Digestive Diseases and Sciences (2023) 68:3119–3128
https://doi.org/10.1007/s10620-023-07897-2

ORIGINAL ARTICLE

# Ustekinumab Versus Anti-tumour Necrosis Factor Alpha Agents as Second-Line Biologics in Crohn's Disease

Carl Eriksson[1,2] · Jonas Söderling[2] · Sara Karlqvist[1] · Gabriella Bröms[2,3] · Åsa H. Everhov[2,4,8] · Daniel Bergemalm[1] · Jonas F. Ludvigsson[4,5,6] · The SWIBREG study group · Ola Olén[2,7,8] · Jonas Halfvarson[1]

Received: 12 September 2022 / Accepted: 21 February 2023 / Published online: 17 March 2023


## Abstract

**Background** There are little data on positioning biologics in Crohn's disease (CD).

**Aims** We aimed to assess the comparative effectiveness and safety of ustekinumab vs tumour necrosis factor-alpha (anti-TNF) agents after first-line treatment with anti-TNF in CD.

**Methods** We used Swedish nationwide registers to identify patients with CD, exposed to anti-TNF who initiated second-line biologic treatment with ustekinumab or second-line anti-TNF therapy. Nearest neighbour 1:1 propensity score matching (PSM) was used to balance the groups. The primary outcome was 3-year drug survival used as a proxy for effectiveness. Secondary outcomes included drug survival without hospital admission, CD-related surgery, antibiotics, hospitalization due to infection and exposure to corticosteroids.

**Results** Some 312 patients remained after PSM. Drug survival at 3 years was 35% (95% CI 26–44%) in ustekinumab compared to 36% (95% CI 28–44%) in anti-TNF-treated patients (p = 0.72). No statistically significant differences were observed between the groups in 3-year survival without hospital admission (72% vs 70%, p = 0.99), surgery (87% vs 92%, p = 0.17), hospital admission due to infection (92% vs 92%, p = 0.31) or prescription of antibiotics (49% vs 50%, p = 0.56). The proportion of patients continuing second-line biologic therapy did not differ by reason for ending first-line anti-TNF (lack of response vs intolerance) or by type of first-line anti-TNF (adalimumab vs infliximab).

**Conclusion** Based on data from Swedish routine care, no clinically relevant differences in effectiveness or safety of second-line ustekinumab vs anti-TNF treatment were observed in patients with CD with prior exposure to anti-TNF.

**Keywords** Crohn's disease · Ustekinumab · Anti-TNF · Comparative effectiveness · Comparative safety · Population-based study

## Abbreviations

| | |
|---|---|
| Anti-TNF | Tumour necrosis factor-alpha agents |
| CD | Crohn's disease |
| CI | Confidence interval |
| IBD | Inflammatory bowel disease |
| ICD | International Classification of Diseases |
| IQR | Interquartile range |
| NPR | National Patient Register |
| PSM | Propensity score matching |
| SWIBREG | The Swedish National Quality Register for Inflammatory Bowel Disease |

Ola Olén and Jonas Halfvarson have contributed equally to this work.

The members of the SWIBREG study group have been listed in acknowledgements.

An editorial commenting on this article is available at https://doi.org/10.1007/s10620-023-07898-1.

✉ Carl Eriksson
carl.eriksson@regionorebrolan.se

Extended author information available on the last page of the article

## Introduction

The therapeutic landscape for Crohn's disease (CD) is rapidly evolving and the introduction of novel drugs raises questions about drug positioning and how to optimize treatment algorithms [1]. The tumour necrosis factor-alpha agents (anti-TNF) infliximab and adalimumab were the first biologic agents to be approved for the treatment of moderate to severe CD refractory or intolerant to conventional therapy (Supplementary Table 1).

During the past decade, alternative biologics with novel mechanisms of action have become available [2]. The interleukin-inhibitor ustekinumab, a humanized monoclonal antibody directed toward the common p40 subunit of interleukin-12 and interleukin-23, is the most recently approved agent [3]. In several countries, choice of first-line biologic treatment and treatment patterns have been heavily influenced by the introduction of anti-TNF biosimilars and the cost savings associated with these drugs. However, many patients with CD do not respond to first-line anti-TNF treatment, lose response over time or stop treatment due to intolerance [4, 5].

While head-to-head trials directly comparing the efficacy and tolerability of different biologic agents by order of exposure have been performed in other inflammatory disorders (e.g., rheumatoid arthritis [6], plaque psoriasis [7] and ulcerative colitis) [8], only one such study (the SEAVUE trial) has been conducted in patients with CD [9]. However, the SEAVUE trial was restricted to adult biologic-naïve patients with CD without concurrent treatment with immunomodulators [9]. Therefore, it remains unclear whether patients with CD who have failed first-line anti-TNF treatment should be treated with ustekinumab or an alternative anti-TNF agent.

Observational studies on the comparative effectiveness of biologics in CD have reported inconsistent and contradictory findings [10–13]. Their interpretation is challenged by the inclusion of heterogeneous patient populations (e.g., a mix of patients with first- and second-line biologic treatment).

In clinical practice, the most common reasons for discontinuation of a biologic agent are lack or loss of effectiveness and adverse drug reactions [14, 15]. Therefore, drug survival may be used as a context-specific proxy for effectiveness and safety [16]. However, other factors may influence drug-survival rates, including patient population characteristics. If channelling bias is present, there may be an imbalance in these factors by drug or treatment line. One way to limit the influence of channelling bias is to restrict comparisons to second-line biologic treatment, where the initial channelling was to a different biologic agent [16], and to apply propensity score matching (PSM).

We conducted a nationwide population-based cohort study to compare drug survival and tolerability of ustekinumab vs anti-TNF treatment as second-line treatment in CD. We performed propensity score-matched analyses to account for potential confounding.

## Materials and Methods

### Setting

The Swedish healthcare system is primarily tax-funded and offers universal access to health care. Prescription of medicines above SEK 2300 a year (approximately 230 EUR) is provided free of charge. In Sweden, all health care providers (public and private) must report information to National administrative and healthcare registers.

