BMJ Open Gastroenterology

Impact of antitumour necrosis factor therapy on surgery in inflammatory bowel disease: a population-based study

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To cite: Hawthorne AB, Arms-Williams B, Cannings-John R, *et al*. Impact of antitumour necrosis factor therapy on surgery in inflammatory bowel disease: a population-based study. *BMJ Open Gastroenterol* 2024;**11**:e001373. doi:10.1136/bmjgast-2024-001373

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjgast-2024-001373).

Received 5 February 2024
Accepted 2 May 2024

Check for updates

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ABSTRACT

Objective It is unclear whether widespread use of biologics is reducing inflammatory bowel disease (IBD) surgical resection rates. We designed a population-based study evaluating the impact of early antitumour necrosis factor (TNF) on surgical resection rates up to 5 years from diagnosis.

Design We evaluated all patients with IBD diagnosed in Cardiff, Wales 2005–2016. The primary measure was the impact of early (within 1 year of diagnosis) sustained (at least 3 months) anti-TNF compared with no therapy on surgical resection rates. Baseline factors were used to balance groups by propensity scores, with inverse probability of treatment weighting (IPTW) methodology and removing immortal time bias. Crohn's disease (CD) and ulcerative colitis (UC) with IBD unclassified (IBD-U) (excluding those with proctitis) were analysed.

Results 1250 patients were studied. For CD, early sustained anti-TNF therapy was associated with a reduced likelihood of resection compared with no treatment (IPTW HR 0.29 (95% CI 0.13 to 0.65), p=0.003). In UC including IBD-U (excluding proctitis), there was an increase in the risk of colectomy for the early sustained anti-TNF group compared with no treatment (IPTW HR 4.6 (95% CI 1.9 to 10), p=0.001).

Conclusions Early sustained use of anti-TNF therapy is associated with reduced surgical resection rates in CD, but not in UC where there was a paradoxical increased surgery rate. This was because baseline clinical factors were less predictive of colectomy than anti-TNF usage. These data support the use of early introduction of anti-TNF therapy in CD whereas benefit in UC cannot be assessed by this methodology.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anti-TNF therapy is of proven effectiveness in Crohn's disease and ulcerative colitis (UC) in controlled trials, but there has been conflicting evidence about whether antitumour necrosis factor (TNF) can reduce the need for surgical resection in normal clinical practice.

WHAT THIS STUDY ADDS

⇒ Observational studies comparing early anti-TNF therapy against no use of anti-TNF can demonstrate reduction in surgical resection in Crohn's disease when using propensity scores based on baseline clinical factors. In UC, however, baseline factors are insufficient to balance treated versus not-treated groups as the use of anti-TNF therapy is the most significant predictor of colectomy and baseline factors are less strongly associated with colectomy risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Other design methodology should be used to assess real-world effects of anti-TNF in UC, such as comparing groups tolerating or intolerant of the treatment.

INTRODUCTION

Medical therapy for inflammatory bowel disease (IBD) has changed significantly over the past four decades with increasing use of anti-TNF therapy since the early 2000s.[1] Rates of surgery have fallen during this period for both Crohn's disease (CD)[2 3] and for ulcerative colitis (UC) in many studies,[4–6] although not all report this trend.[7] There is a strong evidence from prospective controlled clinical trials of efficacy for anti-TNF therapy in CD and UC,[8] similarly early therapy after diagnosis is more effective than later treatment in CD.[9 10] For UC, it is unclear whether earlier therapy is more beneficial.[11]

Controlled clinical trials of biologics are generally not powered or have insufficient follow-up duration to evaluate surgical endpoints, and patients at high risk of surgery are generally excluded from these studies. As agreed recently in the Standard Protocol Items: Recommendations for Interventional Trials initiative, from the International Organisation for the study of IBD, the ultimate therapeutic goal of IBD treatment is to reduce the disease impact on patients' lives.[12]

Surgical resection is one of the more objective measures of disease impact and can be evaluated in observational studies. A recent meta-analysis of trials and case series in CD and UC showed that early biological therapy is associated with lower surgery rates in CD, but higher rates in UC.[13] Other observational studies of CD have also shown reduced surgery rates with anti-TNF therapy,[14 15] but others have not shown reduction,[16] particularly when propensity scores (PS) or other methods are used to match treated and non-treated groups.[1 17] In UC, an observational study using matched treated and non-treated groups has shown reduction in colectomy rates,[1] but other larger administrative database studies showing conflicting results for UC.[15 18] Observational studies vary considerably in the population studied (large administrative databases, case series or population-based cohorts), in the granularity of clinical data available and in the statistical methodology used to correct for differences in groups studied.

We, therefore, designed a population-based IBD cohort study, with at least 5 years follow-up after diagnosis, collecting detailed phenotypic and treatment data, to evaluate the impact of early anti-TNF therapy on the rate of surgical resection for CD and UC, with matching of patients in the treated and non-treated groups using PSs, to avoid confounding by indication. We hypothesised that early anti-TNF therapy would reduce surgical resection rates in CD and UC.

MATERIALS AND METHODS

Design and participants

The study is a retrospective population-based cohort study of all patients with IBD diagnosed within the 12 years from 2005 to 2016 while living in Cardiff Local Authority area and the nearby towns of Barry, Penarth and Dinas Powys (population 436 000), in the catchment area of the two Cardiff hospitals. Adults and children were included if they had documented diagnosis of CD, IBD Unclassified (IBD-U) or UC (ICD11 code K50, K51, K52.3) with one or more follow-up events after diagnosis.

