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ORIGINAL ARTICLE

Tumour necrosis factor inhibitors in Crohn's disease and the effect on surgery rates

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Abstract

Aim: Surgery is an important therapeutic option for Crohn's disease. The need for first bowel surgery seems to have decreased with the introduction of tumour necrosis factor inhibitors (TNFi; adalimumab or infliximab). However, the impact of TNFi on the need for intestinal surgery in Crohn's disease patients irrespective of prior bowel resection is not known. The aim of this work is to compare the incidence of bowel surgery in Crohn's disease patients who remain on TNFi treatment versus those who discontinue it.

Method: We performed a nationwide register-based observational cohort study in Sweden of all incident and prevalent cases of Crohn's disease who started first-line TNFi treatment between 2006 and 2017. Patients were categorized according to TNFi treatment retention less than or beyond 1 year. The study cohort was evaluated with regard to incidence of bowel surgery from 12 months after the first ever TNFi dispensation.

Results: We identified 5003 Crohn's disease patients with TNFi exposure: 3748 surgery naïve and 1255 with bowel surgery prior to TNFi initiation. Of these patients, 7% (n = 353) were subjected to abdominal surgery during the first 12 months after the start of TNFi and were subsequently excluded from the main analysis. A majority (62%) continued TNFi for 12 months or more. Treatment with TNFi for less than 12 months was

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associated with a significantly higher surgery rate compared with patients who continued on TNFi for 12 months or more (hazard ratio 1.26, 95% CI 1.09–1.46; $p = 0.002$).

Conclusion: Treatment with TNFi for less than 12 months was associated with a higher risk of bowel surgery in Crohn's disease patients compared with those who continued TNFi for 12 months or more.

KEYWORDS
biologics, bowel surgery, Crohn's disease

INTRODUCTION

The range of therapeutic options for Crohn's disease has grown substantially with the introduction of biologicals. Tumour necrosis factor inhibitors (TNFi) have increased the likelihood of clinical and endoscopic remission in patients with Crohn's disease [1–3]. However, surgery remains an essential part of the therapeutic arsenal, and is often required to treat disease complications such as stricturing or perforating disease, or when the response to medical treatment is inadequate [4]. In a recent Swedish population-based study including patients with inflammatory bowel disease (IBD) between 1990 and 2014, the cumulative incidence of first intestinal surgery within 5 years of diagnosis of Crohn's disease decreased from 54.8% between 1990 and 1995 to 17.3% between 2009 and 2014, with ileocaecal resection being the most frequent intervention. No significant decrease was seen in repeat surgery from the year 2000 and later [5]. The question has been raised whether surgery rates have decreased after the introduction of TNFi. Randomized controlled trials (RCTs) have reported fewer hospital admissions as well as lower rates of surgery for Crohn's disease [1–3,6]. However, in real-life observational studies, the impact of biologicals on surgery rates has been ambiguous, with reports on reduction as well as no certain effects of TNFi treatment [7–12]. Interestingly, several studies suggest that the need for surgery was reduced even before the biological era and has continued to decline after TNFi were introduced, which might reflect a more conservative strategy with regard to bowel resection [5,7,13–17].

We are only aware of one RCT including a generalizable cohort that compared surgery in ileocaecal Crohn's disease with TNFi during a period of 12 months, namely the LIR!C study [18]. The follow-up study, although retrospective, reported a long-term (median 63.5 months) frequency of Crohn's related surgery of 48% in the TNFi arm [19]. We have previously investigated whether taking TNFi drugs for ≥12 months reduced first ever bowel surgery rates compared with <12 months in a cohort of 1856 Crohn's disease patients between 2006 and 2014 [20]. Somewhat unexpectedly, we found similar cumulative surgery rates (28% after 7 years) regardless of treatment retention less than or beyond 1 year. Since this cohort was restricted to surgery-naïve patients, we have now set out to investigate whether TNFi is associated with reduced rates of surgery in all Crohn's disease patients and whether there are any differences between surgery-naïve patients and patients with prior bowel surgery. We performed a register-based cohort study in Sweden between 2006 and 2017 to test the hypothesis that Crohn's disease patients who are still on TNFi after 12 months (indicating that they have responded to and tolerated TNFi) are less likely to undergo bowel surgery than patients who stop TNFi before 12 months of treatment, regardless of their history of abdominal surgery.

What does this paper add to the literature?

Previous studies have not unambiguously been able to show reduction of surgery after therapy with tumour necrosis factor inhibitors (TNFi. To our knowledge this is the largest study on real-life use of TNFi and surgery in Crohn's disease. A majority of patients (62%) continued on TNFi for 12 months or more, and this was associated with a reduced rate of surgery compared to drug survival of TNFi less than 12 months.

METHOD

Study design

We constructed an observational retrospective cohort of Crohn's disease patients based on data recorded prospectively in routine medical practice. The incidence of post-TNFi bowel surgery and any differences between the frequency of first ever abdominal surgery and repeat operation were compared between patients with continuous treatment for ≥12 months since start of TNFi (presumed sustained response and tolerance to TNFi) and patients who stopped treatment <12 months from initiation, likely because of lack of response or intolerance to TNFi.

Setting

In Sweden, all residents have universal access to publicly funded healthcare irrespective of place of residence, socioeconomic status or severity of disease. Virtually all IBD patients are seen by a gastroenterologist. Through the unique personal identity number issued to all Swedish residents, data from national and virtually complete administrative and clinical registers on demographics, morbidity and mortality can be linked [21–24].