In this population-based nationwide study we used the unique personal identification number (PIN) issued to all Swedish residents to link data from the National Patient Register (NPR) with the Prescribed Drug Register and the Swedish Quality Register for Inflammatory Bowel Disease (SWIBREG) [17]. The NPR contains information on inpatient care, with nationwide coverage since 1987. From 1997 onwards, information about surgical day care procedures was added. Since 2001, the register has had complete coverage of all non-primary care outpatient visits (e.g., all outpatient visits to gastroenterologists, paediatric gastroenterologists or surgeons) [18]. Although the NPR includes some data on infusion therapies, including biologics, the coverage of infusion therapies is generally poor and varies between counties [19].

The Prescribed Drug Register, launched in 2005, includes all prescribed drugs dispensed at Swedish pharmacies. However, it does not have data on over-the-counter medication and infusion biologics are poorly covered [20].

SWIBREG, founded in 2005, contains information about clinical inflammatory bowel disease (IBD) variables such as date of diagnosis, disease phenotype and medical treatment. Using the NPR as the gold standard, SWIBREG covers > 65% of all patients with IBD in Sweden, with coverage of 100% at 4 hospitals and 90% at 12 hospitals [21]. Since infusion biologics are incompletely captured in the NPR, information on biologics was supplemented with data from SWIBREG [19]. In SWIBREG, the following criteria are used to classify reasons for drug termination: lack of response (termination because of primary or secondary non-response), intolerance (discontinuation due to side effects, including infusion reactions) and other reasons (e.g., pregnancy).

### Patients

Patients with CD were identified from the NPR and SWIBREG. CD was defined as having at least one relevant International Classification of Diseases (ICD) code in the NPR along with at least one diagnosis of CD in SWIBREG (Supplementary Table 2). According to patient chart data, a previous validation study found that > 99% of patients fulfilling this definition were confirmed to have CD [22]. Data from the SWIBREG and NPR were used to classify phenotypes of CD according to the Montreal classification (Supplementary Table 4) [23]. All patients with CD who were exposed to an anti-TNF (infliximab or adalimumab) as a first-line biologic treatment and received ustekinumab or an anti-TNF agent (infliximab or adalimumab) as a second-line

biologic treatment between 1999 and 2019 were identified. IBD drugs were classified according to Anatomical Therapeutic Chemical [ATC] codes and are summarized in Supplementary Table 3.

Patients were excluded if they were aged < 18 years at the start of second-line biologic treatment, were exposed to natalizumab, vedolizumab or an anti-TNF agent not approved for the treatment of CD (e.g. etanercept), as first-line treatment or exposed to any biologics before the date of diagnosis of CD. Switching from a reference product to a biosimilar was not considered discontinuation. The biosimilars for infliximab available in Sweden are Flixabi®, Zessly®, Remsima® and Inflectra® and those for adalimumab are Amgevita®, Imraldi®, Hyrimoz®, Idaco®, and Hulio®. To allow a minimum follow-up of 12 months, patients were followed from initiation of second-line biologic until emigration, death or end of the study period (i.e. 31 December 2020), whichever occurred first.

### Outcomes

The primary outcome was drug survival, used as a proxy for clinical effectiveness and safety. Information from the SWIBREG, the Prescribed Drug Register and the NPR was combined to determine drug survival rates. The earliest available start date and latest available stop date were used when treatment initiation and termination dates were inconsistently recorded in the different registers (detailed information is provided in the Supplementary Methods section).

Secondary outcomes were clinical effectiveness and safety assessed by survival without (a) hospital admission because of CD or CD-related surgery (Supplementary Tables 2 and 5), (b) CD-related surgery (Supplementary Table 5), (c) prescription of antibiotics (used as a proxy for infection, Supplementary Table 6) and (d) hospital admission with infection as principal or secondary diagnosis (as a proxy for severe infection, Supplementary Table 7). We also assessed the cumulative steroid dose in prednisolone equivalents (Supplementary Table 8). Five categories of corticosteroid exposure were used during the first 3 years after the start of second-line biologic treatment, corresponding to approximately 0–4 courses of corticosteroids (Supplementary Table 9).

In addition, we performed explorative analyses and examined drug survival of second-line biologic agents by reason for cessation of first anti-TNF treatment, according to the criteria used in SWIBREG (lack of response or intolerance). Finally, we assessed drug survival of the second-line biologic agent as a function of the first anti-TNF used. Four switching patterns were compared in this analysis: infliximab to adalimumab, adalimumab to infliximab, infliximab to ustekinumab, and adalimumab to ustekinumab.

### Propensity Score

To control for potential confounders we performed 1:1 nearest neighbour PSM. The propensity score for ustekinumab exposure was estimated by a logistic regression model including the following covariates available at baseline: sex, year of diagnosis, year of initiation of the first anti-TNF treatment, year of the start of the second-line biologic treatment, disease duration, age, disease behaviour, presence of perianal disease, disease location, previous CD-related surgery, corticosteroid use within the last 6 months, combination therapy with an immunomodulator, reason for termination of the first anti-TNF therapy according to the criteria used in SWIBREG (lack of response, intolerance, other) and the first anti-TNF agent (infliximab or adalimumab). We assessed the covariate balance in the matched cohort by checking standardized differences between matched groups and plotting histograms of propensity scores before and after matching. A covariate was considered well balanced if the standardized difference was < 10% [24].

### Statistics

Non-normally distributed data on a continuous scale are presented as median with interquartile range (IQR), and differences between groups were assessed using the Mann–Whitney U-test. Categorical data are expressed as frequencies and percentages. Differences between groups were assessed using the Pearson Chi-square test or Fisher's exact test when appropriate. Kaplan–Meier curves were plotted to visualize time-dependent outcomes. Univariable Cox proportional hazard regression analyses were used to compare groups.

All tests were two-tailed and p-values < 0.05 were considered statistically significant. Statistical analyses were performed using SAS® version 9.4 software (SAS Institute Inc., Cary, NC, USA).

## Results

### Cohort of Second-Line Treated Patients

We identified 17,633 patients with CD, of whom 5761 were exposed to first-line anti-TNF (adalimumab or infliximab) treatment between 1999 and 2019. Of these 5761 patients, 973 started second-line biologic therapy (anti-TNF, n = 815; ustekinumab, n = 158; Supplementary Fig. 1) before 2019/31/12. After PSM, 312 patients were included in the study cohort (anti-TNF, n = 156; ustekinumab, n = 156; Supplementary Fig. 1). Table 1 describes the cohort's clinical and demographic characteristics before and after PSM. In the propensity score-matched cohort all baseline characteristics, as assessed by standardized differences, were well

balanced between the groups. Histograms of estimated propensity scores and switching patterns between different biologic treatments are presented in Supplementary Figs. 1 and 2.

