Predictors of drug survival: A cohort study comparing anti-tumour necrosis factor agents using the Swedish inflammatory bowel disease quality register

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Summary

Background: Whether long-term effectiveness differs between anti-tumour necrosis factor (anti-TNF) agents is unknown.

Aims: To examine drug survival of first-line anti-TNF agents and identify predictors of discontinuation. To reduce channelling bias, we also compared drug survival of the second anti-TNF.

Methods: Biologic-naive patients (N = 955) recorded in the Swedish IBD Quality Register (SWIBREG) were examined. We used propensity score matching, comparing drug survival over up to three years of follow-up. Cox regression estimated adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs).

Results: In Crohn’s disease, discontinuation because of lack/loss of response was 32% [95%CI = 26%-38%] for infliximab versus 16% [95%CI = 11%-21%] for adalimumab. Infliximab [vs adalimumab; aHR = 1.96; 95%CI = 1.20-3.21] and colonic disease (L2) [vs no L2; aHR = 2.17; 95% CI = 1.26-3.75] were associated with higher discontinuation rates, whereas normalised CRP at three months [aHR = 0.40; 95% CI = 0.19–0.81] with a lower rate. Consistently, patients who switched from adalimumab to infliximab (vs infliximab to adalimumab) had earlier discontinuation (P = 0.04). Concomitant use of immunomodulators was associated with a lower adverse drug reaction-mediated discontinuation rate [aHR = 0.46; 95% CI = 0.28-0.77], in part explained by fewer infusion reactions [aHR = 0.27; 95% CI = 0.08-0.89]. In ulcerative colitis, the probability of discontinuation because of lack/loss of response was 40% [95% CI = 33%-47%] for infliximab versus 37% [95% CI = 21%-53%] for adalimumab. Disease duration...
1 | INTRODUCTION

Anti-tumour necrosis factor (anti-TNF) agents have dramatically improved the management of inflammatory bowel disease (IBD), but data from randomised controlled trials and observational studies indicate that up to 50% of the patients do not respond, lose response over time or become intolerant within the first year of treatment. Whether long-term clinical effectiveness differs between various anti-TNF agents is unknown, since there are no randomised controlled trials comparing individual anti-TNF agents and real-world data are conflicting. Previous comparisons of first-line anti-TNF agents may have been influenced by channelling bias, that is drugs with similar therapeutic indications are used differently in patient groups with prognostic differences. Besides this, the generalisability of most previous observational studies may be questioned since most studies involved patients treated at tertiary referral centers.

In clinical practice, switching to a second anti-TNF agent is a common strategy when the first one has failed, the rationale being that individual anti-TNF agents differ in their molecular composition, immunological properties, and immunogenicity. The use of a second-line anti-TNF agent is supported by both clinical trial- and real-world data, even though decreased efficacy and real-world effectiveness are well described among second-line treated patients. Interestingly, data from other chronic inflammatory diseases indicate that the effectiveness of a second anti-TNF also varies according to the type of first anti-TNF agent and the reason for discontinuation of the first anti-TNF treatment. Few studies have determined the effectiveness of a second anti-TNF in IBD, according to the specific switching pattern between individual anti-TNF agents.

In fact, comparison of different anti-TNF agents is more reliable when stratifying the analyses by line of therapy and validating findings from first-line anti-TNF treatment among patients who received second-line treatment, since the initial channelling among those who received second-line treatment was to another anti-TNF agent. Even though this study design does not preclude bias, it can be used to reduce the effect of channelling bias, that is reducing the likelihood that groups of patients with prognostic differences were systematically allocated to treatment with different anti-TNF agents. Various measures have been used to define real-world outcomes in the long-term. Among these, drug survival reflects overall clinical effectiveness and tolerability. However, the effectiveness-tolerability ratio may differ between drugs, and predictors of effectiveness may not necessarily predict tolerance and vice versa.

Therefore, to assess clinical effectiveness and tolerability, we examined drug survival of anti-TNF treatment and identified predictors of treatment discontinuation, stratified by reason for termination of treatment, in a well-characterised cohort of biologic-naive patients recorded in the Swedish IBD quality register (SWIBREG). We hypothesised that the use of individual first-line anti-TNF agents may differ between groups of patients with prognostic differences, based on their characteristics at the when the drug is prescribed. To reduce potential channelling bias from drug-related effects, we also compared the drug survival of second anti-TNF agents, according to type of first anti-TNF agent, and by reason for termination of first anti-TNF treatment.