Study population

All individuals in Sweden registered with a diagnosis of IBD in the Swedish National Patient Register (inpatient care or nonprimary outpatient care) from 1 January 1987 until 31 December 2016 were identified (Figure 1) [22,25]. The following codes were used to identify IBD patients from 1996 (ICD-10): Crohn's disease, K50; ulcerative colitis, K51; and indeterminate colitis, K52.3. From 1987 (ICD-9) the following codes were used: Crohn's disease, 555; ulcerative colitis, 556. The study population was limited to patients who had received two or more IBD diagnoses on two separate occasions, of which at least one IBD diagnosis was a main diagnosis in the departments of internal medicine, gastroenterology or paediatrics [26].

The two most recent IBD diagnoses prior to TNFi therapy were used to categorize patients as either Crohn's disease (two ICD-10 codes K50, either as primary or secondary diagnosis) or ulcerative colitis (two ICD-10 codes K51). The rationale was to reduce the influence of incorrect registration in the records or a change in diagnosis. If the two most recent diagnoses were not the same, the patient was classified as inflammatory bowel disease unclassified (IBDU), which also included ICD-10 code K52.3. Crohn's disease patients were then further selected by identifying those who had been dispensed at least one first-ever dose of TNFi (infliximab or adalimumab) between 1 January 2006 and 30 June 2016, as registered in the Swedish Prescribed Drug Register which began on 1 July 2005. Since there has been limited off-label use of golimumab for Crohn's disease in Sweden, this drug was also included in the analysis. Individuals who underwent surgery during the first year of treatment with TNFi were excluded to avoid confounding by surgical indications that were already present before TNFi initiation. Further, main analyses were restricted to patients with 6 months or more of follow-up time (beginning 1 year after the first TNFi treatment) (Figure 1). The Montreal classification was used to define age of onset, localization and perianal disease [27,28]. Relevant definitions and diagnostic codes are summarized in Table S1 and Table S2 in the Supporting Information.

Exposure to TNFi

We used nationwide registers to acquire information on use of TNFi in IBD: infliximab (ATC code L04AB02; L04AA12 before 2008), adalimumab (L04AB04; L04AA17 before 2008) and golimumab (L04AB06). The majority of treatment episodes were captured in the national Swedish register for IBD (SWIBREG) [29]. In addition to SWIBREG, TNFi use was captured in the Swedish Prescribed Drug Register (filled prescriptions) and the inpatient and outpatient parts of the National Patient Register (infusions performed in hospital) [24]. According to a recent validation study based on 2323 treatment episodes with biological treatments, more than 80% of episodes were captured when only having access to the Swedish Prescribed Drug Register or National Patient Register, which is why use of SWIBREG was recommended to achieve even better coverage [30].

Treatment retention

Patients with Crohn's disease were categorized into those who stopped TNFi within 12 months and those who continued TNFi for 12 months or more after initiation of TNFi treatment. If a patient was captured in SWIBREG, the start and stop dates in SWIBREG were used. If a stop date in SWIBREG was not followed by a new start date within 90 days (in any of the registers), that treatment episode was considered to have stopped. For patients not in SWIBREG, treatment with TNFi in hospital, as captured in the

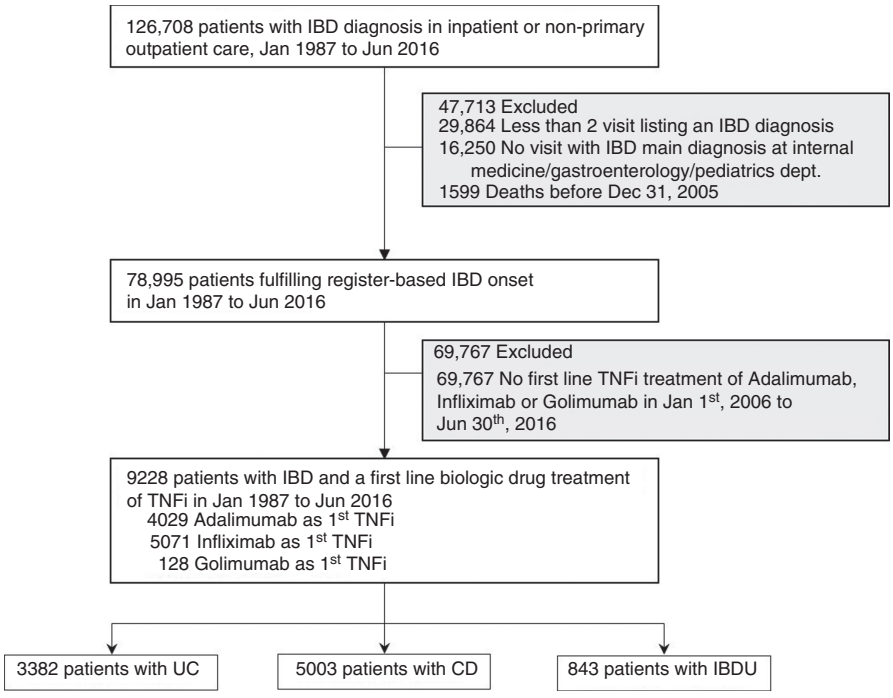

FIGURE 1 Flow chart of register-identified patients with inflammatory bowel disease (IBD) and treated with tumour necrosis factor inhibitors (TNFi) (CD, Crohn's disease; IBDU, inflammatory bowel disease unclassified; UC, ulcerative colitis)

National Patient Register, was considered ongoing until 90 days after the last infusion. For patients not in SWIBREG or the National Patient Register, filled prescriptions in the Swedish Prescribed Drug Register were regarded as ongoing TNFi treatment until 180 days since the last filled prescription (i.e. patients would need at least three filled prescriptions to be regarded as having been treated with TNFi for 12 months). For individuals captured in multiple registers, the earliest available start date and latest available stop date were used. For patients in both SWIBREG and the Swedish Prescribed Drug Register or National Patient Register and with no stop date in SWIBREG, the treatment was considered to have stopped 90 days after the last treatment episode in the National Patient Register or after the last filled prescription in the Swedish Prescribed Drug Register.