### Effectiveness

Among patients treated with ustekinumab as second-line biologic treatment, drug survival at 1 year was 58% (95% CI 50–65%) as compared to 58% (95% CI 50–65%) in patients who received anti-TNF treatment (p = 0.87; Fig. 1). The corresponding figures at 3 years were 35% (95% CI 26–44%) and 36% (95% CI 28–44%), respectively (p = 0.72). At 3 years from treatment start, reasons for termination were similar between patients who received ustekinumab (lack of response, n = 26; intolerance, n = 11; other reason, n = 54) and anti-TNF treatment (lack of response, n = 30; intolerance, n = 21; other reason, n = 52).

The 3-year survival without CD-related hospital admission did not differ between patients treated with second-line ustekinumab (72%, 95% CI 62–80%) and anti-TNF (70%, 95% CI 60–78%) (p = 0.99; Fig. 2A). No difference in 3-year survival without CD-related surgery (87%, 95% CI 93–76%) vs (92%, 95% CI 85–96%; p = 0.33; Fig. 2B) or prescription of corticosteroids (53%, 95% CI 42–62%) vs (55%, 95% CI 45–63%; p = 0.95) was observed between patients with ustekinumab and patients with adalimumab, respectively. The cumulative corticosteroid exposure at 3 years stratified by second-line biologic therapy is depicted in Fig. 3.

### Safety

At 3 years, survival without at least one course of antibiotics was similar between patients treated with second-line ustekinumab (49%, 95% CI 34–62%) and an anti-TNF agent (50%, 95% CI 37–61%) (p = 0.56; Fig. 2C). No significant difference in survival without hospital admission due to an infection as the primary or secondary diagnosis was found between the groups: 92% (95% CI 85–96%) in ustekinumab vs 92% (95% CI 83–96%; p = 0.31; Fig. 2D) in anti-TNF.

### Drug Survival by Switching Strategies

When assessing the drug survival of second-line biologic therapy by different switching patterns, no statistically significant differences were observed. Drug survival at 3 years was 39% (95% CI 27–50%) in patients switching from infliximab to adalimumab, 35% (95% CI 24–47%) in patients switching from infliximab to ustekinumab, 33% (95% CI 23–44%) in patients switching from adalimumab to infliximab and 36% (95% CI 24–49%) in patients switching from adalimumab to ustekinumab.

### Drug Survival by Reason for Suspension of the First Anti-TNF Agent

When comparing the second-line biologic therapies by reason for termination of the first-line biologic treatment, no statistically significant differences were noted. Among patients with CD who stopped first-line anti-TNF because of lack of response, the 3-year drug survival was 29% (95% CI 17–43%) in patients treated with ustekinumab compared to 34% (95% CI 23–46%) in patients treated with an anti-TNF agent (p = 0.46). The corresponding figures for patients who discontinued first-line anti-TNF due to intolerance were 38% (95% CI 21–55%) and 44% (95% CI 26–61%; p = 0.75).

## Discussion

In this nationwide propensity score-matched cohort study of patients with CD in Sweden, we compared long-term drug survival and safety of ustekinumab vs anti-TNF as a second-line biologic treatment after first-line anti-TNF exposure. In a propensity score-matched cohort of 312 patients, assembled from 5761 patients with CD exposed to first-line anti-TNF treatment, similar short- and long-term estimates of clinical effectiveness and safety were observed for ustekinumab and anti-TNF.

We have previously shown that less than half of all patients with CD who initiate first-line anti-TNF treatment in Sweden continue the drug after 3 years [25]. Accordingly, many patients require sequential therapies over their disease course. Unfortunately, data to guide clinicians on how to position different biologics are inadequate, with limited external validity due to strict inclusion criteria [9, 26, 27]. No differences in clinical remission, endoscopic remission or infections were seen between groups in the recent head-to-head SEAVUE trial, where biologic-naïve patients with CD were randomized to ustekinumab or adalimumab [9]. Thus, our results indicate that the outcome from the SEAVUE trial may apply to a broader population of patients with CD, including those who have previously failed an anti-TNF agent.

Our results are also supported by a recent network meta-analysis, where the authors ranked different biologics by combining the results from six randomized trials involving 1606 patients with CD [28]. In the meta-analysis, ustekinumab and adalimumab were top-ranked for induction of clinical remission in patients with CD with prior exposure to anti-TNF [28]. Despite a similar summary estimate, the certainty in the evidence for adalimumab was downgraded for indirectness (because of inclusion of patients with prior response or intolerance to anti-TNF agents only) and imprecision (because of few events). In patients with response to induction therapy the maintenance rate over 12 months was