2 | MATERIALS AND METHODS

2.1 | Study population and clinical variables

Patients managed at six hospitals with well-characterised patient populations, including both in- and outpatients, who had started treatment with an anti-TNF agent as first-line biological treatment between April 2006 and April 2016 were included in this observational cohort study. Follow-up started at initiation of first anti-TNF treatment and ended with the termination of last anti-TNF treatment, death or April 2016, that is the end of the study period. Data on termination of treatment and switch to a second or third anti-TNF agent (including date of initiation and, if discontinued, date and reason for discontinuation) were collected. We recorded baseline data on sex, age at diagnosis, smoking habits, disease duration, year of initiation of anti-TNF treatment, type of anti-TNF agent, concomitant treatment with immunomodulators, CRP levels, disease characteristics including location (ileal, colonic or ileocolonic), behaviour (inflammatory, stricturing or penetrating), previous bowel surgery in Crohn’s disease and disease extent in ulcerative colitis (proctitis, left-sided colitis or extensive colitis). Patients who moved from treatment with a reference product to a biosimilar were not considered as switchers. Patients who stopped treatment for >3 months were considered to have discontinued their anti-TNF agent. Information on C-reactive protein (CRP) levels at baseline (if measured within one month before and one week after anti-TNF treatment initiation) and after three months [aHR = 0.25; 95% CI = 0.10-0.58] and normalised CRP after three months [aHR = 0.39; 95% CI = 0.18-0.84] were associated with lower discontinuation rates. Conclusions: Clinical characterisation of patients may aid decision-making on anti-TNF treatment. The consistently shorter drug survival for infliximab (vs adalimumab) in Crohn’s disease, suggests a potential difference between the two drugs.
The primary outcome was the probability of discontinuation of the first anti-TNF agent, stratified by reason for termination of treatment. To allow comparisons with existing literature, a three-year follow-up period from initiation of each line of anti-TNF therapy was applied. The reason for drug discontinuation was classified according to the criteria used in SWIBREG, that is lack/loss of response (primary non-response or loss of response), intolerance or other reasons for termination. As secondary outcomes, discontinuation because of lack/loss of response of the second anti-TNF agent, stratified by type of first anti-TNF agent and reason for termination of first anti-TNF treatment, as well as predictors of discontinuation of first anti-TNF agent, were examined.

The study was approved by the Stockholm Ethics Review Board (approval no. 2016/191-31/2).

2.3 | Statistics

Continuous variables with a skewed distribution are presented as median (interquartile range [IQR]). Life tables, survival plots and the cumulative probability of drug discontinuation were constructed by Kaplan–Meier analyses. Log-rank tests were performed to compare groups. To identify predictors of first anti-TNF treatment discontinuation, we performed univariate Cox proportional hazards regression models and multilevel survival regression models using Weibull distribution, with 1:n (n is an integer ≥1 and is not fixed) propensity score-matched patient blocks as random effects to evaluate potential predictors of discontinuation of first anti-TNF treatment. Propensity scores for infliximab as the first anti-TNF treatment were calculated using logistic regression models based on concomitant medication with immunomodulators, CRP levels, disease duration, and perianal disease at baseline for Crohn's disease, or based on concomitant immunomodulators, CRP levels, and disease duration at baseline for ulcerative colitis.

Potential clinical predictors of first-line drug discontinuation including sex, disease duration, year of starting first anti-TNF treatment, type of anti-TNF agent, concomitant treatment with immunomodulators, CRP levels, disease characteristics including location (ileal, colonic or ileocolonic), behaviour (inflammatory, strictureing or penetrating) and previous bowel surgery in Crohn's disease and extent of inflammation in ulcerative colitis (proctitis, left-sided colitis or extensive colitis), at baseline were entered into the models. We used discrete variables with nominal or ordinal data. In order to address whether normalisation of elevated CRP levels within three months from initiation of first anti-TNF was associated with the discontinuation rate, additional Cox regression analyses were performed. In these analyses, all events that occurred within 3 months from initiation were excluded, and the start of follow-up was delayed by 3 months in order to avoid bias. An elevated CRP level was defined as a level >3 mg/L. Discontinuation because of lack/loss of response and because of intolerance were analysed separately and stratified by diagnosis, that is Crohn's disease and ulcerative colitis. Patients with ulcerative colitis who had undergone colectomy before the start of anti-TNF were excluded (N = 14). The proportional hazards assumption was tested with the statistical significance of time-dependent covariates or visually for all analyses. Pearson correlation was used to avoid multicollinearity. Additionally, sensitivity analyses with adverse drug events restricted to infusion reactions were performed. Differences in cumulative survival of second-line anti-TNF were assessed by log-rank tests. The cumulative survival of second-line anti-TNF was analysed (a) depending on the switching pattern (ie infliximab to adalimumab, adalimumab to infliximab, etc) and (b) by reason for termination of first anti-TNF (ie lack/loss of response or intolerance). A P-value <0.05 or 95% confidence intervals not including 1.00 was considered statistically significant. The statistical analyses were executed in IBM SPSS Statistics for Windows, version 25.0 (IBM Corp.).