Follow-up and occurrence of bowel surgery

The outcome measure was abdominal surgery, which was defined according to validated surgical procedure codes in the National Patient Register (for the NOMESCO Classification of Surgical Procedures see Table S2) [22,31]. Patients with early surgery (within 12 months of the first TNFi dose) were excluded from the long-term analysis of surgery rates in patients with TNFi ≥ 12 months compared with <12 months. Thus, the long-term surgery analysis starts 12 months after TNFi initiation. Patients were hence considered at risk of bowel surgery from 12 months after the first TNFi administration and until the first event of emigration, death or end of follow-up (31 December 2017).

Statistics

Crude incidence rates (events per 1000 person-years) of bowel surgery were calculated by dividing the number of first bowel resections during follow-up by the corresponding person-time at risk. Relative risks of bowel surgery were computed using Cox proportional-hazard models between patients who were treated with TNFi for more or less than 12 months. The Cox models were stratified by birth year and sex and adjusted for age at index date. We calculated hazard ratios (HRs) overall as well as stratum-specific HRs for the calendar period of first Crohn's disease diagnosis, sex, age at first Crohn's disease diagnosis and phenotype according to the Montreal and Paris classifications. All analyses were performed using the SAS software package v.9.4 (SAS Institute, Cary, NC, USA).

Sensitivity analyses

The available registers lack detailed information on the reasons for discontinuing TNFi, and therefore patients who were treated for <12 months represent a mix of primary nonresponders, patients with loss of response, side effects, poor compliance or drug discontinuation after achieving remission [32]. Sensitivity analyses of the incidence of bowel surgery were therefore also performed in patients who stopped treatment at ≤6 months (Table S10, Figure S2).

The suboptimal coverage of infliximab in the Swedish Prescribed Drug Register or National Patient Register means that, for example, some adalimumab treatments may seem to be first-line treatments while they were in fact second-line treatments. We therefore performed sensitivity analyses in which the study population was restricted to IBD centres with >70% coverage in SWIBREG (the overall coverage in included counties/centres turned out to be >85%) which can be assumed to result in accurate registration of TNFi administered as infusions (Table S3, Figure S1).

RESULTS

Between January 1987 and June 2016, we identified 126,708 patients with IBD of whom 5003 were Crohn's disease patients treated with first-line TNFi between 2006 and 2017 (Figure 1). Roughly half of the included patients were women, 70% of the patients had received their first Crohn's disease diagnosis after the year 2000 and mean the age at TNFi initiation was 37 years (Table 1). At start of TNFi treatment, 17% had isolated colitis without small bowel involvement, 25% had perianal disease and 25% had a history of bowel resection. Of the included patients, 2584 (52%) received adalimumab and 2391 (48%) infliximab (Table 1).

Twelve months after initiation of therapy, 7% of patients had undergone early bowel surgery (<12 months after TNFi initiation), 62% were still being treated with TNFi and 31% had stopped the treatment (Table 1). The early surgery group had a slightly higher proportion of patients with prior bowel resection compared with the whole cohort (31% vs. 25%). Age at TNFi start, phenotypes according to the Montreal and Paris classifications, time between Crohn's disease diagnosis and start of TNFi, and a history of bowel resection were similar in patients with drug survival of more or less than 12 months (Table 1). Patients with TNFi survival ≥12 months more often used immunomodulators at the start of TNFi than patients with shorter drug survival (61% vs. 39%; $p < 0.001$) (Table 1). The cumulative rates of abdominal surgery (including early surgery) in all Crohn's disease patients treated with TNFi regardless of TNFi retention during the observation period of 2006–2017 were 7% (1 year after initiation of treatment), 16% (3 years after), 22% (5 years after), 27% (7 years after), 32% (9 years after) and 35% (11 years after).

Bowel surgery in all patients

After excluding patients with early surgery, patients who discontinued the drug before 12 months had a significantly higher incidence of abdominal surgery than patients who continued treatment with TNFi for 12 months or more (HR 1.26, 95% CI 1.09–1.46; $p = 0.002$) (Figure 2). The greatest relative risk of surgery comparing TNFi < 12 months with ≥12 months was in the first year of follow-up, in patients over 60 years of age at Crohn's disease diagnosis, with

TABLE 1 Characteristics of Crohn's disease (CD) patients diagnosed in Sweden between 1964 and 2016 at disease onset and start of tumour necrosis factor inhibitors (TNFi). Values in *n* (%) unless otherwise stated

