 1. Age distribution at time of diagnosis in patients with inflammatory bowel disease later treated with infliximab.

Disease duration

Overall, the mean time from IBD diagnosis to first IFX exposure was 6.5 years in both UC and CD patients and 6.0 years in CD patients when analyzing years 2004–2014 only.

Time to first IFX exposure did not change during the study period among patients with UC (reduction of 0.26 years/calendar year; 95% CI, -0.78 to 0.26; *P* = 0.30), while in patients with CD, a decrease in time to first exposure of approximately

7 months or 0.6 years per calendar year (95% CI, -0.84% to -0.33% ; $P < 0.001$) was observed. This was also the case when studying years 2004–2014 only (a decrease of approximately 5 months or 0.41 years per calendar year; 95% CI, -0.72% to -0.01% ; $P < 0.03$).

Indications

The indication for starting treatment with IFX was known for 93% of UC patients. Of these, 32% had severe acute UC and 68% had chronically active UC. The indication was known for 62% of CD patients, with 23% having fistulizing disease and 77% having luminal disease. Although the absolute number of patients receiving IFX during the period increased, the distribution of indications did not change significantly from before 2010 to 2010–2014, when comparing proportions of severe acute and chronically active disease in UC (32% vs 68% in both periods, $P = 1.00$) and fistulizing and luminal disease in CD (21% and 79% before 2010 vs 24% and 76% in 2010–2014, $P = 0.66$).

Disease Extent

Data on disease extent were available for 149 (71%) of UC patients and 284 (67%) of CD patients. Disease extent at diagnosis in patients exposed to IFX in the first vs the second calendar period is shown in Fig. 2 for UC and in Fig. 3 for CD. The proportion of UC patients with pancolitis was higher in the group initiating IFX treatment between 2005 and 2009 (40%) than in patients initiating treatment between 2010 and 2014 (24%) ($P = 0.04$) (Fig. 3). In the latter period, patients were more likely to have left-sided colitis. In patients with CD, we observed an increase in the proportion of patients with isolated ileal disease exposed to IFX from the period 2005–2009 (4%) to the period 2010–2014 (13%), while the proportion of patients with more extensive disease decreased ($P = 0.006$) (Fig. 3).

Duration of Treatment

In patients with UC, the median interval from start of treatment with IFX to discontinuation increased significantly from 0.34 years in patients exposed to IFX during 2005–2009 to 1.11 years in patients starting treatment during 2010–2014, as reflected by an HR of 1.42 (95% CI, 1.02 to 1.98; $P = 0.04$) (Fig. 4).

In patients with CD, the median duration of IFX treatment was almost 3 years in both 2005–2009 (2.57 years) and 2010–2014 (2.96 years), and, accordingly, our regression analysis showed an HR of 0.93 (95% CI, 0.71 to 1.22; $P = 0.60$) (Fig. 5).

Causes for discontinuation are shown in Table 2. Remission was the cause for discontinuation in slightly more UC (41.8%) than CD (31.8%) patients ($P = 0.05$). This was also the case for poor response (35.3% in UC vs 23.4% in CD, $P = 0.01$). Adverse events were an almost equally common course in UC

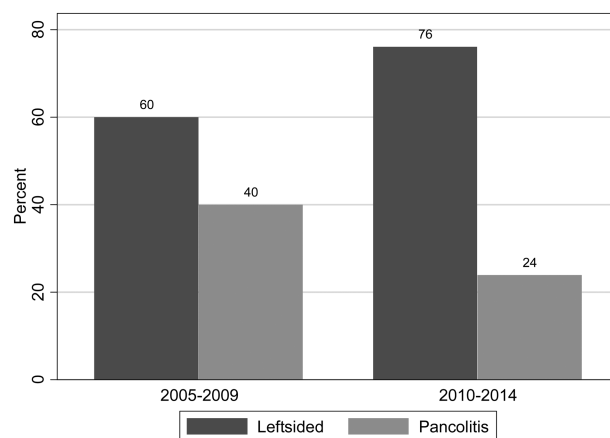


FIGURE 2. Disease extent at time of diagnosis of ulcerative colitis by period of first infliximab prescription (n = 147).