**Table 1** Baseline demographics and clinical characteristics of patients with Crohn's disease

| | Overall cohort (N = 973) | | Standardized difference | Propensity score-matched cohort (N = 312) | | Standardized difference |
|---|---|---|---|---|---|---|
| | Ustekinumab n = 158 | Anti-TNF n = 815 | | Ustekinumab n = 156 | Anti-TNF n = 156 | |
| Sex, no (%) | | | | | | |
| Male | 89 (56.3%) | 419 (51.4%) | 0.099 | 88 (56.4%) | 94 (60.3%) | −0.078 |
| Female | 69 (43.7%) | 396 (48.6%) | −0.099 | 68 (43.6%) | 62 (39.7%) | 0.078 |
| Year of Crohn's disease onset, no (%) | | | | | | |
| 1961–1990 | 19 (12.0%) | 73 (9.0%) | 0.100 | 17 (10.9%) | 20 (12.8%) | −0.060 |
| 1991–2000 | 20 (12.7%) | 103 (12.6%) | 0.001 | 20 (12.8%) | 27 (17.3%) | −0.126 |
| 2001–2010 | 46 (29.1%) | 250 (30.7%) | −0.034 | 46 (29.5%) | 43 (27.6%) | 0.043 |
| 2011–2019 | 73 (46.2%) | 389 (47.7%) | −0.031 | 73 (46.8%) | 66 (42.3%) | 0.090 |
| Year of first-line anti-TNF treatment, no (%) | | | | | | |
| 1999–2009 | 21 (13.3%) | 123 (15.1%) | −0.052 | 21 (13.5%) | 30 (19.2%) | −0.156 |
| 2010–2014 | 47 (29.7%) | 356 (43.7%) | −0.292 | 46 (29.5%) | 67 (42.9%) | −0.283 |
| 2015–2019 | 90 (57.0%) | 336 (41.2%) | 0.319 | 89 (57.1%) | 59 (37.8%) | 0.392 |
| Year of second-line treatment, no (%) | | | | | | |
| 2014–2015 | 2 (1.3%) | 253 (31.0%) | −0.885 | 2 (1.3%) | 46 (29.5%) | −0.849 |
| 2016–2017 | 35 (22.2%) | 299 (36.7%) | −0.323 | 35 (22.4%) | 63 (40.4%) | −0.394 |
| 2018–2019 | 121 (76.6%) | 263 (32.3%) | 0.993 | 119 (76.3%) | 47 (30.1%) | 1.043 |
| Disease duration in years | | | | | | |
| Mean (SD) | 12.5 (12.1) | 10.0 (9.9) | 0.225 | 12.0 (11.3) | 11.9 (11.3) | 0.007 |
| Median (IQR) | 8.6 (3.8–17.7) | 6.8 (2.6–14.5) | – | 8.5 (3.6–16.8) | 8.9 (2.5–17.7) | – |
| Range, min–max | 0.2–56.6 | 0.1–51.5 | – | 0.2–47.6 | 0.2–51.5 | – |
| Age in years | | | | | | |
| Mean (SD) | 42.2 (14.6) | 36.7 (15.5) | 0.363 | 41.9 (14.4) | 41.5 (15.9) | 0.029 |
| Median (IQR) | 41.4 (30.0–53.9) | 33.6 (24.3–48.2) | – | 41.2 (29.9–53.8) | 40.7 (26.8–53.1) | – |
| Range, min–max | 12.5–74.8 | 9.1–78.8 | – | 12.5–74.8 | 11.6–75.3 | – |
| Categories, no (%) | | | | | | |
| < 18 years | 5 (3.2%) | 69 (8.5%) | −0.228 | 5 (3.2%) | 6 (3.8%) | −0.035 |
| 18–39 years | 71 (44.9%) | 438 (53.7%) | −0.177 | 71 (45.5%) | 70 (44.9%) | 0.013 |
| 40–59 years | 59 (37.3%) | 230 (28.2%) | 0.195 | 59 (37.8%) | 55 (35.3%) | 0.053 |
| ≥ 60 years | 23 (14.6%) | 78 (9.6%) | 0.154 | 21 (13.5%) | 25 (16.0%) | −0.072 |
| Behaviour, no (%) | | | | | | |
| Non-stricturing, non-penetrating (B1) | 83 (52.5%) | 518 (63.6%) | −0.225 | 83 (53.2%) | 78 (50.0%) | 0.064 |
| Stricturing (B2) or Penetrating (B3) | 75 (47.5%) | 297 (36.4%) | 0.225 | 73 (46.8%) | 78 (50.0%) | −0.064 |
| Perianal disease, no (%) | | | | | | |
| Yes | 43 (27.2%) | 207 (25.4%) | 0.041 | 42 (26.9%) | 40 (25.6%) | 0.029 |
| No | 115 (72.8%) | 608 (74.6%) | −0.041 | 114 (73.1%) | 116 (74.4%) | −0.029 |
| Location, no (%) | | | | | | |
| Ileal (L1) or Ileocolonic (L3) or location not defined (LX) | 124 (78.5%) | 637 (78.2%) | 0.008 | 122 (78.2%) | 125 (80.1%) | −0.047 |
| Colonic (L2) | 34 (21.5%) | 171 (21.0%) | 0.013 | 34 (21.8%) | 31 (19.9%) | 0.047 |
| Missing (no diagnosis after 1997) | 0 | 7 (0.9%) | −0.132 | 0 | 0 | – |
| Medication, no (%) | | | | | | |
| Corticosteroids within the last 6 months | 66 (41.8%) | 314 (38.5%) | 0.066 | 65 (41.7%) | 61 (39.1%) | 0.052 |
| Combination therapy with an immunomodulatory | 57 (36.1%) | 328 (40.2%) | −0.086 | 57 (36.5%) | 58 (37.2%) | −0.013 |
| Previous IBD-related surgery, no (%) | | | | | | |
| Yes | 63 (39.9%) | 219 (26.9%) | 0.278 | 61 (39.1%) | 62 (39.7%) | −0.013 |

**Table 1** (continued)

| | Overall cohort (N = 973) | | Standardized difference | Propensity score-matched cohort (N = 312) | | Standardized difference |
|---|---|---|---|---|---|---|
| | Ustekinumab n = 158 | Anti-TNF n = 815 | | Ustekinumab n = 156 | Anti-TNF n = 156 | |
| No | 95 (60.1%) | 596 (73.1%) | −0.278 | 95 (60.9%) | 94 (60.3%) | 0.013 |
| Reason for termination of first anti-TNF, no (%) | | | | | | |
| Lack of response | 76 (48.1%) | 260 (31.9%) | 0.335 | 74 (47.4%) | 76 (48.7%) | −0.026 |
| Intolerance | 31 (19.6%) | 224 (27.5%) | −0.186 | 31 (19.9%) | 31 (19.9%) | 0.000 |
| Other reason | 51 (32.3%) | 331 (40.6%) | −0.174 | 51 (32.7%) | 49 (31.4%) | 0.027 |
| Type of first anti-TNF, no (%) | | | | | | |
| Infliximab | 72 (45.6%) | 636 (78.0%) | −0.709 | 72 (46.2%) | 74 (47.4%) | −0.026 |
| Adalimumab | 86 (54.4%) | 179 (22.0%) | 0.709 | 84 (53.8%) | 82 (52.6%) | 0.026 |
| Propensity score | | | | | | |
| Mean (SD) | 0.25 (0.14) | 0.15 (0.11) | 0.813 | 0.24 (0.13) | 0.24 (0.13) | 0.033 |
| Median (IQR) | 0.23 (0.13–0.35) | 0.11 (0.07–0.18) | – | 0.23 (0.13–0.34) | 0.22 (0.12–0.34) | – |
| Range, min–max | 0.04–0.62 | 0.03–0.51 | – | 0.04–0.55 | 0.04–0.51 | – |