Variable	All CD[a]	Drug survival ≥12 months	Drug survival <12 months	Early surgery[b]
N	5003 (100%)	3107 (62%)	1526 (31%)	353 (7%)
Sex				
Female	2435 (49%)	1390 (45%)	870 (57%)	164 (46%)
Male	2568 (51%)	1717 (55%)	656 (43%)	189 (54%)
First IBD diagnosis				
2011–2016	1264 (25%)	821 (26%)	363 (24%)	76 (22%)
2006–2010	1269 (25%)	797 (26%)	389 (25%)	82 (23%)
2001–2005	979 (20%)	603 (19%)	292 (19%)	81 (23%)
1996–2000	476 (10%)	293 (9%)	150 (10%)	32 (9%)
1991–1995	318 (6%)	198 (6%)	93 (6%)	25 (7%)
1986–1990	270 (5%)	153 (5%)	89 (6%)	27 (8%)
1981–1985	196 (4%)	113 (4%)	68 (4%)	14 (4%)
1976–1980	125 (2%)	72 (2%)	41 (3%)	8 (2%)
1971–1975	90 (2%)	49 (2%)	34 (2%)	7 (2%)
1964–1970	16 (0%)	8 (0%)	7 (0%)	1 (0%)
Age at disease onset (years)				
Mean age (SD)	28.7 (14.2)	28.1 (13.9)	29.4 (14.3)	30.1 (15.6)
Median age (IQR)	25.2 (18.1–36.3)	24.7 (17.7–35.4)	25.8 (18.5–37.7)	25.8 (18.6–38.9)
<17	1054 (21%)	686 (22%)	304 (20%)	64 (18%)
17–40	2993 (60%)	1865 (60%)	908 (60%)	214 (61%)
41–60	783 (16%)	461 (15%)	260 (17%)	56 (16%)
>60	173 (3%)	95 (3%)	54 (4%)	19 (5%)
Age at TNFi start (years)				
Mean age (SD)	37.3 (16.0)	36.4 (15.8)	38.5 (16.2)	39.0 (16.0)
Median age (IQR)	35.5 (23.6–49.4)	34.3 (22.9–48.0)	36.8 (24.6–51.4)	37.4 (25.6–51.6)
<17	390 (8%)	256 (8%)	116 (8%)	18 (5%)
17–40	2648 (53%)	1701 (55%)	757 (50%)	188 (53%)
41–60	1471 (29%)	873 (28%)	487 (32%)	107 (30%)
>60	494 (10%)	277 (9%)	166 (11%)	40 (11%)
Montreal and Paris classification[c]				
L1/L3/LX	4110 (82%)	2535 (82%)	1250 (82%)	309 (88%)
L2	893 (18%)	572 (18%)	276 (18%)	44 (12%)
P	1230 (25%)	802 (26%)	341 (22%)	84 (24%)
Comorbidities				
PSC	67 (1%)	41 (1%)	22 (1%)	3 (1%)
History of bowel surgery	1255 (25%)	747 (24%)	391 (26%)	109 (31%)
Treatment				
Adalimumab as first biological	2584 (52%)	1616 (52%)	775 (51%)	183 (52%)
Infliximab as first biological	2391 (48%)	1469 (47%)	746 (49%)	169 (48%)
Golimumab as first biological	28 (1%)	22 (1%)	5 (0%)	1 (0%)
Switch at least once	448 (9%)	368 (12%)	58 (4%)	22 (6%)
Mean time in years from first diagnosis to start of TNFi (SD)	8.6 (9.6)	8.3 (9.4)	9.1 (10.0)	8.9 (9.6)

TABLE 1 (Continued)

Variable	All CD[a]	Drug survival ≥12 months	Drug survival <12 months	Early surgery[b]
Mean time in years from last bowel surgery to TNFi start (SD)	4.8 (4.3)	4.8 (4.4)	4.8 (4.3)	4.7 (4.2)
Immunomodulatory drugs during biological therapy	2671 (53%)	1888 (61%)	602 (39%)	177 (50%)

Abbreviations: IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis; SD, standard deviation.

[a]Seventeen patients died <12 months after the start of TNFi therapy and were only included in the all-CD patient group.

[b]Underwent bowel surgery <12 months after start of anti-TNF therapy and were therefore not included in main analysis comparing drug survival ≥ or <12 months.

[c]L, location of CD, according to the *last* used ICD codes *before* the start of biological treatment: L1, small bowel disease; L2, colon; L3, small bowel and colon. Patients with codes for an unspecified location are reported as LX. P, perianal disease, according to the corresponding ICD codes, if *ever* used, *before* the start of biological treatment. PSC, primary sclerosing cholangitis in CD, according to the corresponding ICD code, if *ever* used, *before* the start of biological treatment.

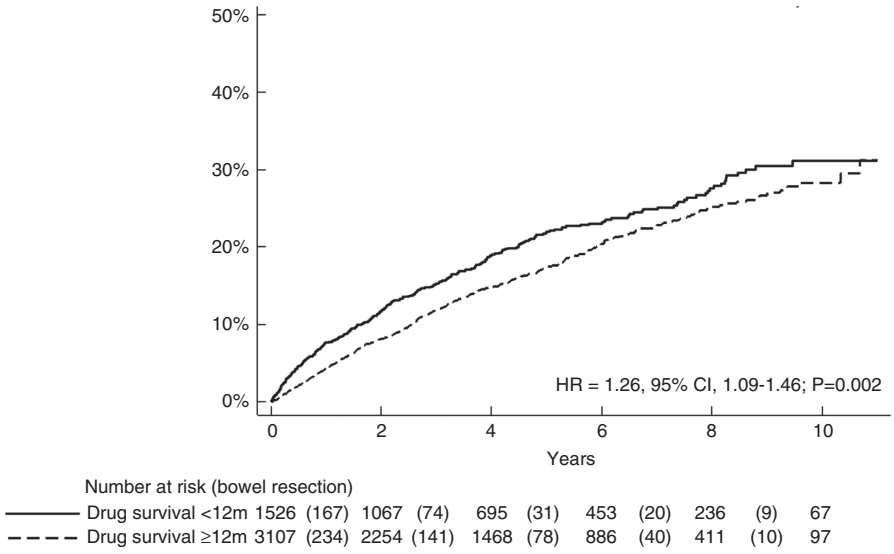

FIGURE 2 Time to bowel surgery by response assessment at 12 months (i.e. follow-up started 12 months after start of tumour necrosis factor inhibitor therapy in patients with drug survival ≥12 months and <12 months) (HR, hazard ratio)

TNFi monotherapy and during the latest calendar period (Table 2). The relative risk of surgery was similar in patients irrespective of disease duration before the start of TNFi and across the Montreal and Paris classifications (Table 2). The types of bowel surgery performed between 2006 and 2017 in this Crohn's disease population are reported in Table S4.