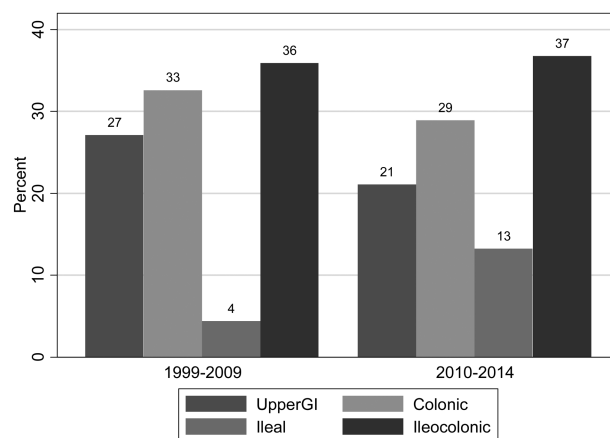


FIGURE 3. Disease extent at time of diagnosis of Crohn's disease by period of first infliximab prescription (n = 284).

patients (5.2%) and CD patients (11.3%, $P = 0.07$), whereas surgery was the cause in only 6.7% of CD patients vs 19.6% of UC patients ($P < 0.001$).

DISCUSSION

In the present population-based cohort study, we describe real-life use of IFX in a geographically well-defined IBD population observed from the beginning of the biological era and 16 years ahead. Our data revealed that IFX was introduced at an increasingly younger age in UC during the observation period and that the interval from diagnosis to IFX exposure became shorter in CD. Further, the proportion of patients treated for extensive disease decreased during the period in both CD and UC, whereas indications (acute vs chronic disease in UC and fistulizing vs luminal in CD) did not change over time. Of note, time to discontinuation of treatment remained stable in patients with CD during the study period, but it increased in patients with UC, without reaching the level observed in patients with CD, however.

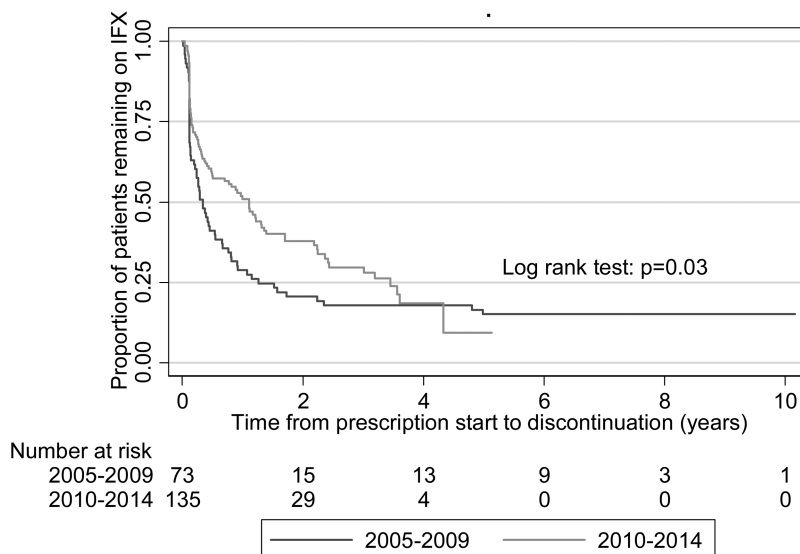


FIGURE 4. Time from first infliximab prescription to discontinuation in a population-based cohort of patients with ulcerative colitis (n = 208).