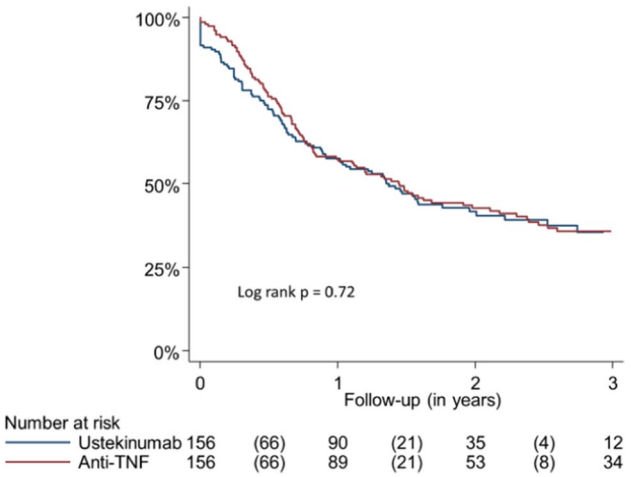


**Fig. 1** Kaplan–Meier curves in a propensity score-matched cohort of patients with Crohn's disease illustrating drug survival on second-line biologic treatment

lower for ustekinumab (39%) than adalimumab (58%) and infliximab (48%), although the results of the network meta-analysis have been questioned [29].

Contrary to the results of the SEAVUE trial and our propensity score-matched cohort, Ahmed et al. reported a lower clinical response/remission rate after 4–16 weeks of ustekinumab therapy (50%) compared to adalimumab treatment (73%) among 163 patients with CD at a tertiary referral center in Alabama, USA [10]. However, this cohort represented a mix of patients with first- and second-line treatment. After stratification by previous anti-TNF exposure, ustekinumab was associated with a numerically higher clinical response rate among patients exposed to anti-TNF [10].

The overall drug survival rates for ustekinumab and anti-TNF in our cohort are consistent with some previous real-world cohort studies [30, 31]. For instance, in a Belgian study of 152 patients with CD, of whom 99% were previously exposed to an anti-TNF agent, 93 (61%) continued ustekinumab therapy until week 52 [32]. In a meta-analysis of 37 observational studies, Gasport et al. reported differences in response to second-line anti-TNF depending on the reason for discontinuance of the first anti-TNF treatment [30]. Higher response and remission rates were observed when the reason for termination of the first anti-TNF was intolerance than when it was treatment failure, i.e. secondary loss of response or primary non-response. We could not confirm these findings in the patients treated with anti-TNF or ustekinumab. One possible explanation was our inability to distinguish patients with primary and secondary loss of response. In Gasport et al.'s meta-analysis 45% of patients who switched to adalimumab due to secondary loss of response to infliximab achieved remission. In contrast, the corresponding figure in patients with a primary non-response to infliximab was 31% [30]. Another potential explanation could be differences between patient populations. We included patients treated with second-line ustekinumab or anti-TNF therapy in various care contexts, including regional and university hospitals, whereas the origin of most of the cohorts in the meta-analysis was from referral centers.

In the network meta-analysis described above Singh et al. also ranked biologics based on the risk of infections [28]. Overall, infliximab and ustekinumab had the lowest risk