Bowel surgery in patients with prior resection

We identified 1255 Crohn's disease patients with a history of bowel surgery prior to TNFi initiation (mean 4.8 years prior to TNFi) and 3748 surgery-naïve patients. While patients with a record of bowel surgery were older at TNFi initiation, TNFi retention rates were similar in the two groups (Table S5 and Table S6). The cumulative risk of surgery during follow-up was significantly higher in patients with a history of surgery than in surgery-naïve patients, regardless of drug survival ($p < 0.001$) (Figure 3). TNFi drug survival <12 months was associated with an increased HR for bowel surgery in both surgery-naïve and experienced patients [HR = 1.22 (1.01–1.47) and HR = 1.25 (0.94–1.66), respectively] albeit not statistically significant in the latter group (Figure 4). The highest HR for surgery when stopping TNFi before 12 months was seen during the latest observation period (2014–2016) (Table S7 and Table S8).

Sensitivity analyses

We performed a sensitivity analysis restricted to 3206 patients registered in SWIBREG in IBD centres with close to complete coverage (a list of centres is given in Table S3 and patient characteristics in Table S9). In this study population infliximab use was slightly more frequent relative to adalimumab, whereas patient demography and early surgery rates were similar to the nationwide cohort (Tables S9 and 1). The HR for bowel surgery after the start of follow-up at 12 months was similar to the main results (HR 1.37, 95% CI 1.14–1.64; $p = 0.001$; Figure S1).

In another sensitivity analysis, in which early surgery was defined as <6 months of TNFi treatment (vs. ≥6 months), 940 (19%) patients had drug survival <6 months and the HR was similar to that

TABLE 2 Number of bowel surgeries, total person-years at risk and incident rates of intestinal surgery in patients with drug survival <12 months and ≥12 months as well as hazard ratios (HRs) between the groups

	N (%)		Time at risk (years)		No. of surgeries		Incidence rate (95% CI) per 1000 person-years		
Group	Drug survival <12 months	Drug survival ≥12 months	Drug survival <12 months	Drug survival ≥12 months	Drug survival <12 months	Drug survival ≥12 months	Drug survival <12 months	Drug survival ≥12 months	HR[a] (95% CI)
Overall	1526 (33%)	3107 (67%)	6492	13360	301	505	46 (41–52)	38 (35–41)	1.26 (1.09–1.46)
Follow-up (years)									
0–1	1526 (33%)	3107 (67%)	1426	2989	115	131	81 (66–95)	44 (36–51)	1.79 (1.38–2.32)
>1–2	1299 (32%)	2760 (68%)	1191	2504	52	103	44 (32–56)	41 (33–49)	1.10 (0.78–1.56)
>2–3	1067 (32%)	2252 (68%)	955	2027	40	82	42 (29–55)	40 (32–49)	1.04 (0.70–1.54)
>3–4	858 (32%)	1827 (68%)	781	1643	34	59	44 (29–58)	36 (27–45)	1.28 (0.82–1.99)
>4–5	695 (32%)	1467 (68%)	695	1467	24	40	35 (21–48)	27 (19–36)	1.34 (0.79–2.27)
>5	561 (32%)	1186 (68%)	1514	2869	36	90	24 (16–32)	31 (25–38)	0.77 (0.51–1.18)
Sex									
Male	656 (28%)	1717 (72%)	2817	7289	133	266	47 (39–55)	36 (32–41)	1.31 (1.06–1.63)
Female	870 (38%)	1390 (62%)	3675	6072	168	239	46 (39–53)	39 (34–44)	1.22 (0.99–1.49)
Age at IBD onset (years)									
<17	304 (31%)	686 (69%)	1296	2984	64	127	49 (37–61)	43 (35–50)	1.08 (0.77–1.51)
17–40	908 (33%)	1865 (67%)	3918	8062	173	283	44 (38–51)	35 (31–39)	1.30 (1.06–1.59)
41–60	260 (36%)	461 (64%)	1109	1968	49	81	44 (32–57)	41 (32–50)	1.05 (0.71–1.55)
>60	54 (36%)	95 (64%)	169	346	15	14	89 (44–134)	40 (19–62)	3.97 (1.38–11.43)
Age at TNFi start (years)									
<17	116 (31%)	256 (69%)	501	1053	17	33	34 (18–50)	31 (21–42)	1.17 (0.62–2.22)
17–40	757 (31%)	1701 (69%)	3208	7476	153	278	48 (40–55)	37 (33–42)	1.31 (1.07–1.61)
41–60	487 (36%)	873 (64%)	2147	3743	96	147	45 (36–54)	39 (33–46)	1.16 (0.89–1.52)
>60	166 (37%)	277 (63%)	635	1088	35	47	55 (37–73)	43 (31–56)	1.39 (0.86–2.24)
Year of TNFi start									
2014–2016	499 (33%)	1006 (67%)	797	1654	54	55	68 (50–86)	33 (24–42)	2.32 (1.53–3.52)
2011–2013	396 (29%)	950 (71%)	1579	3865	65	149	41 (31–51)	39 (32–45)	1.00 (0.73–1.37)
2009–2010	280 (33%)	580 (67%)	1574	3468	73	141	46 (36–57)	41 (34–47)	1.08 (0.78–1.48)
2006–2008	351 (38%)	571 (62%)	2542	4373	109	160	43 (35–51)	37 (31–42)	1.20 (0.91–1.57)
TNFi									
Adalimumab	775 (32%)	1616 (68%)	3087	6562	165	264	53 (45–62)	40 (35–45)	1.39 (1.12–1.71)