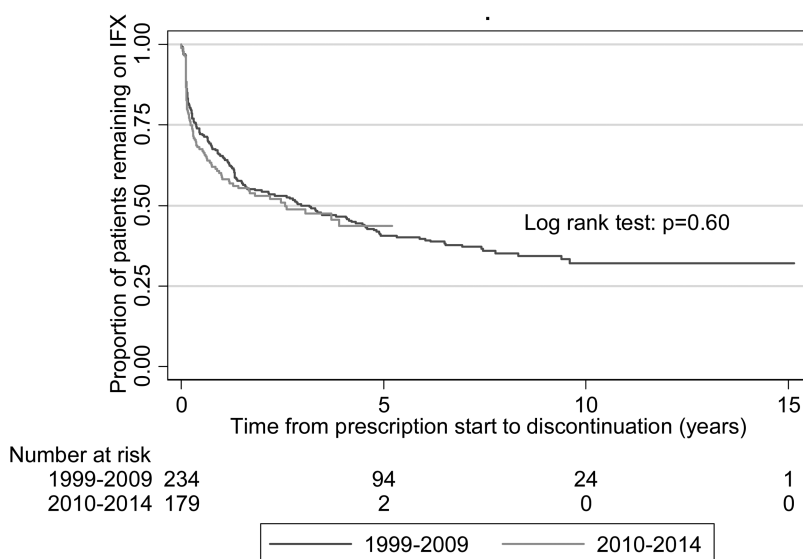


FIGURE 5. Time from first infliximab prescription to discontinuation in a population-based cohort of patients with Crohn's disease (n = 413).

The present study has several strengths. First, data were collected in 1 center with the same core of physicians throughout the period. Second, the population is geographically well defined and covers 583,000 citizens, which allows the study of the real-life use of the first available biological agent, IFX, in an unselected population during the first 16 years postmarketing. This is an incomparably long study period. Third, our study reflects the daily life of a large outpatient clinic offering biological therapy. Representing a real-life setting, which is less controlled than phase 3 drug testing, our population enables the study of the true and broad spectrum of patients with no selection related to age, previous surgery, or other common exclusion criteria.

The study also has potential limitations, which need to be considered. First, while Aalborg University Hospital is a primary center for the part of the population in the North Denmark Region centered on the city of Aalborg, it is also a secondary center for patients living farther away in the region. These patients have a different primary center that does not offer biological therapy, and therefore, there could be a delay in referring these patients to treatment. This could not be taken into account in the present study, but it hardly affects results, as there has been no change in the organization of health care during the study period. Second, there is no knowledge on how the missing data are distributed in this study. Initially, GASTROBIO did not register disease extent

TABLE 2. Causes for Discontinuation of Infliximab Treatment in a Population-Based Cohort of Patients With Inflammatory Bowel Disease (1999–2014)

	Ulcerative Colitis No. (%)	Crohn's Disease No. (%)	<i>P</i>	Total No. (%)
No. (%)	153 (100)	239 (100)		392 (100)
Remission	64 (41.8)	76 (31.8)	0.05	140 (35.7)
Poor response	54 (35.3)	56 (23.4)	0.01	110 (28.1)
Adverse events	8 (5.2)	27 (11.3)	0.07	25 (6.4)
Cancer	0 (0.0)	1 (0.4)	1.00	1 (0.3)
Change of hospital	1 (0.7)	4 (1.7)	0.65	5 (1.3)
Infection	1 (0.7)	0 (0.0)	0.39	1 (0.3)
Surgery	30 (19.6)	16 (6.7)	0.000	46 (11.7)
Clinical trial participation	0 (0.0)	2 (0.8)	0.52	2 (0.5)
Lost to follow-up	1 (0.7)	2 (0.8)	1.00	3 (0.8)
Deceased	0 (0.0)	4 (1.7)	0.16	4 (1.1)
Other	14 (9.2)	40 (16.7)	0.04	54 (13.8)
Unknown	4 (2.6)	11 (4.6)	0.42	15 (3.8)