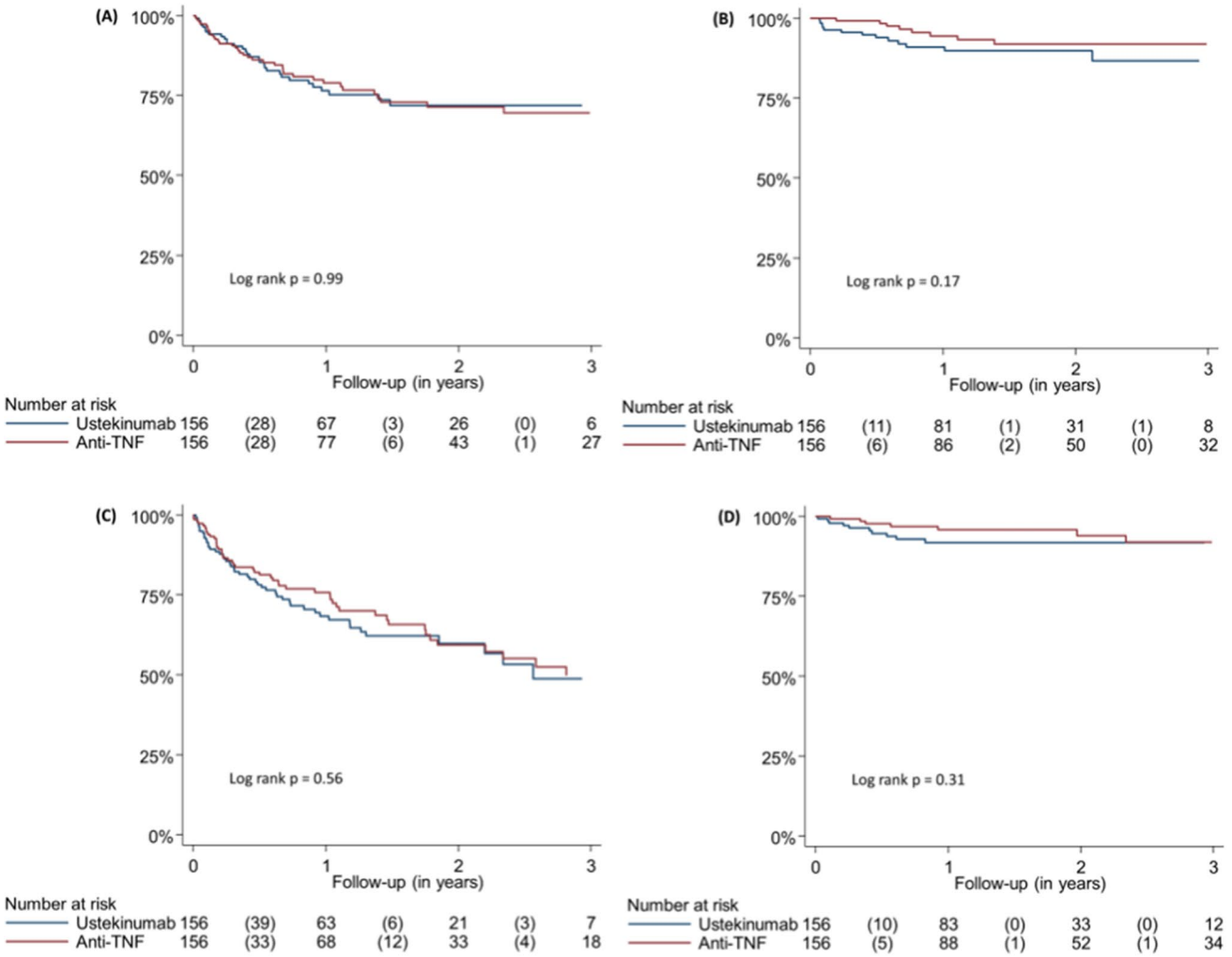


**Fig. 2** Kaplan–Meier curves in a propensity score-matched cohort of patients with Crohn's disease illustrating time to **A** Crohn's disease-related hospital admission or surgery, **B** Crohn's disease-related surgery, **C** prescription of antibiotics and **D** hospital admission due to infection in patients on second-line biologic treatment

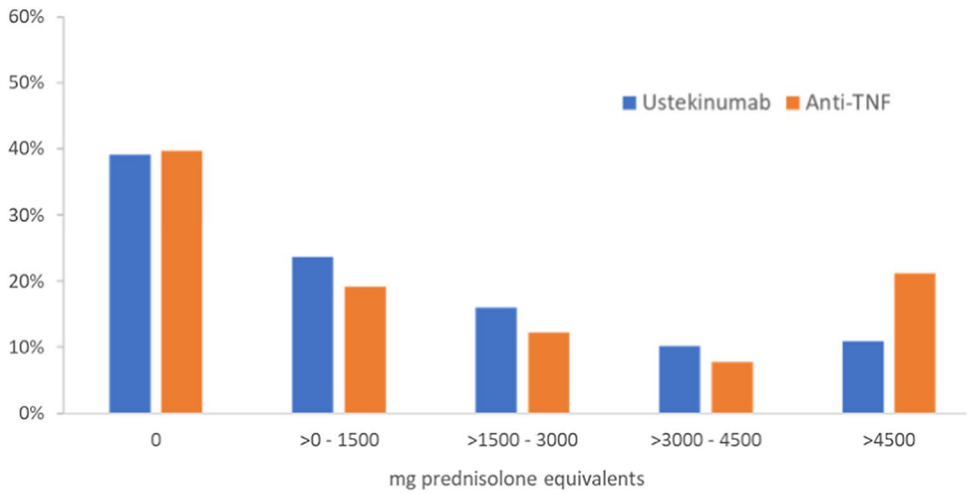


**Fig. 3** Cumulative corticosteroid exposure (mg prednisolone equivalents) during the first 3 years after the start of second-line biologic treatment in a propensity score-matched cohort of patients with Crohn's disease. The five categories roughly correspond to 0–4 courses of corticosteroids

of infections in maintenance trials, while adalimumab was associated with a higher risk. However, differences in disease control, clinical characteristics and study design may have influenced these findings because high disease activity, corticosteroid exposure and narcotic use represent important risk factors of severe infections, irrespective of which biologic therapy is applied [33–35]. We used prescriptions of antibiotics as a proxy for infections and hospital admission, with infection as a primary or secondary diagnosis as a surrogate marker for severe infections. Compared to the general Swedish population, the observed rate of severe infections seemed to be increased [36]. However, no statistically significant differences in drug survival without prescription of antibiotics or hospital admission due to infection were detected between patients on second-line ustekinumab and anti-TNF therapy. Comparing our results with those from the network meta-analysis is challenging because second-line anti-TNF therapy in our study represented an equal mix of infliximab and adalimumab treatment. Furthermore, we could not include the use of narcotics or endoscopic activity at baseline in our propensity score matching.

To our knowledge, this is the first real-world cohort study to address the long-term comparative effectiveness and safety of ustekinumab vs anti-TNF when used as a second-line biological treatment after anti-TNF exposure. Real-world observational studies that assess and compare clinical effectiveness or safety of different biologics are vulnerable to channelling bias due to confounding by indication and disease severity. Channelling bias is introduced when drugs with similar indications are non-randomly prescribed to groups of patients with prognostic differences. By restricting the study population to patients on second-line therapy after previous anti-TNF exposure, we could limit the impact of channelling bias (i.e. patients with ustekinumab were enrolled from a pool of patients initially directed to treatment with infliximab or adalimumab). Another major strength is the nationwide design, which ensures generalizability to patients exposed to ustekinumab in routine medical practice. Access to a large study population with information on possible confounders allowed us to perform propensity score matching to address potential confounders further. Unique to every Swedish resident, the PIN allowed us to follow patients regardless of their residential area and with virtually complete follow-up.

An important limitation of this study is the observational design. Although we attempted to reduce the impact of channelling by including patients with prior anti-TNF exposure only and balancing groups by PSM, residual confounding from other unknown factors cannot be excluded. The absence of information about therapeutic drug monitoring, smoking habits, dose optimization, clinical disease activity, biochemical markers, potential side effects and endoscopic activity are other limitations. Methods to determine anti-TNF concentrations and detect anti-drug antibodies became available in Sweden in 2012–2013 [37]. Information on drug concentration and potential anti-drug antibodies may have influenced the decision to switch from anti-TNF to ustekinumab instead of another anti-TNF agent. Another potential limitation was applying drug survival as a proxy for clinical effectiveness. Using this surrogate marker, we assume that patients continue treatment if it reduces disease activity and prevents flares without causing unacceptable side effects. However, other factors may affect drug survival, including dose optimization, compliance, psychological factors and the number of alternative treatment options [38].

In conclusion, in this large population-based cohort of patients with CD no evidence of clinically relevant differences in drug survival or safety could be discerned between patients treated with ustekinumab and anti-TNF as second-line biologic therapy in Swedish routine care.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s10620-023-07897-2.