TABLE 2 (Continued)

Group	*N* (%)		Time at risk (years)		No. of surgeries		Incidence rate (95% CI) per 1000 person-years		
	Drug survival <12 months	Drug survival ≥12 months	Drug survival <12 months	Drug survival ≥12 months	Drug survival <12 months	Drug survival ≥12 months	Drug survival <12 months	Drug survival ≥12 months	HR[a] (95% CI)
Infliximab	746 (34%)	1469 (66%)	3392	6728	136	241	40 (33–47)	36 (31–40)	1.14 (0.90–1.42)
Golimumab	5 (19%)	22 (81%)	13	70	0	0	0	0	–
Time from diagnosis to TNFi start (years)									
≤1	322 (31%)	722 (69%)	1208	2795	60	85	50 (37–62)	30 (24–37)	1.44 (0.96–2.18)
2–5	426 (32%)	891 (68%)	1838	3926	73	141	40 (31–49)	36 (30–42)	1.15 (0.84–1.57)
6–10	258 (32%)	545 (68%)	1135	2482	56	104	49 (36–62)	42 (34–50)	1.12 (0.76–1.66)
>10	520 (35%)	949 (65%)	2311	4156	112	175	48 (39–57)	42 (36–48)	1.25 (0.96–1.62)
Immunomodulatory drugs during biological therapy									
Yes	602 (24%)	1888 (76%)	2756	8487	116	347	42 (34–50)	41 (37–45)	1.08 (0.87–1.36)
No	924 (43%)	1219 (57%)	3736	4874	185	158	50 (42–57)	32 (27–37)	1.58 (1.25–2.00)
Montreal and Paris classification[b]									
L1/L3/LX	1250 (33%)	2535 (67%)	5254	10758	258	432	49 (43–55)	40 (36–44)	1.27 (1.08–1.50)
L2	276 (33%)	572 (67%)	1237	2602	43	73	35 (24–45)	28 (22–34)	1.20 (0.77–1.88)
P	341 (30%)	802 (70%)	1485	3440	84	149	57 (44–69)	43 (36–50)	1.49 (1.10–2.03)
History of bowel surgery									
Yes	391 (34%)	747 (66%)	1666	3326	108	159	65 (53–77)	48 (40–55)	1.25 (0.94–1.66)
No	1135 (32%)	2360 (68%)	4826	10034	193	346	40 (34–46)	34 (31–38)	1.22 (1.01–1.47)

Abbreviations: IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis; SD, standard deviation.

[a]Adjusted for age at start of TNFi and stratified by birth year and sex.

[b]L, location of Crohn's disease, according to the *last* used ICD codes *before* the start of biological treatment. B is behaviour and P is perianal disease according to the corresponding ICD codes, if *ever* used, *before* the start of biological treatment.

(Continues)

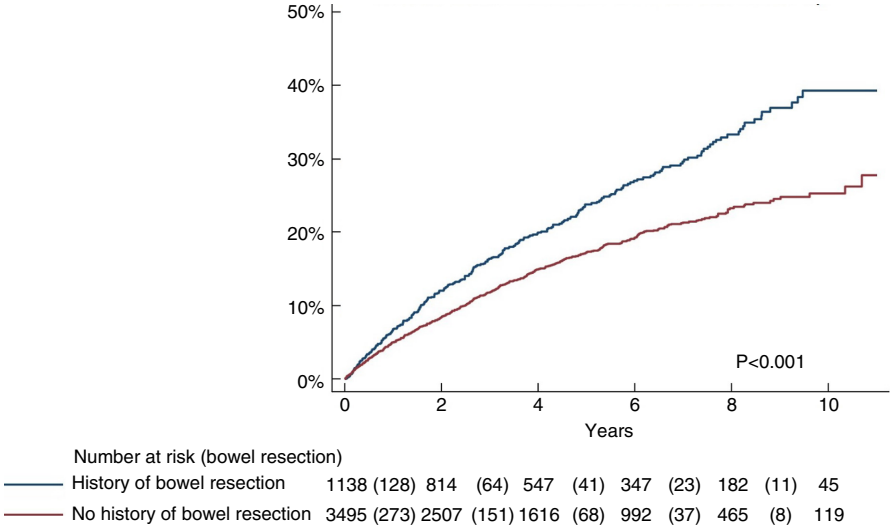

FIGURE 3 Time to bowel surgery from 12 months after the start of tumour necrosis factor inhibitor therapy in patients stratified by history of abdominal surgery regardless of drug survival

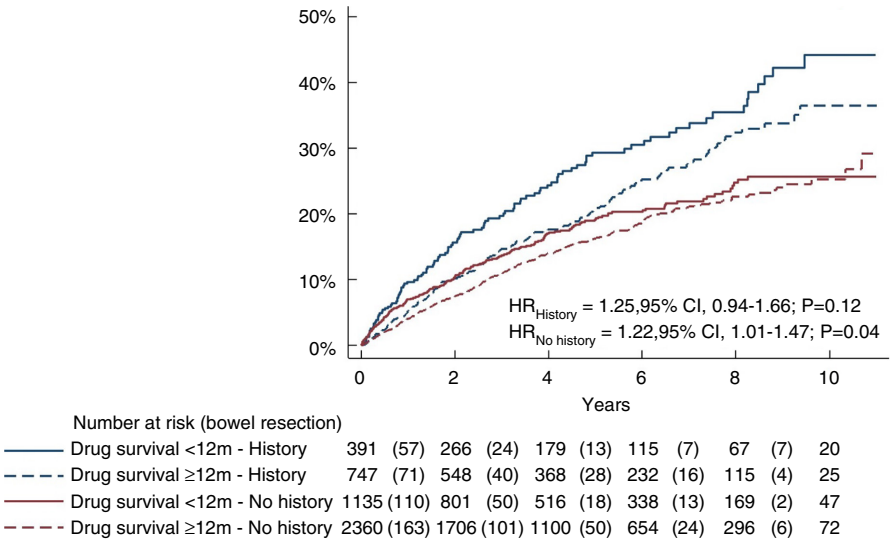

FIGURE 4 Time to intestinal surgery by response assessment at 12 months (i.e. follow-up started 12 months after start of tumour necrosis factor inhibitor therapy) in patients stratified by history of bowel surgery and drug survival ≥12 months versus <12 months (HR, hazard ratio)

in the main analysis (HR 1.34, 95% CI 1.15–1.55; $p < 0.001$; Table S10, Figure S2).

DISCUSSION

Main findings

In this register-based study, we used real-world data to investigate the association of TNFi drug survival more or less than 12 months with the risk of bowel surgery in Crohn's disease patients. Surgery rates were significantly higher among patients who discontinued TNFi before 12 months compared with patients with drug survival ≥12 months.

Findings compared with earlier studies

We have previously published the only report on first ever bowel surgery rates in Crohn's disease patients on maintenance TNFi ≥12 months compared with patients who stopped treatment before 12 months [20]. The drug survival rates in our previous report and the current one were almost identical at 12 months (62% in the present cohort and 65% in the earlier report) [20]. In contrast to the earlier published cohort of resection-naïve patients, in which TNFi <12 months was not significantly associated with an increased surgery rate (HR 1.17, 95% CI 0.88–1.56), the current larger and more recent study, including both surgery-naïve patients and patients with prior bowel surgery, demonstrated statistically significant higher rates of surgery for TNFi drug survival <12 months compared with ≥12 months (HR 1.26, 95% CI 1.08–1.46), an association which was even more pronounced in the sensitivity analyses. The somewhat higher HR and tighter confidence intervals in the latter cohort is logical, since a larger number of patients were included in the current study with data retrieved from the Swedish National Patient Register and the Swedish Prescribed Drug Register, but importantly also from the Swedish national quality register SWIBREG. Moreover, the increased use of TNFi in more recent years further improved our statistical power.

Considering the very similar point estimates and the overlapping CIs between the two studies, increased statistical power is likely be the most important reason for this. Since the publication of our previous study, we have also assessed how well the national registers capture TNFi use, which has resulted in an improved algorithm for capturing infliximab [30]. The treat-to-target strategy with dose optimization of TNFi by therapeutic drug monitoring, which is used in clinical routines in some Swedish centres, might also result in improved clinical efficacy in patients with drug survival >12 months compared with <12 months. However, treatment strategies or dose escalation cannot be caught in this study due to the lack of such granularity in the data.

Moreover, the current study found higher rates of drug survival ≥12 months among users of immunomodulators than among nonusers, an observation that may reflect the results from earlier studies demonstrating the higher clinical efficacy of combining infliximab with thiopurines [33,34]. In our previous smaller study, HRs for bowel surgery were similar across strata of TNFi treatment with or without immunomodulators. In the current study, drug survival <12 months was not a risk factor for bowel surgery within the group of TNFi-treated patients exposed to immunomodulators, whereas among patients only exposed to TNFi monotherapy it was (Table 2).

As expected, the cumulative rates of first bowel surgery during follow-up were significantly higher in the current cohort of patients with at least one previous abdominal resection compared with the surgery-naïve patient population (42% vs. 21% 9 years after introduction of TNFi; $p < 0.001$). Previous reports have shown that inflammatory recurrence can be observed within 2 years of ileocaecal resection in up to 80% of Crohn's disease patients, and after first resection, repeat surgery rates of 11%–32% have been reported within 5 years and 20%–44% within 10 years, which is in keeping with our results [35–38]. However, the impact of prior surgery per se on further resections is difficult to assess in the current study since this group was older and exhibited longer disease duration than the surgery-naïve patients. Moreover, the indication for TNFi after surgery is prophylactic to prevent recurrent resection, in distinction to treating surgery-naïve patients with TNFi, which may introduce a bias in any comparison between the patient groups.

While we found no significantly increased risk of bowel resections in surgery-experienced patients with drug survival <12 months, the efficacy of postoperative TNFi prophylaxis with regards to endoscopic recurrence in patients undergoing ileocaecal resection has been demonstrated in several studies [39–41]. The PREVENT study showed a protective role of infliximab in endoscopic but not clinical recurrence, whereas a significant effect on repeat surgery could not be seen within the 76-week follow-up [39]. The POCER study investigated the role of immunosuppressants and adalimumab as postoperative prophylaxis. The authors demonstrated superior efficacy of adalimumab compared with thiopurines in preventing endoscopic recurrence within 6 months, but no patients in the study underwent repeat surgery during the observation period [40,41]. In addition to these two pivotal RCTs, a meta-analysis including eight additional small studies of medical prevention of postoperative recurrence suggested that TNFi was superior to both immunosuppressants and mesalamine (312 patients) [42]. However, to our knowledge no study has demonstrated a significant effect of TNFi treatment on repeat bowel resections. Moreover, in contrast to previous trials of highly selected study populations followed for a relatively short time, our study reflects real-life use of TNFi in Crohn's disease patients with prior bowel surgery and includes 1255 patients, compared with the next largest study, the PREVENT trial, which included 297 patients [39]. Finally, when comparing the cumulative rates of abdominal surgery in patients without prior surgery and who continued TNFi for more than 12 months with the resection rates of all TNFi-treated patients regardless of TNFi retention, the following question arises: is surgery prevented in surgery-naïve patients or only delayed in a substantial proportion of these patients? Such postponing of surgery may of course be of value in many cases, as long as simultaneous slow deterioration is avoided as this may affect the results from surgery when needed [43].