3 | RESULTS

3.1 | Crohn's disease population

In total, we identified 570 patients with Crohn's disease naïve to biologics, who started an anti-TNF agent during the study period (Table 1). First-line anti-TNF initiators were followed for a median of 18 (IQR: 7-36) months, corresponding to 952 person-years. Altogether, 351 (62%) patients discontinued their first anti-TNF agent, and 184 (52%) of these patients started a second anti-TNF (Figure 1A).

3.2 | Drug discontinuation of first anti-TNF agent

3.2.1 | Lack/loss of response

The cumulative probability of discontinuation of infliximab because of lack/loss of response, at three years after initiation of treatment, was 32% [95% CI = 26%-38%] and the corresponding figure for adalimumab was 16% [95% CI = 11%-21%; Figure 2A]. At baseline, use of infliximab [aHR = 1.96; 95% CI = 1.20-3.21] and colonic disease (L2) [aHR = 2.17; 95% CI = 1.26-3.75] were associated with higher discontinuation rates (Table 2). Initiation of first anti-TNF between April 2011 and April 2016 [aHR = 0.50; 95%CI = 0.31-0.81] and a normalised CRP at 3 months [aHR = 0.40; 95%CI = 0.19-0.81] were associated with lower discontinuation rates.

3.2.2 | Intolerance

The cumulative probability of discontinuation of infliximab because of intolerance, that is adverse drug reactions, was 20% [95% CI = 15%-25%] and the corresponding figure for adalimumab was 24% [95% CI = 18%-30%; Figure 2B]. The following adverse drug reactions were observed: infusion reactions, N = 18; dermatologic diseases/skin manifestations, N = 14; bacterial infections, N = 11; arthralgia/arthritis, N = 9; paraesthesia/neuropathy, N = 5; viral infection, N = 5; cancer, N = 4; hepatotoxicity, N = 3; other, N = 25. Female sex [aHR = 1.66; 95% CI = 1.03-2.68] and ileal disease (L1) [aHR = 2.05; 95% CI = 1.15-3.64] was tested with the statistical significance of time-dependent covariates or visually for all analyses. Pearson correlation was used to avoid multicollinearity. Additionally, sensitivity analyses with adverse drug events restricted to infusion reactions were performed. Differences in cumulative survival of second-line anti-TNF were assessed by log-rank tests. The cumulative survival of second-line anti-TNF was analysed (a) depending on the switching pattern (ie infliximab to adalimumab, adalimumab to infliximab, etc) and (b) by reason for termination of first anti-TNF (ie lack/loss of response or intolerance). A P-value <0.05 or 95% confidence intervals not including 1.00 was considered statistically significant. The statistical analyses were executed in IBM SPSS Statistics for Windows, version 25.0 (IBM Corp.).
TABLE 1  Demographic and clinical characteristics at baseline, that is initiation of first-line anti-TNF treatment, of 949 patients with IBD, stratified for subtype of IBD and anti-TNF treatment