Data collection

Using the methodology of previous population-based Cardiff IBD studies,[19] patients with IBD were identified from electronic clinical records, pathology, pharmacy and endoscopy databases, and phenotype data at diagnosis collected. This included Montreal classification,[20] in-patient admission, smoking, corticosteroids use and serum albumin, C reactive protein (CRP) and haemoglobin (Hb) at diagnosis or within 3 months before or after diagnosis (but excluding results if corticosteroids or other treatment given during the intervening period).

Medication use and surgical definitions

The use of anti-TNF therapy (infliximab or adalimumab) was defined as never use, ever use and early sustained use (started within 1 year of diagnosis and continued for 3 months or more) and usage after surgical resection was excluded from analysis. Surgery for CD was recorded as resection (used here to mean any bowel resection, stricturoplasty or defunctioning stoma formation without resection) and non-resection surgery (examination under anaesthetic, insertion of setons, drainage of abscess and stoma closure). Temporary stoma formation was defined as closure within 1 year and permanent stoma for longer than 1 year.

Outcomes

The primary outcome was the impact of anti-TNF therapy on the time to first resection surgery up to 5 years from diagnosis for patients receiving early sustained therapy versus never use. A follow-up was censored at the earliest of first resection surgery, last clinical contact or death. Secondary outcomes included a comparison of early therapy (including sustained and those not necessarily sustained) versus non-early use on time to resection surgery, and the UC group without including IBD-U patients.

Surgical outcomes occurring on the date of diagnosis were excluded from the analysis. For the never used therapy group, time zero was the date of diagnosis and for those receiving therapy (ever or early sustained use), time zero was the therapy start date or 3 months after start, respectively.

Outcomes were assessed for CD and UC separately. The UC and IBD-U group were combined as numbers of IBD-U were too low to analyse separately and all those with isolated proctitis were removed, as anti-TNF use and colectomy rates were likely to be low (3.9% colectomy rate at the end of follow-up in proctitis compared with 13.9% in pancolitis in a Swiss IBD cohort study).[5]

Immortal time bias

Duration in the study was from time zero to either outcome or censored date. If treated after resection, the time from diagnosis to resection was attributed to the untreated group. To address immortal time bias,[21] the time period between diagnosis and anti-TNF treatment was attributed to the untreated group (online supplemental figure 1). For the early sustained treated group, the first 3 months from treatment start was also attributed to the untreated group.

Statistics

Patient's data at diagnosis were characterised using summary statistics (frequency, percentage, median alongside IQR and reporting results to two significant digits). Baseline laboratory measures were defined as abnormal as follows: CRP >50 mg/L, albumin ≤30 g/L and anaemia (female: Hb <115 g/L or >165 g/L; male: Hb <130 g/L or >180 g/L. Categorical variables were assessed by Pearson χ^2 test; non-parametric data were compared using Kruskal-Wallis test. The association of drug use with baseline factors was examined using univariable (unadjusted) logistic regression models with estimates presented as OR alongside 95% CI and p value. Differences in resection

surgery stratified by treatment use were shown using Kaplan-Meier survival analysis, and unadjusted HR alongside 95% CI and p value.

Inverse probability of treatment weighting (IPTW) based on the PS was used so that the distribution of confounders was similar in both the treated and untreated groups. The PS is the probability of treatment assignment conditional on observed baseline covariates (age, gender, diagnosed in hospital, date of diagnosis, early corticosteroid exposure and smoking, disease behaviour/location, abnormal blood results at diagnosis). An average treatment effect (ATE) at the population level (the difference between average outcome when all exposed and average outcome when nobody is) was calculated by a Cox proportional hazards model. The ATEs are presented as HRs alongside 95% CI and p value. To avoid a complete-case analysis (reducing statistical power), we handled partially observed variables by imputing five datasets using the multiple imputation chained equations approach, using all variables and the outcome in the imputation model.[22] Generation of the PS was via a logistic regression model and a Cox proportional hazards model incorporating IPTW to estimate the impact of treatment (HR) in each imputed dataset. Rubin's rules were used to combine estimates to obtain an overall estimate; shown to be the preferred strategy in terms of bias reduction.[22]

All analyses were performed by using Stata V.16 (StataCorp) and R Studio.

RESULTS

In 2011, the population of the study area was 435 788. From 2005 to 2016, 419 patients were diagnosed with CD, 754 with UC and 77 with IBD-U. The total duration of follow-up for the cohort was 11 246 person-years (mean duration 9.0 years) and 88% (n=1106) at least 5 years. Clinical features are shown in table 1.

Surgery

Crohn's disease

Resection surgery was performed in CD in 118 (28.2%) within 5 years. The most common operation was ileocaecal resection in 110 (26.3%) patients, followed by subtotal colectomy in 17 (4.1%). Non-resection surgery was performed in 57 (13.6%) of patients within 5 years of diagnosis, usually examination under anaesthetic, perianal abscess drainage or ileostomy closure. There was no increase in resection rates by diagnosis era during the 12-year period (table 2). Clinical factors at diagnosis affect resection surgery in-patient status, low serum albumin,and disease location and behaviour (table 2). Resection rates were higher in <16 compared with 17–40 and >40 years at diagnosis.