Limitations

We were unable to compare degree of disease activity or symptom severity across exposure groups since such variables are not at all available in the Swedish National Patient Register and are currently poorly covered in SWIBREG. The limited nationwide coverage of infliximab in the Swedish National Patient Register and Prescribed Drug Register mainly concerns the identification of second-line adalimumab patients wrongly categorized as first-line treatment with adalimumab since prior infliximab infusions might be missed. Similarly, adalimumab-treated patients who have switched to infliximab might have been misclassified in the nationwide sample as stopping biologicals. There is also a risk that the few patients treated with biologicals before the start of SWIBREG and the Prescribed Drug Register in 2005 have been mistakenly identified as first-time users. However, while infliximab use had suboptimal coverage nationwide in the National Patient Register and Prescribed Drug Register, this limitation was compensated by the supplemental SWIBREG data from IBD centres with close to complete coverage (Table S3). The fact that patients from the high-coverage hospitals had very similar patient characteristics and results to the national cohort is reassuring. Additional limitations are that the data set does not allow for more refined analysis, such as the use of therapeutic drug monitoring and optimization of TNFi therapy. Finally, although the coverage of prescribed TNFi (adalimumab) is complete, we only have information on the syringes patients have obtained at the pharmacy and not how many syringes any given patient actually administered.

Strengths

Through the National Patient Register, we were able to identify all Crohn's disease patients without being limited to restrictive

inclusion criteria of randomized trials or the selected patient population in highly specialized university or tertiary referral clinics. Thus, generalizability was optimized [22]. Moreover, the size of the study has allowed for more accurate risk estimates, and the long observation period of 11 years made it possible to estimate the long-term risk of surgery. In Sweden, clinical data have been collected prospectively through the national registers based on routine clinical care with nearly complete coverage for most parameters, and the validity of the main variables has been shown to be excellent [22,24,31].

CONCLUSION

Treatment with TNFi for less than 12 months was associated with more frequent bowel surgery in Crohn's disease patients compared with patients who were treated with TNFi for 12 months or more.

CONFLICT OF INTEREST

ME has received honoraria for lectures and consultancy from AbbVie, Merck (MSD), Takeda, Ferring, Orion Pharma, Otsuka, Tillotts, ITH, Novartis, Pfizer and Janssen, and received research funding from AbbVie and MSD. JKS has served as an external consultant to Parexel and Janssen. OO has been Principal Investigator on projects at Karolinska Institutet partly financed by investigator-initiated grants from Janssen and Ferring, and also reports a grant from Pfizer in the context of a national safety monitoring program. None of those studies have any relation to the present study. Karolinska Institutet also has received fees for OO's lectures and participation on advisory boards from Janssen, Ferring, Takeda and Pfizer regarding topics not related to the present study. PM has received honoraria for lectures from Ferring, AbbVie and Takeda and has served as an external consultant to Janssen and AbbVie and has been Principal Investigator for a research project partly funded by Takeda. CH has received honoraria for lectures from Ferring, AbbVie, Janssen and Takeda and has served as an external consultant to Pfizer. ÅHE has worked on projects at Karolinska Institutet and SWIBREG partly financed by grants from Ferring and Jansen.

AUTHOR CONTRIBUTIONS

Guarantors of the article: JKS and ME. Author contributions: JKS had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: ME, AE, OO, PM. Acquisition of data: OO. Analysis and interpretation of data: all authors. First draft of manuscript: ME, PM. Critical revision of the manuscript for important intellectual content: all authors. Study supervision: OO.

ETHICAL APPROVAL

The study was approved by the regional ethics committee in Stockholm (Dnr 2007/785-31/5, 2011/1509-32, 2014/1287-31/4, 2015/0004-31, 2016/192-31/2). Since this was a strictly register-based study, individual informed consent was not required.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by the Swedish National Patient Register, Swedish Prescribed Drug Register and SWIBREG by permission. Data can be obtained with permission of these registers.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX A

STROBE statement

	Item no.	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **OK**
INTRODUCTION		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **OK**
Objectives	3	State specific objectives, including any prespecified hypotheses **OK**
METHODS		
Study design	4	Present key elements of study design early in the paper **OK**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **OK**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **OK**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **OK**
Data sources/ measurement	8[a]	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **OK**
Bias	9	Describe any efforts to address potential sources of bias **OK**
Study size	10	Explain how the study size was arrived at **NA**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **OK**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **OK**
RESULTS		
Participants	13[a]	(*a*) Report numbers of individuals at each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **OK**
		(*b*) Give reasons for nonparticipation at each stage **OK**
		(*c*) Consider use of a flow diagram **OK**
Descriptive data	14[a]	(*a*) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **OK**
		(*b*) Indicate number of participants with missing data for each variable of interest **NA**
		(*c*) Summarize follow-up time (e.g. average and total amount) **OK**
Outcome data	15[a]	Report numbers of outcome events or summary measures over time **OK**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included **OK**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done, e.g. analyses of subgroups and interactions, and sensitivity analyses **OK**

APPENDIX A (Continued)

	Item no.	Recommendation
DISCUSSION		
Key results	18	Summarize key results with reference to study objectives **OK**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **OK**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **OK**
Generalizability	21	Discuss the generalisability (external validity) of the study results **OK**
OTHER INFORMATION		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **OK**

[a] Give information separately for exposed and unexposed groups.