| Parameter | Crohn’s disease | Ulcerative colitis |
|-----------|-----------------|-------------------|
|           | IFX TNF1, N = 328 | ADA TNF1, N = 240 | P-value | IFX TNF1, N = 324 | ADA TNF1, N = 57 | P-value |
| Sex | | | | | | |
| Male, N (%) | 173 (53) | 125 (52) | 0.88 | 187 (58) | 33 (58) | 0.98 |
| Age at diagnosis, N (%) | | | | | | |
| A1 ≤ 16 years | 86 (26) | 38 (16) | <0.01 | 49 (15) | 9 (16) | 0.90 |
| A2 17 - 40 years | 193 (59) | 166 (69) | 0.01 | 211 (65) | 35 (61) | 0.59 |
| A3 > 40 years | 49 (15) | 36 (15) | 0.98 | 64 (20) | 13 (23) | 0.60 |
| Disease duration until first anti-TNF, N (%) | | | | | | |
| <1 year | 84 (26) | 50 (21) | 0.19 | 92 (28) | 8 (14) | 0.02 |
| 1-9 years | 140 (43) | 76 (32) | 0.01 | 149 (46) | 30 (53) | 0.35 |
| ≥10 years | 104 (32) | 114 (48) | <0.01 | 83 (26) | 19 (33) | 0.23 |
| Year of initiation of first anti-TNF, N (%) | | | | | | |
| April 10, 2006- April 10, 2011 | 193 (59) | 128 (53) | 0.19 | 142 (44) | 28 (49) | 0.46 |
| April 11, 2011- April 10, 2016 | 135 (41) | 112 (47) | 0.19 | 182 (56) | 29 (51) | 0.46 |
| Crohn’s disease location, N (%) | | | | | | |
| L1 Ileal (± L4) | 56 (17) | 47 (20) | 0.44 | | | |
| L2 Colonic (± L4) | 104 (32) | 64 (27) | 0.20 | | | |
| L3 Ileocolonic (± L4) | 163 (50) | 125 (52) | 0.56 | | | |
| L4 Upper gastrointestinal tract | 4 (1) | 2 (1) | 0.32 | | | |
| Unknown location | 1 (0) | 2 (1) | 0.39 | | | |
| Crohn’s disease behaviour, N (%) | | | | | | |
| B1 Non-stricturing, non-penetrating | 203 (62) | 131 (55) | 0.08 | | | |
| B2 Stricturing | 91 (28) | 75 (31) | 0.37 | | | |
| B3 Penetrating | 31 (9) | 32 (13) | 0.15 | | | |
| Unknown behaviour | 3 (1) | 2 (1) | 0.92 | | | |
| Perianal disease | 102 (31) | 62 (26) | 0.18 | | | |
| Unknown perianal disease | 6 (2) | 5 (2) | 0.83 | | | |
| Ulcerative colitis extent at baseline, N (%) | | | | | | |
| E1 Proctitis | 19 (6) | 4 (7) | 0.75 | | | |
| E2 Left-sided colitis | 87 (27) | 17 (30) | 0.66 | | | |
| E3 Extensive colitis | 216 (67) | 36 (63) | 0.56 | | | |
| Unknown extent | 2 (1) | 0 (0) | 0.55 | | | |
| Concomitant Immunomodulators‡, N (%) | | | | | | |
| Yes | 171 (52) | 106 (44) | 0.05 | 149 (46) | 24 (42) | 0.57 |
| Unknown | 2 (1) | 0 (0) | 0.23 | 1 (0) | 0 (0) | 0.67 |
| CRP value, N (%) | | | | | | |
| <3 mg/L | 83 (25) | 72 (30) | 0.08 | 89 (27) | 16 (28) | 0.35 |
| >3 mg/L | 200 (61) | 122 (51) | 0.08 | 192 (59) | 25 (44) | 0.35 |
| Unknown | 45 (14) | 46 (19) | 0.08 | 43 (13) | 16 (28) | <0.01 |
| Previous IBD surgery, N (%) | | | | | | |
| Yes | 152 (46) | 122 (51) | 0.29 | 11 (3) | 3 (5) | 0.49 |
| Smoking habits, N (%) | | | | | | |
| Never smoker | 158 (48) | 118 (49) | 0.85 | 183 (56) | 38 (67) | 0.35 |
| Former smoker | 90 (27) | 70 (29) | 0.67 | 81 (25) | 13 (23) | 0.53 |

(Continues)
were associated with higher discontinuation rates, whereas concomitant use of immunomodulators at baseline [aHR = 0.46; 95% CI = 0.28-0.77] with a lower discontinuation rate (Table 3). The association with combination therapy seemed to in part be explained by fewer infusion reactions [aHR = 0.27, 95% CI = 0.08-0.89].

3.3 | Discontinuation of second anti-TNF as a function of the type of first anti-TNF

During the first three years after switching, 79/184 (43%) patients stopped their second anti-TNF treatment because of lack/loss of response (N = 37), intolerance (N = 30) and other reasons (N = 12). To separate potential channelling bias from drug-related effects, the discontinuation rates of the second anti-TNF agents were compared, taking the anti-TNF switching pattern into account. In total, four different switching groups were identified (Figure 1A). The cumulative probability of discontinuation of the second anti-TNF because of lack/loss of response was lower among patients who switched from infliximab to adalimumab (21% [95% CI = 13%-29%]), compared to those who switched from adalimumab to infliximab (40% [95% CI = 21%-59%]; P = 0.04; Figure 2C). The infliximab to certolizumab pegol/golimumab and adalimumab to certolizumab pegol/golimumab groups were too small to allow any comparisons.

3.4 | Discontinuation of second anti-TNF by reason for discontinuation of first anti-TNF

Among patients who switched to a second anti-TNF agent, 85/184 (46%) patients switched because of lack/loss of response of the first

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**TABLE 1** (Continued)

| Parameter | Crohn’s disease | Ulcerative colitis |
|-----------|-----------------|------------------|
| IFX TNF1, N = 328 | ADA TNF1, N = 240 | P-value | IFX TNF1, N = 324 | ADA TNF1, N = 57 | P-value |
| Active smoker | 54 (16) | 34 (14) | 0.44 | 23 (7) | 3 (5) | 0.53 |
| Unknown | 26 (8) | 18 (8) | 0.85 | 37 (11) | 3 (5) | 0.16 |

Abbreviation: IFX, infliximab; ADA, adalimumab; CRP, C-reactive protein.

*Information on patients (N = 6) treated with certolizumab pegol or golimumab is not included.

*Immunomodulators were defined as thiopurines or methotrexate.

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**FIGURE 1** Treatment patterns of first, second and third anti-TNF agent. (A) Treatment patterns among patients with Crohn’s disease. (B) Treatment patterns among patients with ulcerative colitis. Percent presented within treatment rows. IFX, infliximab; ADA, adalimumab; CZP/GLM, certolizumab pegol/golimumab; MOA, mechanism of action.
anti-TNF agent, 58 (32%) because of intolerance and 41 (22%) for other reasons (e.g., pregnancy and patient’s preference). The cumulative probability of discontinuation of the second anti-TNF treatment because of lack/loss of response was 30% [95% CI = 20%-40%] among patients who stopped the first anti-TNF because of lack/loss of response. The cumulative probability of discontinuation of the second anti-TNF treatment was 19% [95% CI = 7%-32%] among those who stopped the first anti-TNF because of adverse drug reactions (P = 0.22; Figure 2D).

3.5 | Ulcerative colitis population

In total, we identified 385 patients with ulcerative colitis naïve to biologics, who started an anti-TNF agent during the study period (Table 1). First-line anti-TNF initiators were followed for a median of 8 (IQR: 2-24) months, corresponding to 431 person-years. Altogether, 277 (72%) patients discontinued their first anti-TNF agent, 95 (34%) of these patients started a second anti-TNF (Figure 1B).

3.6 | Drug discontinuation of first anti-TNF agent

3.6.1 | Lack/loss of response

The cumulative probability of discontinuation of infliximab because of lack/loss of response within the first three years of treatment was 40% [95% CI = 33%-47%] and the corresponding figure for adalimumab was 37% [95% CI = 21%-53%; Figure 3A]. At baseline, disease duration ≥10 years [aHR = 0.25; 95% CI = 0.10-0.58] was associated with a lower discontinuation rate (Table 4). In addition, normalisation of CRP at three months [aHR = 0.39; 95% CI = 0.18-0.84] was associated with a lower discontinuation rate.
3.6.2 | Intolerance

The cumulative probability of drug discontinuation of infliximab because of intolerance, that is adverse drug reactions was 22% [95% CI = 15%-29%] and the corresponding figure for adalimumab was 23% [95% CI = 9%-37%; Figure 3B]. The following adverse drug reactions were observed: infusion reactions, N = 16; arthralgia arthritis, N = 7; dermatologic diseases/skin manifestations, N = 5; bacterial infections, N = 4; paraesthesia/neuropathy, N = 3; viral infections, N = 1 and other, N = 13. Disease duration <1 year was associated with discontinuation because of intolerance to the first anti-TNF [aHR = 2.42; 95% CI = 1.11-5.30] (Table 5).

3.7 | Discontinuation of second anti-TNF as a function of the type of first anti-TNF

During the first three years after switching to a second anti-TNF agent, 64/95 (67%) patients stopped their second anti-TNF treatment, 38 (59%) because of lack/loss of response, 14 (22%) adverse drug reactions and 12 (19%) for other reasons. In total, three different switching groups were identified (Figure 1B). The cumulative probability of discontinuation of the second anti-TNF because of lack/loss of response did not differ between patients who switched from infliximab to adalimumab (52% [95% CI = 37%-67%]) vs those who switched from adalimumab to infliximab (44% [95% CI = 12%-76%]; P = 0.49; Figure 3C). The infliximab to certolizumab pegol/golimumab group was too small to allow any comparisons.

3.8 | Drug discontinuation of second anti-TNF by reason for discontinuation of first anti-TNF

Among patients who switched to a second anti-TNF agent, 48/95 (51%) patients switched because of lack/loss of response of the first anti-TNF agent, 23 (24%) because of intolerance and 24 (25%) for other reasons (eg pregnancy and patient’s preference). The cumulative probability of discontinuation of the second anti-TNF treatment because of lack/loss of response was 56% [95% CI = 38%-74%] among patients who stopped the first anti-TNF because of lack/loss of response vs 46% [95% CI = 17%-75%] among those who stopped the first anti-TNF because of adverse drug reactions (P = 0.48; Figure 3D).

| TABLE 2 | Predictors at baseline of first-line discontinuation because of lack/loss of response to first anti-TNF, among patients with Crohn’s disease |

| Predictor | Univariate HR [95%CI] | P | Multivariable HR [95%CI] | P |
|-----------|------------------------|---|------------------------|---|
| Female    | 0.93 [0.63-1.37]       | 0.72 | 0.86 [0.54-1.35]       | 0.512 |
| Disease duration [years] | | | | |
| <1        | 1.22 [0.76-1.97]       | 0.41 | 1.30 [0.74-2.28]       | 0.359 |
| 2-9       | Reference              |      | Reference              |      |
| ≥10       | 0.86 [0.55-1.36]       | 0.53 | 0.83 [0.46-1.50]       | 0.542 |
| Year of anti-TNF initiation | | | | |
| April 2006- April 2011 | Reference              |      | Reference              |      |
| April 2011- April 2016 | 0.68 [0.45-1.03]       | 0.07 | 0.50 [0.31-0.81]       | 0.005 |
| Disease location | | | | |
| L1 Ileal [+ L4] | 0.97 [0.54-1.74]       | 0.92 | 0.69 [0.33-1.45]       | 0.327 |
| L2 Colonic [+ L4] | 1.83 [1.20-2.79]       | 0.01 | 2.17 [1.26-3.75]       | 0.005 |
| L3 Ileocolonic [+ L4] | Reference              |      | Reference              |      |
| Disease behaviour | | | | |
| B1 Non-stricturing/ non-penetrating | Reference | | Reference | |
| B2 Stricturing | 0.87 [0.56-1.36]       | 0.54 | 1.61 [0.85-3.05]       | 0.143 |
| B3 Penetrating | 0.76 [0.39-1.48]       | 0.42 | 0.95 [0.36-2.53]       | 0.914 |
| Concomitant immunomodulators | 0.95 [0.65-1.40]       | 0.79 | 0.74 [0.47-1.16]       | 0.191 |
| CRP >3 mg/L at baseline | 1.04 [0.66-1.62]       | 0.88 | 0.96 [0.60-1.55]       | 0.880 |
| Previous Crohn’s disease related surgeries | 0.83 [0.56-1.22]       | 0.34 | 0.85 [0.51-1.44]       | 0.555 |
| Infliximab as first anti-TNF | 1.92 [1.27-2.92]       | <0.01 | 1.96 [1.20-3.21]       | 0.007 |

Abbreviation: CRP, C-reactive protein. Multilevel survival model using Weibull distribution was used, with 1:n propensity score-matched blocks as random effects.
Based on real-world data obtained from the Swedish IBD quality register (SWIBREG), this study demonstrates that the use of infliximab as a first-line anti-TNF agent in patients with Crohn’s disease (as compared to adalimumab) may be predictive of higher drug discontinuation rate because of poor clinical effectiveness, that is lack/loss of response. Consistently, patients with Crohn’s disease who switched from adalimumab to infliximab had shorter drug survival because of the poor clinical effectiveness of the second anti-TNF agent compared to those who switched from infliximab to adalimumab. No significant differences were observed between infliximab and adalimumab in patients with ulcerative colitis. A normalisation of CRP at three months was associated with improved effectiveness in both Crohn’s disease and ulcerative colitis, and an association between concomitant use of an immunomodulator and a lower adverse drug reaction-mediated discontinuation rate, specifically infusion reactions, was observed in patients with Crohn’s disease.

The effectiveness of anti-TNF treatment has been described in numerous studies, but few studies have assessed outcomes by specific switching patterns outside the setting of tertiary-referral centers.6,17 Interestingly, the effectiveness of individual anti-TNF agents may differ at the level of the patient, and individuals who do not respond to a particular anti-TNF agent may benefit from another anti-TNF agent.6,17,18,24,25,30 No randomised controlled trial has compared the efficacy of different anti-TNF agents. In Crohn’s disease, we observed a higher drug discontinuation rate among infliximab-initiators compared with those who started first-line treatment with adalimumab. The higher drug discontinuation rate may be explained by immunogenicity, ascribed to the chimeric properties of infliximab,20,31 which beyond a lower adverse drug reaction-mediated discontinuation rate seems to translate into lower drug levels, and possibly remission rates.32 Because of the real-world setting, our findings must be interpreted in the light of a number of potential differences between patients who initiated infliximab treatment and patients who started adalimumab treatment. Channelling of a certain type of patients to adalimumab, such as those with lower disease severity,33 or those who are expected to cope better, may have contributed to the observed difference. The previously reported shorter time to loss of response to adalimumab as compared to infliximab among 218 Canadian Crohn’s disease patients emphasises that our data should be interpreted with caution.12 However, to limit potential channelling bias, discontinuation rates of the second anti-TNF agents were also compared. Longer drug survival on the second anti-TNF was seen among patients with Crohn’s disease.
who switched from infliximab to adalimumab, compared to those who switched from adalimumab to infliximab. This finding may point to a potential difference, possibly explained by different inhibition mechanisms as demonstrated in other chronic inflammatory diseases. These findings are in part supported by a recent network meta-analysis, where ranking of different biologics were assessed using surface under the cumulative ranking probabilities. In patients with prior anti-TNF exposure, adalimumab was ranked highest for induction of clinical remission. However, the quality of evidence was low and infliximab was not included due to lack of data. The fact that several other studies have arrived at a different conclusion, may question the generalisability of our results. In contrast to the observed association with colonic disease, Vermeire et al reported a lower response rate in patients with ileal disease, while others have not identified any associations. In this study, the discontinuation rate in patients with Crohn’s disease, by low statistical power since fewer patients with ulcerative colitis than Crohn’s disease were included. Discontinuation of first-line anti-TNF treatment was numerically more likely in patients with ulcerative colitis than Crohn’s disease, while moving to a second anti-TNF agent seemed less likely (Figure 1). These observations indicate that differences in treatment algorithms and selection of patients for anti-TNF treatment may exist between patients with Crohn’s disease and ulcerative colitis. Recent approval of several targeted drugs in IBD highlight the need for clinical predictors of long-term treatment outcomes. Beyond the use of infliximab, colonic disease and initiation of first anti-TNF during the first 5 years of the study period were identified as predictive of drug discontinuation among patients with Crohn’s disease. The extent to which disease phenotype may offer some predictive value is disputed. In contrast to the observed association with colonic disease, Vermeire et al reported a lower response rate in patients with ileal disease, while others have not identified any associations. In this study, the discontinuation rate in patients with Crohn’s disease,
but not ulcerative colitis, decreased over the calendar period. This may indicate that anti-TNF treatments are increasingly optimised in patients with Crohn's disease who respond, but do not achieve remission. Another potential explanation could be that we had insufficient power to identify temporal changes in patients with ulcerative colitis since fewer patients with ulcerative colitis than Crohn's disease were included. Among patients with ulcerative colitis, we identified fewer significant clinical predictors, which may in part be explained by fewer patients with ulcerative colitis than with Crohn's disease in our cohort. In accordance with the reported association between short disease duration and increased risk of colectomy in the Active Ulcerative Colitis Trials (ACT) 1 and 2, we observed an association between long

### TABLE 4 Predictors at baseline of first-line discontinuation because of lack/loss of response to first anti-TNF, among patients with ulcerative colitis

| Predictor                          | Univariate HR [95%CI] | P   | Multivariable HR [95%CI] | P   |
|-----------------------------------|-----------------------|-----|--------------------------|-----|
| Female                            | 0.73 [0.48-1.11]      | 0.14| 0.69 [0.42-1.12]         | 0.131|
| Disease duration [years]          |                       |     |                          |     |
| <1                                | 1.28 [0.83-1.98]      | 0.27| 1.06 [0.62-1.80]         | 0.843|
| 2-9                               | Reference             |     | Reference                |     |
| ≥10                               | 0.35 [0.19-0.68]      | <0.01| 0.25 [0.10-0.58]         | 0.001|
| Year of anti-TNF initiation       |                       |     |                          |     |
| April 2006- April 2011             | Reference             |     | Reference                |     |
| April 2011- April 2016            | 1.05 [0.70-1.56]      | 0.83| 1.06 [0.65-1.73]         | 0.812|
| Disease extent                    |                       |     |                          |     |
| E1 Proctitis                      | 0.87 [0.35-2.15]      | 0.76| 1.33 [0.47-3.77]         | 0.594|
| E2 Left-sided colitis             | 1.02 [0.66-1.59]      | 0.93| 0.98 [0.58-1.66]         | 0.933|
| E3 Extensive colitis              | Reference             |     | Reference                |     |
| Concomitant immunomodulators      | 0.67 [0.45-1.01]      | 0.06| 0.92 [0.57-1.49]         | 0.739|
| CRP >3 mg/L at baseline           | 1.96 [1.19-3.23]      | 0.01| 1.67 [0.99-2.82]         | 0.056|
| Infliximab as first anti-TNF      | 1.00 [0.58-1.71]      | >0.99| 0.96 [0.50-1.83]         | 0.898|

Abbreviation: CRP, C-reactive protein. Multilevel survival model using Weibull distribution was used, with 1:n propensity score-matched blocks as random effects.

### TABLE 5 Predictors at baseline of first-line discontinuation because of intolerance to first anti-TNF, among patients with ulcerative colitis

| Predictor                          | Univariate HR [95%CI] | P   | Multivariable HR [95%CI] | P   |
|-----------------------------------|-----------------------|-----|--------------------------|-----|
| Female                            | 1.44 [0.82-2.53]      | 0.20| 1.60 [0.84-3.04]         | 0.151|
| Disease duration [years]          |                       |     |                          |     |
| <1                                | 1.72 [0.89-3.32]      | 0.11| 2.42 [1.11-5.30]         | 0.027|
| 2-9                               | Reference             |     | Reference                |     |
| ≥10                               | 1.16 [0.58-2.32]      | 0.69| 1.22 [0.51-2.94]         | 0.652|
| Year of anti-TNF initiation       |                       |     |                          |     |
| April 2006- April 2011             | Reference             |     | Reference                |     |
| April 2011- April 2016            | 0.69 [0.40-1.22]      | 0.21| 0.95 [0.49-1.84]         | 0.872|
| Disease extent                    |                       |     |                          |     |
| E1 Proctitis                      | 0.67 [0.16-2.79]      | 0.58| 1.16 [0.26-5.10]         | 0.848|
| E2 Left-sided colitis             | 1.00 [0.53-1.86]      | 0.99| 0.98 [0.48-1.99]         | 0.954|
| E3 Extensive colitis              | Reference             |     | Reference                |     |
| Concomitant immunomodulators      | 0.98 [0.56-1.71]      | 0.94| 1.12 [0.57-2.23]         | 0.738|
| CRP >3 mg/L at baseline           | 1.23 [0.65-2.31]      | 0.53| 1.00 [0.50-2.00]         | 0.995|
| Infliximab as first anti-TNF      | 0.87 [0.42-1.79]      | 0.70| 0.63 [0.28-1.39]         | 0.251|

Abbreviation: CRP, C-reactive protein. Multilevel survival model using Weibull distribution was used, with 1:n propensity score-matched blocks as random effects.
disease duration and a lower discontinuation rate. The inflammatory burden is primarily defined by endoscopic activity, and numerous studies have shown that endoscopic remission is associated with improved long-term outcomes. In clinical practice, inflammatory markers are often used as surrogates, since endoscopy is an invasive procedure and associated with certain risks. The observed associations between a normalisation of CRP at three months and improved long-term outcomes are supported by previous studies, and indicate that CRP may provide guidance on further treatment.

In Crohn's disease, concomitant use of immunomodulators was associated with a lower adverse drug reaction-mediated discontinuation rate, specifically infusions reactions, as reported elsewhere. Treatment outcomes did not differ between patients who switched because of intolerance to the first anti-TNF and those who switched because of poor clinical effectiveness.

This study has several strengths but is also associated with some weaknesses. The use of the personal identity number, unique to every Swedish resident, allowed us to follow patients over time. Retrieval of data from the national quality register, increases the generalisability in that the results reflect treatment practices in a variety of care contexts, including both regional and university hospitals. By restricting the study, to a period when both adalimumab and infliximab were available, we reduced the risk of selection bias. In order to reduce the risk of including patients who receive an anti-TNF as a temporary treatment, for example as bridging therapy, we stratified our analyses by reason for termination and analysed patients who discontinued treatment due to poor clinical effectiveness separately.

The main potential limitation of this study was the observational cohort study design, which may have introduced bias due to confounding by indication. Even though we aimed to balance groups by propensity score matching, we cannot exclude residual confounding from other known or unknown factors, for example different patient compliance to (different) anti-TNF agents depending on their route of administration, endoscopic disease activity or disease severity. However, we did not observe any differences between patients on first-line infliximab vs adalimumab treated patients with respect to CRP levels, steroid-dependent/refractory disease or previous IBD-related surgery at baseline (Supplementary Material 2). To limit the influence of channelling bias further, we assessed drug discontinuation in both first-line and second-line treated patients. However, channelling of infliximab to patients with more severe disease may still have occurred and may have contributed to increased discontinuation of infliximab (vs adalimumab) in patients with Crohn's disease. The study is also limited by the fact that differences in cumulative survival of second-line anti-TNF were assessed by log-rank test only. However, the coverage of clinical data, including CRP levels, at the initiation of second-line treatment was too low to allow multivariable analyses and assessment of potential interactions between markers of disease severity. The definition of poor clinical effectiveness represents another important limitation. In SWIBREG, the reason for drug discontinuation is entered by the treating physician, and poor clinical effectiveness does not require assessment of endoscopic activity or other objective measures of disease activity. The absence of information on drug concentrations and potential anti-drug antibodies represents another potential source of bias. Assessment of these laboratory measures may have influenced the decision to use another anti-TNF agent or a biological agent with an alternative mechanism of action as second-line treatment, and potentially also treatment outcomes. Other limitations were the absence of information on smoking habits and dose-escalations. However, dose-escalation has more commonly been reported among infliximab-treated than adalimumab-treated patients in Sweden, indicating that the observed difference probably represents an underestimation of the true difference if dose-escalation would have been taken into account.

In conclusion, by using data from the Swedish IBD quality register (SWIBREG), we demonstrate that infliximab was associated with a higher drug discontinuation rate because of poor clinical effectiveness compared to adalimumab, among patients with Crohn's disease. The fact that this was observed both when used as first anti-TNF agent and as second-line treatment, may indicate that this finding is not solely explained by channelling bias, but suggests that there could be a potential difference between the two drugs. Furthermore, we identified a number of clinical variables at baseline that independently predicted long-term outcome, and confirmed the previously reported association between normalisation of CRP after induction treatment and improved long-term outcome in both Crohn's disease and ulcerative colitis. The application of these predictive factors may provide clinical guidance and personalise the treatment of patients with IBD.

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AUTHORSHIP
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Author contributions: JH, JFL, OO, IV and EM planned the conception and design of the study. IV and EM performed the data collection. IV, CE and YC performed the data analyses. IV, CE, JFL, JH and SM interpreted the data. IV, CE, EM, YC, JFL and JH drafted the manuscript. All authors revised and approved the final version of the manuscript to be submitted.

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DATA AVAILABILITY STATEMENT
The data underlying this article cannot be shared publicly due to legal reasons, since they are obtained from a Swedish quality register. However, summary statistics can be provided on request.

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**SUPPORTING INFORMATION**

Additional supporting information will be found online in the Supporting Information section.

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