UC and IBD-U

Colectomy was performed in 50 (6.6%) of UC and 5 (6.5%) of IBD-U patients within 5 years of diagnosis. Of the subset of 237 UC patients with proctitis at diagnosis, 6 (2.5%) had colectomy within 5 years. UC colectomy rates did not alter significantly during the 12-year study period. Risk factors at diagnosis associated with colectomy for UC included young age, (much higher likelihood of colectomy in <16 years compared with older patients); being an in-patient, (although only 26/102 (25%) UC patients were in-patients at diagnosis); early corticosteroid use, high CRP, low albumin and extensive disease (table 2).

Anti-TNF use and resection surgery

Crohn's disease

168/419 (40%) patients with CD received anti-TNF therapy and infliximab (21%) and adalimumab (19%) were the first biologic used. (Four patients received vedolizumab, but none ustekinumab as the first biologic—not discussed further here). The use of anti-TNF therapy increased significantly with diagnosis era (p=0.001). At 5 years from diagnosis, 23% had received anti-TNF therapy (diagnosis 2005–2008), 30% (2009–2012) and 41% (2013–2016), p<0.001 (online supplemental figure 2). Similarly, there was a significant increase in early sustained use (within 1 year of diagnosis, continued for at least 3 months) with diagnosis era, (from 6.8% (diagnosis 2005–2008) to 23% (2013–2016), p=0.0028. Patients given early sustained anti-TNF therapy were younger at diagnosis (p<0.001), more likely to use corticosteroids within the first 3 months of diagnosis (p<0.001), more likely to have colonic or ileocolonic location than terminal ileal disease, p=0.0004 and less likely to have stricturing behaviour (p=0.024).

A total of 81/90 (90%) received their infliximab prior to resection surgery, as did 57/78 (73%) receiving adalimumab. For those receiving anti-TNF therapy before resection, infliximab was started at median 12 months (IQR 3.9–44), and adalimumab started at median 30 months (IQR 8.3–56) from diagnosis. The duration of first biologic was 22 months (IQR 12–51).

Of the 138 patients with CD using anti-TNF prior to resection, 57 (41%) were early sustained users (those who started anti-TNF within the first year of diagnosis and continued for at least 3 months), and 81 (59%) started anti-TNF 1 year or more after diagnosis (figure 1A). In an unadjusted analysis, there was no significant difference in likelihood of resection between early sustained users and non-users of anti-TNF, (HR 0.51, 95% CI: 0.25 to 1.0, p=0.06) (table 3). When a propensity model with correction for immortal time bias was used, there was evidence of a benefit from the early sustained use of anti-TNF (compared with never use) on the risk of resection (IPTW model: HR 0.29 (95% CI 0.13 to 0.65), p=0.003) (table 3). The survival curve shows that the most obvious difference between early use and non-use is in the first 2 years after diagnosis (figure 1B). The probability of avoiding resection after 1 year was 95% in the early use vs 83% in the non-use group, at 2 years: 88% vs 79%, respectively, and at 5 years: 85% vs 74%). There was a numeric difference (not reaching significance) difference between early sustained and use that was not early sustained (table 3, figure 1C).

Table 1 Clinical features at diagnosis

	Diagnosis		
	CD N=419 (33.5)	**IBD-U N=77 (6.2)**	**UC N=754 (60.3)**
Age (years) median (IQR)	30 (22–49)	32 (23–49)	40 (27–56)
Montreal age			
16 years or younger	52 (12.4)	9 (11.7)	36 (4.8)
17–40 years	220 (52.5)	43 (55.8)	352 (46.7)
Over 40 years	147 (35.1)	25 (32.5)	366 (48.5)
Sex: male	206 (49.2)	37 (48.1)	404 (53.6)
Diagnosed in hospital	87 (20.8)	8 (10.4)	111 (14.7)
Diagnosis era (number (%) within era)			
2005–2008	138 (35.1)	21 (5.3)	234 (59.5)
2009–2012	139 (32.5)	27 (6.3)	262 (61.2)
2013–2016	142 (33.1)	29 (6.8)	258 (60.1)
Mode of diagnosis			
Endoscopy histology	263 (62.8)	75 (97.4)	742 (98.4)
Radiology	113 (27.0)	0 (0.0)	1 (0.3)
Surgery	34 (8.1)	2 (2.6)	5 (0.7)
Capsule endoscopy	5 (1.2)	0 (0.0)	0 (0.0)
Missing	4 (1.0)	0 (0.0)	5 (0.7)
Smoking status at diagnosis			
Never smoked	210 (50.1)	40 (51.9)	364 (48.3)
Ex-smoker	60 (14.3)	20 (26.0)	239 (31.7)
Current smoker	122 (29.1)	9 (11.7)	78 (10.3)
Missing	27 (6.4)	8 (10.4)	73 (9.7)
Early use of steroids*	230 (54.9)	34 (44.2)	293 (38.9)
Length of follow-up (years) median (IQR)	9.4 (5.7–12.4)	9.0 (5.5–11.7)	8.9 (5.7–12.1)
Laboratory results†			
CRP (mg/L)	n=344	n=54	n=509
Median (IQR)	28 (9–94.5)	8 (2–38)	8 (3–27)
CRP>50	129 (37.5)	12 (22.2)	82 (16.1)
Missing	75	23	245
Haemoglobin (Hb) (g/L)	n=362	n=62	n=561
Median (IQR)	125 (111–137)	131 (122–140)	132 (121–143)
Anaemia (Hb <115 (female) or <130 (male))	165 (45.6)	14 (22.6)	163 (29.1)
Missing	57	15	193
Albumin (g/L)	n=351	n=58	n=542
Median (IQR)	36 (32–40)	38 (33 –43)	38.5 (35–42)
Albumin≤30	77 (21.9)	8 (13.8)	63 (11.6)
Missing	68	19	212
Involvement of gut regions			
Perianal	48 (11.6)	0 (0.0)	1 (5.9)
Rectal	205 (48.9)	72 (93.5)	751 (100)
Left colon	236 (56.3)	64 (84.2)	512 (68.4)
Right colon	218 (52.0)	39 (51.3)	211 (28.4)
Terminal ileal	239 (57.5)	0 (0.0)	0 (0.0)