P values reflect comparison of patients with ulcerative colitis and Crohn's disease by χ^2 test for each cause of discontinuation. The same patient can appear in more than 1 category due to competing causes of discontinuation.

at diagnosis if the index endoscopy was performed at a different hospital. Although we have tried to handle this through manual scrutiny of patient files, this explains the missing data on disease extent in a subpart of the cohort. Third, it may be seen as a limitation that disease extent subject to analysis in the present study corresponds to the extent at time of diagnosis rather than at time of exposure. Fourth, the number of hospitalizations during the study period was not recorded systematically, so any change in hospitalization pattern could not be assessed. Fifth, the categorization into remission or poor response was based on physicians ticking a box when deciding to discontinue treatment for the patient. Finally, in relation to investigative practice, we know that the use of magnetic resonance enterography (MRE) has increased during the study period, although the magnitude of such use was not measured. The increasing use of MRE is expected to result in increased identification of cases with mild disease, hence not explaining the increasing use of biological therapy during the study period.

We observed that age at first IFX exposure decreased in patients with UC during the study period, whereas this was not the case in CD. On the other hand, patients with CD were exposed to IFX after increasingly shorter disease duration during the study period, whereas a similar finding in UC did not reach statistical significance. As a possible accumulation of patients ready for IFX treatment in the beginning of the study period was not apparent, our observations seem to reflect a genuine change in prescription patterns during the period.

We observed no change in indications for treatment, in terms of acute severe vs chronically active UC and luminal vs

fistulizing CD during the study period, which is in line with the fact that there has been no change in recommendations for treatment of the subgroups of the diseases. However, patients tended to be treated for less extensive disease in the last part of the study period. This was the case in both UC and CD and appears to reflect a change in prescription patterns toward treatment with IFX at an earlier stage of disease in patients with less extensive disease.

Also, time to discontinuation changed over time, at least in patients with UC, with increasing treatment duration during the observation period. Desai et al.²⁴ showed that patients older than 60 years of age were more likely to discontinue therapy within the first year than younger patients. As our population of UC patients was increasingly younger at first exposure, they may have been less likely to discontinue therapy. However, the increasing time to discontinuation may also reflect a tendency in clinical practice toward 1-year continuation of IFX treatment in patients with UC rather than just induction therapy. Overall, we observed several reasons for discontinuation of IFX treatment, remission being the cause in 30%–40% of patients, hence resembling remission rates reported by Schnitzler et al. in 2009 from a single-center cohort study of 614 patients.⁸ It has been speculated that decreasing surgery rates in patients with UC during the same period relate to IFX treatment, but this remains uncertain.²²

In patients with CD, the mean treatment duration was more stable during the study period and longer than the mean time in patients with UC (around 3 years vs 1 year), which remains unexplained. In contrast to our finding of 50% of CD patients discontinuing treatment after 3 years, Pressman et al.²³

reported that 80% discontinued after 3 years. While Pressman and colleagues' study was conducted during the earlier part of our study period, we observed a stable time to discontinuation during the entire period. This may partly be due to a lower frequency of adverse events in our study as compared with several^{10, 15, 20} but not all previous studies.²¹ The lower frequency may be explained by better dose adjustment, a single and experienced center serving a whole region, or other yet unknown factors. Overall, the number of real-life long-term studies on use of biologics in IBD is limited, which minimizes the potential for comparison of the present findings with existing literature.

In conclusion, our unselected cohort study revealed a decrease in age of UC patients and a decrease in duration of CD at the time of first IFX exposure during the initial 16 years of observation postmarketing. Further, we observed a significant change toward less extensive disease in both CD and UC patients exposed to IFX and an increasing time to discontinuation in patients with UC in recent years. This indicates that prescription patterns have changed since IFX was introduced to the market. Better knowledge of and experience in using biological therapies, less hesitation in prescribing IFX to a broader range of patients, and reduction in costs of IFX may to some extent explain our findings. However, determining the causes of these changes requires further studies.

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