**Acknowledgments** We acknowledge the members of the SWIBREG study group: Marie Andersson: Department of Internal Medicine, Södra Älvsborgs Hospital, Borås, Sweden. Jonas Bengtsson: Department of Surgery, Sahlgrenska University Hospital/Östra, Gothenburg, Sweden. Jan Björk: Unit of Internal Medicine, Institute Medicine Solna, Karolinska Institutet, Stockholm, Sweden; Patient Area Gastroenterology, Dermatovenerology and Rheumatology, Inflammation and Infection Theme Karolinska University Hospital, Stockholm, Sweden. Michael Eberhardson: Department of Gastroenterology and Hepatology, Linköping University, Linköping, Sweden. Ulrika L. Fagerberg: Center for Clinical Research, Västmanland Hospital, Västerås, Sweden and Uppsala University, Uppsala, Sweden; Department of Pediatrics, Västmanland Hospital, Västerås, Sweden; Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden. Olof Grip: Department of Gastroenterology, Skåne University Hospital, Malmö, Sweden. Henrik Hjortswang: Department of Gastroenterology, County Council of Östergötland, Linköping, Sweden; Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden. Susanna Jäghult: Stockholm Gastro Center, Karolinska Institutet, Stockholm, Sweden. Pontus Karling: Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden. Pär Myrelid: Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden; Department of Surgery, County Council of Östergötland, Linköping, Sweden. Caroline Nordenvall: Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; Department of Colorectal Cancer, Karolinska University Hospital, Stockholm, Sweden. Malin Olsson: Department of Surgery, County Council of Östergötland, Linköping, Sweden. Martin Rejler: Department of Medicine, Höglandssjukhuset Eksjö, Region Jönköping County Council, Jönköping, Sweden; Jönköping Academy for Improvement of Health and Welfare, Jönköping University, Jönköping, Sweden. Hans Strid: Department of Internal Medicine, Södra Älvsborgs Hospital, Borås, Sweden

**Author's contribution** OO and JFL: acquisition of data. JS and CE: data analysis, creating figures and tables. CE and JH: drafting the article. All authors: Substantial contributions to the study design, method, data interpretation, revision of the manuscript for important intellectual content and final approval of the version to be published.

**Funding** Open access funding provided by Örebro University. This work was funded by Janssen Cilag as an investigator-initiated study (Grant Number CNTO1275CRD0005); the Regional Agreement on Medical Training and Clinical Research between Region Örebro County and Örebro University: ALF (GRANT NUMBER OLL-836791 to CE); Stockholm Region Clinical Postdoctoral Researcher Grant (Grant Number N/A to GB); the Swedish Medical Society (Grant Number SLS-789611 to O.O); The Young Scholar Award from the Strategic Research Area Epidemiology program at Karolinska Institutet (Grant Number N/A to OO); the Regional Agreement on Medical Training and Clinical Research between Stockholm County Council and Karolinska Institutet: ALF (Grant Number 20170720 and 20190638 to OO); and the Swedish Research Council (Grant Number 2020-02002 to OO). The study design, the interpretation of the data and drafting of the manuscript were done by the authors without contribution from any funding organizations.

## Declarations

**Conflict of interest** CE received grant support/lecture fee/advisory board from Takeda, Janssen Cilag, Pfizer, Abbvie. SK received a lecture fee from Takeda. GB has served as a speaker for Takeda and worked on projects at Karolinska Institutet, partly financed by Janssen and Pfizer. ÅE has worked on projects at Karolinska Institutet and SWIBREG, partly financed by grants from Ferring and Janssen. JFL coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). That study has received funding from the Janssen corporation. OO has been PI on projects at Karolinska Institutet partly financed by investigator-initiated grants from Janssen and Ferring, and also report a grant from Pfizer in the context of a national safety monitoring program. None of these studies have any relation to the present study. Karolinska Institutet has received fees for lectures and participation on advisory boards by OO from Janssen, Ferring, Takeda and Pfizer on topics not related to the present study. JH has served as a speaker, a consultant and/or an advisory board member for Abbvie, Celgene, Celltrion, Ferring, Hospira, Janssen, Medivir, MSD, Olink Proteomics, Pfizer, Prometheus Laboratories Inc., RenapharmaVifor, Sandoz, Shire, Takeda, Thermo Fisher and Tillotts Pharma. JH also received research funding from Janssen, MSD and Takeda. MS and SM have no conflicts to report.

**Ethical approval** Ethical approval for this study was granted by the Regional Ethics Committee, Karolinska Institute, Stockholm, Sweden (2007/785-31/5, 2011/1509-32, 2015/0004-31, 2015/2237-32, 2017/1959-32).



## References

1. Lamb CA, Kennedy NA, Raine T et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut.* 2019;68:1–106.
2. Eberhardson M, Söderling JK, Neovius M et al. Anti-TNF treatment in Crohn's disease and risk of bowel resection-a population based cohort study. *Aliment Pharmacol Ther.* 2017;46:589–598.
3. Benson JM, Peritt D, Scallon BJ et al. Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders. *MAbs.* 2011;3:535–545.
4. Colombel JF, Sandborn WJ, Rutgeerts P et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology.* 2007;132:52–65.
5. Hanauer SB, Feagan BG, Lichtenstein GR et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet.* 2002;359:1541–1549.
6. Taylor PC, Keystone EC, van der Heijde D et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. *N Engl J Med.* 2017;376:652–662.
7. Gordon KB, Duffin KC, Bissonnette R et al. A Phase 2 Trial of Guselkumab versus Adalimumab for Plaque Psoriasis. *N Engl J Med.* 2015;373:136–144.
8. Sands BE, Peyrin-Biroulet L, Loftus EV et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. *N Engl J Med.* 2019;381:1215–1226.
9. Sands BE, Irving PM, Hoops T et al. Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with moderately to severely active Crohn's disease: a multicentre, randomised, double-blind, parallel-group, phase 3b trial. *Lancet.* 2022;399:2200–2211.
10. Ahmed Z, Venkata K, Zhang N, Malik TA. Comparative Effectiveness of Ustekinumab Versus Adalimumab in Induction of Clinical Response and Remission in Crohn's Disease: Experience of a Real-World Cohort at a Tertiary Care Inflammatory Bowel Disease Referral Center. *Gastroenterology Res.* 2019;12:245–251.
11. Alric H, Amiot A, Kirchgesner J et al. The effectiveness of either ustekinumab or vedolizumab in 239 patients with Crohn's disease refractory to anti-tumour necrosis factor. *Aliment Pharmacol Ther.* 2020;51:948–957.
12. Biemans VBC, van der Woude CJ, Dijkstra G et al. Ustekinumab is associated with superior effectiveness outcomes compared to vedolizumab in Crohn's disease patients with prior failure to anti-TNF treatment. *Aliment Pharmacol Ther.* 2020;52:123–134.
13. Townsend T, Razanskaite V, Dodd S et al. Comparative effectiveness of ustekinumab or vedolizumab after one year in 130 patients with anti-TNF-refractory Crohn's disease. *Aliment Pharmacol Ther.* 2020;52:1341–1352.
14. Engel T, Yung DE, Ma C et al. Effectiveness and safety of Ustekinumab for Crohn's disease; systematic review and pooled analysis of real-world evidence. *Dig Liver Dis.* 2019;51:1232–1240.
15. Singh S, Heien HC, Sangaralingham LR et al. Comparative Effectiveness and Safety of Anti-Tumor Necrosis Factor Agents in Biologic-Naive Patients With Crohn's Disease. *Clin Gastroenterol Hepatol.* 2016;14:1120–1129.
16. Rundquist S, Sachs MC, Eriksson C, Olén O, Montgomery S, Halfvarson J. Drug survival of anti-TNF agents compared with vedolizumab as a second-line biological treatment in inflammatory bowel disease: results from nationwide Swedish registers. *Aliment Pharmacol Ther.* 2021;53:471–483.
17. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and