Continued

Table 1 Continued

	Diagnosis				
	CD N=419 (33.5)			IBD-U N=77 (6.2)	UC N=754 (60.3)
Small bowel	31 (7.5)			0 (0.0)	0 (0.0)
Stomach duodenal or Oesophageal	11 (2.6)			0 (0.0)	0 (0.0)
Orofacial disease	6 (1.4)			0 (0.0)	0 (0.0)
Montreal extent (UC or IBD-U)					
Proctitis (E1)				11 (14.3)	237 (31.4)
Left sided (E2)				28 (36.4)	303 (40.2)
Extensive (E3)				38 (49.4)	214 (28.4)
Montreal location (CD)		**Montreal modifier**			
Terminal ileum (L1)	122 (29.1)	L1L4	12 (2.9)		
		L1p	8 (1.9)		
Colonic (L2)	173 (41.3)	L2L4	4 (1)		
		L2p	28 (6.7)		
Ileocolonic (L3)	117 (27.9)	L3L4	17 (3.5)		
		L3p	10 (2.4)		
Isolated upper GI (L4)	5 (1.2)	Total L4	38 (9.1)		
Isolated perianal (p)	2 (0.5)	Total p	48 (11.5)		
Montreal behaviour (CD)					
Inflammatory (B1)	314 (74.9)				
Stricturing (B2)	69 (16.5)				
Penetrating (B3)	31 (7.4)				
Missing	5 (1.2)				

All results are number (%) unless otherwise stated.
*Steroid use within 3 months of diagnosis.
†At diagnosis or within 3 months before or after (excluding those treated with steroids or immunosuppression during the intervening period).
CD, Crohn's disease; CRP, C reactive protein; GI, Gastro-intestinal; IBD-U, inflammatory bowel disease-unclassified; UC, ulcerative colitis.

In a sensitivity analysis early (within 1 year of diagnosis) versus late anti-TNF was assessed. Only three patients using early anti-TNF therapy stopped treatment before 3 months so 60/138 (43%) of patients with CD were early users and 78 (57%) late users, and the propensity model similarly demonstrated a significant reduction in resection compared with no anti-TNF (HR=0.35 (95% CI 0.16 to 0.78), p=0.012) but no significant difference between early and late use of anti-TNF (HR=0.55 (95% CI 0.20 to 1.5), p=0.25.

UC and IBD-U

In 39 UC patients, anti-TNF use was unclear due to missing data and these were excluded; therefore, 715 were available for analysis. Of these 106 (15%) UC patients using anti-TNF therapy within 5 years from diagnosis, (9% infliximab, 5% adalimumab used as first biologic). No UC or IBD-U patients received vedolizumab or ustekinumab as the first biological therapy. Anti-TNF therapy was started in UC patients at a median 38.9 (IQR 10.5–73.1) months after diagnosis, and median duration 6.5 (IQR 2.0–19.0) months. For IBD-U patients the start of anti-TNF was a median 28.7 (IQR 6.4–82.2) months after diagnosis, with median duration 6.0 (4.8–16.3) months. Of UC proctitis patients 15/225 (6.7%) used anti-TNF within 5 years.

IBD-U numbers were relatively small and are pooled with UC, and all those with disease limited to the rectum at diagnosis were excluded as risk of colectomy was low (6/237 (2.5%). This grouping (UC and IBD-U excluding proctitis) was used for the primary outcome analyses. In this group of 555 patients with anti-TNF data, anti-TNF use increased significantly by diagnosis era rising from 14 (7.8%) for 2005–2008, to 47 (27%) for 2013–2016, p<0.001 (online supplemental figure 2). Similarly, there was an increase in early sustained use from 0.53% in 2005–2008 to 11.5% in 2013–2016 (p=0.001). UC and IBD-U (excluding proctitis) patients given anti-TNF at any time after diagnosis, as well as early sustained anti-TNF, were younger (p<0.001), and more likely to have used corticosteroids within 3 months of diagnosis, compared with those never receiving anti-TNF. Disease extent at diagnosis was not a predictor.

Table 2 Risk factors for time to resection surgery or colectomy for CD and UC/IBD-U combined excluding those with proctitis

	Crohn's disease		UC and IBD-U (excluding proctitis)	
	Unadjusted HR (95% CI)	P value	Unadjusted HR (95% CI)	P value
Anti-TNF therapy ever (ref=never)	0.59 (0.39 to 0.87)	0.008	2.5 (1.59 to 3.9)	<0.001
Age at diagnosis (years)	0.99 (0.98 to 0.9997)	0.044	0.98 (0.97 to 0.99)	0.001
Sex: (ref=female)				
Male	0.83 (0.59 to 1.17)	0.28	1.5 (0.94 to 2.2)	0.10
Smoking status at diagnosis (ref=never)				
Ex-smoker	1.1 (0.67 to 1.9)	0.63	0.72 (0.43 to 1.2)	0.21
Current smoker	1.3 (0.91 to 2.0)	0.13	0.58 (0.26 to 1.3)	0.18
Steroid use from diagnosis (ref=started ≥3 months)				
Started within first 3 months	1.0 (0.72 to 1.5)	0.89	3.34 (2.1 to 5.5)	<0.001
Diagnosed in hospital				
Yes	1.7 (1.1 to 2.5)	0.011	2.8 (1.8 to 4.4)	<0.001
Diagnosis year (ref=2005–2008)				
2009–2012	0.98 (0.65 to 1.5)	0.93	1.39 (0.85 to 2.3)	0.19
2013–2016	1.0 (0.66 to 1.6)	0.92	0.95 (0.55 to 1.6)	0.85
CRP>50 (ref=normal)				
Abnormal>50	1.4 (0.93 to 2.0)	0.11	1.8 (1.1 to 2.9)	0.019
Anaemia (ref=normal)				
Abnormal	1.3 (0.87 to 1.8)	0.23	1.5 (0.97 to 2.4)	0.07
Albumin (ref=normal)				
Abnormal (≤30)	2.3 (1.5 to 3.4)	<0.001	3.1 (1.9 to 5.0)	<0.001
UC location ref=left (E2)				
Extensive (E3)			3.3 (2.1 to 5.1)	<0.001
CD location ref=terminal ileum (L1)				
Colonic (L2)	0.10 (0.06 to 0.17)	<0.001		
Ileocolonic (L3)	0.48 (0.32 to 0.73)	<0.001		
Upper GI (L4)	0.50 (0.28 to 0.88)	0.016		
Behaviour ref=Inflammatory (B1)				
Stricturing (B2)	4.3 (2.9 to 6.3)	<0.001		
Penetrating (B3)	14 (8.3 to 25)	<0.001		

CD, Crohn's disease; CRP, C reactive protein; GI, Gastro-intestinal; IBD-U, inflammatory bowel disease-unclassified; Ref, reference; UC, ulcerative colitis.

Of UC and IBD-U, excluding proctitis patients, 27 had missing data, 1 was excluded due to surgery on the day of diagnosis and 4 moved to non-treatment group as anti-TNF was used after colectomy (for pouchitis or severe rectal stump inflammation). Thus, 452 were analysed as not using anti-TNF and 103 as ever used anti-TNF. Of the users, 26 had early sustained use and 77 non-early sustained use (figure 2A). Those using early sustained anti-TNF compared with never users had a significantly higher likelihood of colectomy, IPTW model HR=4.6 (95% CI 1.9 to 10), p=0.001, (table 3 and figure 2B) with similar results in the unadjusted model. Comparing ever use of anti-TNF with non-use, IPTW model gave HR=2.8 (95% CI 1.7 to 4.7) (table 3). Colectomy rates were very similar between early sustained and non-early sustained use, IPTW model HR=1.0 (95% CI 0.53 to 1.9) p==0.99 (table 3 and figure 2C).

In a sensitivity analysis, UC patients were analysed without IBD-U but continuing to exclude those with proctitis (n=517 as shown in table 1). Comparing likelihood of colectomy for those receiving early sustained anti-TNF versus not receiving therapy, there was a significantly higher likelihood of colectomy (IPTW HR=4.1 (95% CI 1.6 to 11), p=0.007. A

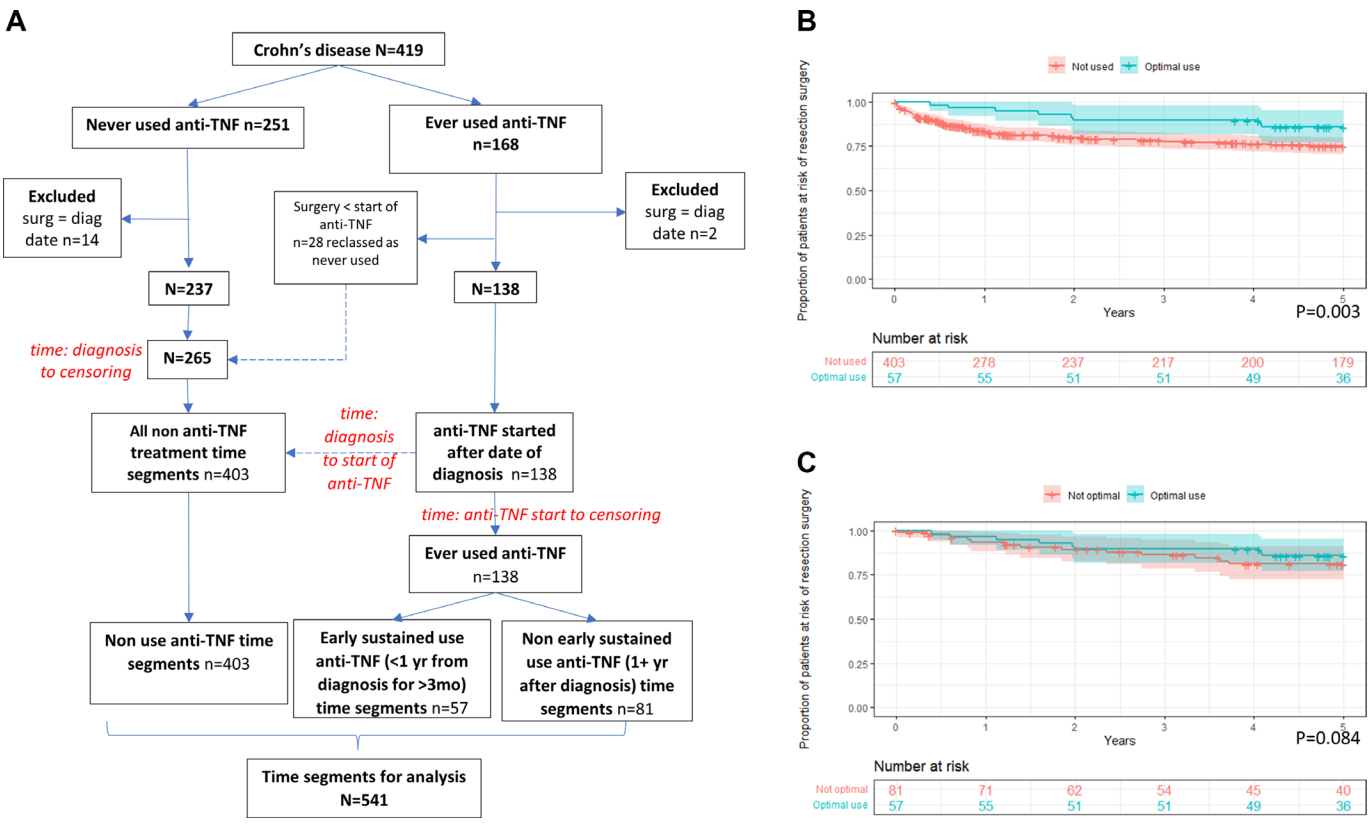

Figure 1 Crohn's disease and impact of anti-TNF therapy on surgical resection. (A) Crohn's disease anti-TNF therapy use, (B) Crohn's disease surgical resection rates: never versus early sustained (optimal) anti-TNF use, (C) Crohn's disease surgical resection rates: early sustained (optimal) versus non-optimal anti-TNF use.

further analysis included all those with proctitis, as well as IBD-U showing no overall difference in results. Overall 48/225 (21%) of patients with proctitis (E1) only at diagnosis progressed to E2 or E3 at 5 years (or time of censoring if shorter). Progression to E2/3 was more likely in those treated with anti-TNF, 11/22 (50%), p<0.001. Of those with E2 at diagnosis, 37/297 (13%) progressed to E3.

Table 3 Association between anti-TNF use and risk of resection surgery up to 5 years from diagnosis

		Ever used versus not used		Early sustained* use versus not used		Early sustained* use versus not early sustained
	N	HR (95% CI), p value	N	HR (95% CI), p value	N	HR (95% CI), p value
Crohn's disease						
Unadjusted model	138 vs 403	0.56 (0.35 to 0.89), 0.013	57 vs 403	0.51 (0.25 to 1.0), 0.06	57 vs 81	0.72 (0.30 to 1.7), 0.47
IPTW model†	138 vs 403	0.66 (0.39 to 1.1), 0.14	57 vs 403	0.29 (0.13 to 0.65), 0.003	57 vs 81	0.42 (0.16 to 1.1), 0.084
UC and IBD-U (excluding proctitis)						
Unadjusted model	103 vs 555	3.0 (1.9 to 4.6), <0.001	26 vs 555	3.2 (1.6 to 6.6), 0.0016	26 vs 77	1.1 (0.60 to 1.9), 0.86
IPTW model†	103 vs 555	2.8 (1.7 to 4.7),<0.001	26 vs 555	4.6 (1.9 to 10), 0.001	26 vs 77	1.0 (0.53 to 1.9), 0.99

*Use within 1 year of diagnosis, continued for at least 3 months.
†Model uses weights based on propensity scores using baseline confounders: age, sex, smoking status at diagnosis, diagnosed in hospital, disease location, behaviour (for Crohn's disease), year of diagnosis, steroid use with 3 months of diagnosis and C reactive protein, albumin, anaemia at diagnosis.
IBD-U, inflammatory bowel disease unclassified; IPTW, Inverse probability of treatment weighting; UC, ulcerative colitis.

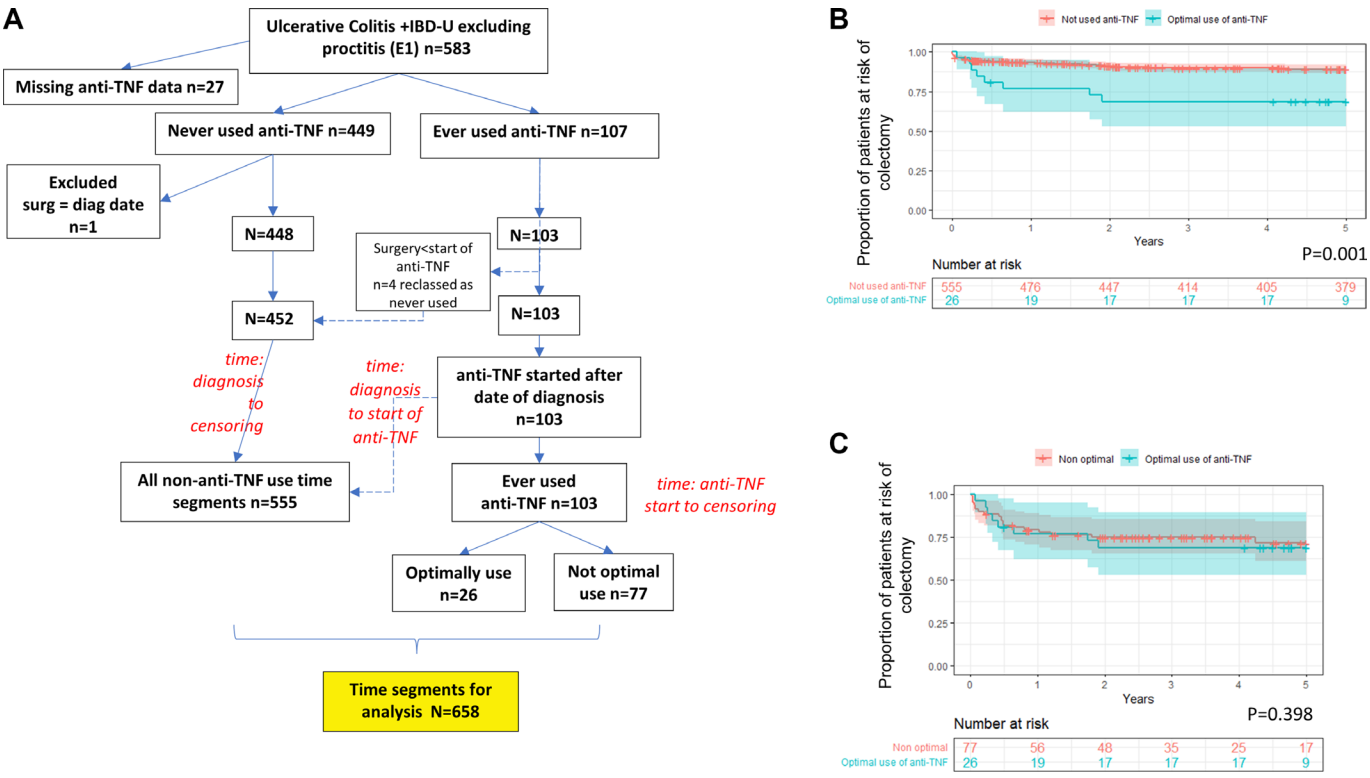

Figure 2 UC+IBDU excluding proctitis: impact of anti-TNF therapy use on colectomy. (A) UC+IBDU excluding proctitis: anti-TNF therapy use, (B) UC+IBDU excluding proctitis: colectomy rates with never versus early sustained (optimal) anti-TNF use, (C) UC+IBDU excluding proctitis: colectomy rates with early sustained (optimal) versus non-optimal anti-TNF use. IBDU, inflammatory bowel disease-unclassified; UC, ulcerative colitis.

It was noted that of UC patients treated with anti-TNF who later had resection—7/23 (33%) were 16 years or less at diagnosis and initially treated in the paediatric service. This compares with those who had colectomy and never received anti-TNF therapy of whom 2/64 (3.1%) were 16 years or under.

DISCUSSION

This work describes the real-world experience of the impact of anti-TNF therapy on surgical resection rates in a previously well-documented population-based cohort.[23] During the study period (2005–2016), surgical resection rates were static for both CD and UC while anti-TNF use increased. The benefits of anti-TNF therapy have been well documented for CD and UC in controlled trials,[8] but the impact on surgical resection rates in normal clinical practice has been more difficult to ascertain and is very dependent on methodology used. Our study corrected for the significant differences between those treated with anti-TNF therapy, compared with those who did not, using methodology enabling the retention of all cases for analysis and correcting for immortal time bias.

We have shown that early sustained anti-TNF therapy in CD is associated with reduced likelihood of surgical resection within the 5 years from diagnosis. Our study used early sustained treatment as the primary analysis. It is increasingly recognised that early anti-TNF therapy in CD is preferable.[11 24] Definitions of early therapy vary but are generally within one or 2 years after diagnosis.[10 11 13] We also excluded those using treatment for less than 3 months, removing those intolerant to treatment or with insufficient time to benefit. The reduction in likelihood of resection in CD was evident when comparing early sustained anti-TNF with never treatment. A comparison of early sustained with non-early sustained treatment showed a non-significant trend in the direction of benefit. Evaluation of all early anti-TNF treatment patients with CD (including the small number treated for less than 3 months) showed the same results. Patients with CD with colonic involvement were more likely to be treated with a biologic, and their total time on biologics was greater. This emphasises the heterogeneous nature of CD, where surgical resection for localised terminal ileal disease is often the preferred treatment.[25] Long-term follow-up of this study supports this approach for localised terminal ileal disease: 26% in the resection arm required infliximab at a median follow-up of 63 months while 48% in the infliximab arm required Crohn's-related resection at a median follow-up of 65 months.[26]

The findings in UC were very different to CD, with a significantly higher likelihood of colectomy in the treated group, both comparing ever treatment with never treated, and early sustained versus never treated. This does not necessarily mean that anti-TNF therapy increases the chance of colectomy, and it is more likely that the propensity matching failed to correct for

differences in clinical features between groups. Matching of the treatment groups used baseline factors, and in UC, this clearly did not adequately correct for the likelihood of later colectomy, whereas it did for CD. In CD, factors such as terminal ileal disease location would not change much over time,[27] whereas UC often progresses from proctitis and left-sided colitis to more extensive disease[28] as shown in our study. Our primary analysis excluded proctitis (E1) at diagnosis, so progression to E2/3 would not affect the analysis, but E1 was included in the sensitivity analysis with no difference in results. Progression also occurred in 13% of E2 patients. Acute severe UC can develop suddenly, even in those with mild disease at diagnosis. Only a quarter of our UC patients having colectomy were in-patients at diagnosis. Predicting those at risk of colectomy using clinical data at diagnosis may thus be less reliable for UC. The use of anti-TNF therapy is, however, a strong predictor of colectomy risk. During the period, we studied, UC patients would have been less likely to receive the rapid induction therapy and dose escalation that is now recommended.[29] Paediatric patients were over-represented in our anti-TNF patients undergoing colectomy and may have had less dose escalation or persistent treatment in those not fully responding to anti-TNF therapy, particularly in the earlier era studied. Our primary analysis evaluated UC and IBD-U patients, as disease behaviour and treatments were similar, and those with proctitis were excluded as being at much lower risk of colectomy and less likely to receive anti-TNF. Secondary analyses of UC without IBD-U and including proctitis did not substantially alter the findings.

There is no doubt that anti-TNF therapy is effective for both CD and UC in controlled clinical trials,[8] but it has been more difficult to demonstrate this in observational studies of normal practice. Avoidance of resection surgery is an objective and clinically important endpoint.[12]A study using the Danish National Patient Registry up to 2011 did not show an association between anti-TNF use and reduced surgery rates for UC or CD,[4] although anti-TNF use was low. A further study using the same source from 2011 to 2018[1] showed no link between rising biologics rates in CD and declining surgery rates, but biologics use remained a significant factor for UC in Cox multivariable regression analysis. The Dutch South Limberg cohort (patients diagnosed 1991–2011) used propensity scoring and showed no association between thiopurine or anti-TNF use and surgical resection for CD (UC was not evaluated).[17] A Swiss IBD cohort evaluating CD[16] showed that early use of anti-TNF therapy was associated with reduced rates of stricture development but not reduced surgery. A study from the Cleveland clinic showed in both paediatric and adult CD that use of biologics was associated with reduced rates of surgery. They excluded surgery during the first year after diagnosis, to avoid bias of advanced disease at diagnosis, and to allow adequate treatment duration.[30] In a large USA database study including incident and prevalent patients from 2015 to 2020, there were decreased surgical rates over 5 years in biologics users versus non-users for CD and UC, but the study was not population based and did not assess treatment or surgery in relation to date of diagnosis.[15] A Canadian administrative database study of 1995–2012, comparing 6 years before and after the introduction of infliximab, did not show reduced surgery for CD or UC.[18] There have been fewer studies of UC than for CD overall. In general, the large database studies were less likely to have detailed clinical information and less likely to be able to accurately match treatment and non-treatment groups. Some studies were not population based and selected groups with more severe disease. Those that did match groups used either multivariable regression or PS methodology. None of these studies corrected for immortal time bias.

A meta-analysis of trials and case series covering both CD and UC[13] focused on early biological treatment and concluded that there was evidence of reduced rates of surgery in CD, but rates were higher in UC, a pattern comparable to our findings. A recent study reported in abstract form (TARGET-IBD)[14] also evaluated early biologics in a prospective cohort of patients with CD. The risk of disease progression and surgery was reduced with early treatment but later treatment (2–5 years after diagnosis) was associated with increased surgery rates. The PROFILE study[31] recently added to the benefit of earlier introduction of infliximab to reduce rates of resection. The 'top-down' arm with the introduction of infliximab at diagnosis had significantly reduced rates of surgical resection at 48 weeks vs the standard 'accelerated step-up' arm. However, long-term outcomes are not yet available.

The strengths of our study include its population-based design, comprising all patients in Cardiff and the surrounding region; all degrees of severity and excluding tertiary referrals diagnosed elsewhere. We had detailed baseline phenotypic data, including laboratory measures of disease activity, used to match treatment groups, and our methodology eliminated immortal time bias. We can, however, only demonstrate an association between treatment and surgical outcomes in an observational study of this type and a causal relationship cannot be established. Because we analysed the impact of anti-TNF for both CD and UC using identical methodology, we have highlighted the divergent data for the two diseases.

Despite the fact that some baseline factors were predictive of increased risk of colectomy for UC, it was clear that we could not adequately match the treated and untreated UC groups. The only simple way to avoid this in an observational study is to evaluate treated patients who tolerate the drug versus those stopping due to toxicity. This would require a significantly larger patient group. It has been done for thiopurines[32] but not for anti-TNF therapy.

In conclusion, we have demonstrated in an observational study of a large regional cohort that anti-TNF therapy in CD, used early and continued for 3 months or more, is associated with a reduction in surgical resection up to 5 years, The UC results did not demonstrate the same association, likely related to the inability to match

treatment with non-treatment groups and this highlights the very different behaviour of the two conditions. These data provide further evidence for the early introduction of anti-TNF therapy in CD.

Declarations of personal interest

Barney Hawthorne has served as a speaker and received honoraria from Takeda UK, Ferring UK and Janssen-Cilag. RP has participated in an advisory board for Galapagos. RP is on the Editorial Board of BMJ Open Gastroenterology.

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Acknowledgements Dr Ben Davies contributed to data collection.

Contributors ABH conceived the study and designed in conjunction with RC-J. BA-W, AB, PH, AT and ABH collected data. RC-J did statistical analysis. ABH and RC-J drafted the paper, which was reviewed and edited by all authors. RCGP offered advice at design and analysis stages. All authors approved the final manuscript, of which ABH is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests ABH has served as a speaker and received honoraria from Takeda UK, Ferring UK and Janssen-Cilag. RCGP has participated in an advisory board for Galapagos. RCGP is on the Editorial Board of BMJ Open Gastroenterology.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and ethical approval was obtained for the study from the UK NHS Health Research Authority, REC reference: 20/YH/0064 IRAS project ID: 275200. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement No data are available. The data used in this study are held within NHS Cardiff and Vale University Healthboard. It contains personal identifiers and the ethics permission for the work prevents it being made available publicly.

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