pitfalls in healthcare and medical research. *Eur J Epidemiol.* 2009;24:659–667.
18. Ludvigsson JF, Andersson E, Ekbom A et al. External review and validation of the Swedish national inpatient register. *BMC Public Health.* 2011;11:450.
19. Bröms G, Söderling J, Sachs MC et al. Capturing biologic treatment for IBD in the Swedish Prescribed Drug Register and the Swedish National Patient Register - a validation study. *Scand J Gastroenterol.* 2021;56:410–421.
20. Wettermark B, Hammar N, Fored CM et al. The new Swedish Prescribed Drug Register–opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf.* 2007;16:726–735.
21. Ludvigsson JF, Andersson M, Bengtsson J et al. Swedish Inflammatory Bowel Disease Register (SWIBREG) - a nationwide quality register. *Scand J Gastroenterol.* 2019;54:1089–1101.
22. Jakobsson GL, Sternegård E, Olén O et al. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). *Scand J Gastroenterol.* 2017;52:216–221.
23. Shrestha S, Olén O, Eriksson C et al. The use of ICD codes to identify IBD subtypes and phenotypes of the Montreal classification in the Swedish National Patient Register. *Scand J Gastroenterol.* 2020;55:430–435.
24. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med.* 2009;28:3083–3107.
25. Visuri I, Eriksson C, Olén O et al. Predictors of drug survival: A cohort study comparing anti-tumour necrosis factor agents using the Swedish inflammatory bowel disease quality register. *Aliment Pharmacol Ther.* 2021;54:931–943.
26. Ha C, Ullman TA, Siegel CA, Kornbluth A. Patients enrolled in randomized controlled trials do not represent the inflammatory bowel disease patient population. *Clin Gastroenterol Hepatol.* 2012;10:1002–1007.
27. Johnson C, Barnes EL, Zhang X, Long MD. Trends and Characteristics of Clinical Trials Participation for Inflammatory Bowel Disease in the United States: A Report From IBD Partners. *Crohns Colitis 360* 2020;2:otaa023. https://doi.org/10.1093/crocol/otaa023.
28. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. *Aliment Pharmacol Ther.* 2018;48:394–409.
29. Varu A, Wilson FR, Dyrda P, Hazel M, Hutton B, Cameron C. Treatment sequence network meta-analysis in Crohn's disease: a methodological case study. *Curr Med Res Opin.* 2019;35:733–756.
30. Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther.* 2015;41:613–623.
31. Honap S, Meade S, Ibraheim H, Irving PM, Jones MP, Samaan MA. Effectiveness and Safety of Ustekinumab in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Dig Dis Sci.* 2022;67:1018–1035.
32. Liefferinckx C, Verstockt B, Gils A et al. Long-term Clinical Effectiveness of Ustekinumab in Patients with Crohn's Disease Who Failed Biologic Therapies: A National Cohort Study. *J Crohns Colitis.* 2019;13:1401–1409.
33. Colombel JF, Sands BE, Rutgeerts P et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut.* 2017;66:839–851.
34. Lichtenstein GR, Feagan BG, Cohen RD et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol.* 2012;107:1409–1422.
35. Osterman MT, Sandborn WJ, Colombel JF et al. Crohn's Disease Activity and Concomitant Immunosuppressants Affect the Risk of Serious and Opportunistic Infections in Patients Treated With Adalimumab. *Am J Gastroenterol.* 2016;111:1806–1815.
36. Ludvigsson JF, Holmgren J, Grip O et al. Adult-onset inflammatory bowel disease and rate of serious infections compared to the general population: a nationwide register-based cohort study 2002–2017. *Scand J Gastroenterol.* 2021;56:1152–1162.
37. Rundquist S, Sachs MC, Eriksson C, Olén O, Montgomery S, Halfvarson J. Editorial: anti-TNF agents against vedolizumab as a second-line treatment? Not surprising tie game-authors' reply. *Aliment Pharmacol Ther.* 2021;53:642–643.
38. Wolfe F. The epidemiology of drug treatment failure in rheumatoid arthritis. *Baillieres Clin Rheumatol.* 1995;9:619–632.



## Authors and Affiliations

**Carl Eriksson[1,2] · Jonas Söderling[2] · Sara Karlqvist[1] · Gabriella Bröms[2,3] · Åsa H. Everhov[2,4,8] · Daniel Bergemalm[1] · Jonas F. Ludvigsson[4,5,6] · The SWIBREG study group · Ola Olén[2,7,8] · Jonas Halfvarson[1]**

1 Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

2 Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

3 Division of Gastroenterology, Department of Specialist Medicine, Danderyd Hospital, Stockholm, Sweden

4 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

5 Department of Paediatrics, Örebro University Hospital, Örebro, Sweden

6 Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA

7 Sachs' Children and Youth Hospital, Stockholm South General Hospital, Stockholm, Sweden

8 Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden