



Limited long-term treatment persistence of first anti-TNF therapy in 538 patients with inflammatory bowel diseases: a 20-year real-world study

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Summary

Background: Anti-TNF antibodies were the first biologic treatment option for patients with inflammatory bowel diseases.

Aims: To assess length of treatment persistence of first anti-TNF therapy and influencing factors used in the standard care of patients with inflammatory bowel diseases.

Methods: Single-centre, retrospective study from a register including patients who received anti-TNF therapy in the last 20 years at the study centre. Kaplan-Meier analysis with log-rank test was used to describe treatment persistence. With multivariable Cox regression analysis, risk factors for treatment failure were investigated.

Results: Five hundred thirty-eight patients (CD, Crohn's disease: 367, UC, ulcerative colitis: 147, inflammatory bowel disease unclassified: 24) with a median follow-up of 8.1 years were included. Median (95% confidence interval) treatment persistence in the total cohort was 2.3 years (28 [22, 38] months), and nearly half of patients withdrew from treatment within 2 years. Male patients were treated longer than females (male: 37 [25, 48] months, female: 23 [14, 33] months, $P = 0.002$). Treatment persistence was longer in CD compared to UC (CD: 39 [30, 50] months, UC: 13 [9, 19] months, $P < 0.001$), and patients with CD remained longer on adalimumab than on infliximab treatment (adalimumab: 67 [55, 95] months, infliximab: 19 [14, 31] months, $P < 0.001$). Treatment failure (52%) and side effects (25%) were the most common reasons for withdrawal from therapy; 14% withdrew due to remission. Female sex was identified as independent predictor for treatment failure in UC (hazard ratio [CI]: 1.73 [1.02-2.92], $P = 0.04$).

Conclusion: Long-term treatment persistence of first anti-TNF therapy was limited in patients with inflammatory bowel diseases, primarily due to treatment failure and side effects.

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1 | INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic immune-mediated inflammatory disorders of the gastrointestinal tract presenting most commonly with chronic diarrhoea and abdominal pain. Causes of these diseases are still poorly understood. Microbiome alterations with epithelial barrier defects, genetic susceptibility and environmental factors are thought to lead to an imbalance of innate and adaptive immune responses.^{1,2}

The first report of successful usage of tumour necrosis factor alpha antibodies (anti-TNF) in CD was published in 1993.³ Infliximab was approved in Europe in 1999 as the first biologic and anti-TNF drug for the treatment of inflammatory bowel diseases.⁴ Subsequently, adalimumab and golimumab followed. Clinical studies have demonstrated efficacy of these medications in induction and maintenance of clinical and endoscopic remission in patients with CD and UC.⁵⁻¹⁰ Phase III trials usually assess their main efficacy endpoint after 1 year of treatment with open-label extension studies being conducted as sequels of these trials. As clinical outcomes may differ, it is important to acquire real-world data from patients not being treated within study conditions of randomised controlled trials. Long-term outcome studies of anti-TNF therapy with an observation time longer than 5 years are limited and showed average treatment persistence rates from 2.1 to 7.3 years.¹¹⁻¹⁶

We conducted an investigator-initiated, retrospective, single-centre, real-world study including patients with inflammatory bowel diseases who started anti-TNF therapy between 1999 and 2020. The primary endpoint was the length of treatment persistence of first anti-TNF therapy. Furthermore, differences in treatment persistence between CD and UC as well as between anti-TNF drug types were explored. Reasons for discontinuation, type of side effects leading to cessation, subsequent treatment after first anti-TNF was stopped, rates of surgical interventions, mortality, and predictors of treatment failure were chosen as secondary endpoints.

2 | MATERIALS AND METHODS

2.1 | Patients

Patients with inflammatory bowel diseases treated with an anti-TNF antibody at the outpatient clinic at the Division of Gastroenterology and Hepatology, Medical University of Graz, Austria, between October 1999 and March 2020 were prospectively identified and included in a register. For the present study, this register was used to identify eligible patients. Data were retrieved from the charts or the hospital information system retrospectively, and patients who did not visit the outpatient clinic within the last year before data closure were contacted by phone to assess follow-up data. Patients with insufficient data available were not recruited for the study. Rescue therapy with anti-TNF in acute severe colitis was not defined as exclusion criteria.

Data collected included demographic information, type, location, onset and duration of disease, laboratory parameters at anti-TNF initiation, prior bowel resections, smoking habits, indication and type of anti-TNF therapy, length of treatment, reasons for discontinuation and concomitant and prior medications (aminosalicylates, steroids, immunomodulators) as well as subsequent medical treatment, bowel resections and mortality after discontinuation of first anti-TNF therapy.

As standard dose, patients received infliximab 5 mg/kg intravenously every 8 weeks, adalimumab 40 mg subcutaneously every second week and golimumab 50 or 100 mg every 4 weeks depending on weight. The maximal dose used in our cohort was infliximab 10 mg/kg body weight every 4 weeks, adalimumab 80 mg once a week and golimumab 100 mg every second week.

2.2 | Definitions

2.2.1 | Disease entities

Patients with CD and UC were diagnosed according to the typical clinical, endoscopic and histological features.¹⁷ To ensure real-world conditions, patients with inflammatory bowel disease unclassified (IBD unclassified) were not generally excluded. However, subanalyses concerning disease types were only performed for patients with CD and UC.

2.2.2 | Treatment persistence

Treatment persistence was defined as the time between initiation and discontinuation of the drug or from initiation to end of follow-up in patients with ongoing first anti-TNF treatment. Intervals of drug holidays of less than 3 months were allowed.

2.2.3 | Reasons for discontinuation

Treatment failure was defined as stopping the first anti-TNF therapy independent of prior dose escalation due to either primary insufficient drug effect or loss of response. The decision was dependent on the assessment of the treating physician. Other reasons for treatment withdrawal were classified as side effects (divided into allergic reactions, skin reactions, infections, malignancy and others), remission, patient's wish, pregnancy and other causes.

2.2.4 | End of observation

Data closure was in May 2020. End of observation was the latest consultation in the outpatient clinic or a telemonitoring visit within the last year (April 2019 to May 2020).

2.3 | Statistical methods

Patient characteristics were reported as absolute and relative frequencies for categorical data and numerical data as medians and interquartile range (q1, q3). Comparisons between groups were done using *t*-tests, Mann-Whitney *U* tests or chi-square tests as appropriate. Treatment persistence of first anti-TNF therapy over time was displayed using the Kaplan-Meier method and compared by the log-rank test. Univariable and multivariable Cox regression analyses were performed to identify risk factors for treatment failure. All variables with a *P*-value < 0.1 in the univariable analysis were included in the multivariable analysis. Hazard ratios (HR) were presented along with their 95% confidence interval (CI). A *P*-value of 0.05 or less was considered statistically significant. All statistical analyses were conducted using R version 4.0.4 (<https://www.r-project.org>).

2.4 | Ethical considerations

The study was approved by the Institutional Review Board of the Medical University of Graz (EK 31-089 ex 18/19) and was registered at clinicaltrials.gov (NCT04575701). The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki and its amendments.

3 | RESULTS

3.1 | Baseline characteristics

Five hundred eighty-six patients were identified. Forty-eight patients had to be excluded due to lack of sufficient data. A total of 538 patients were included in the analysis (367 patients with CD, 147 with UC and 24 with IBD-U) (Table 1). Sex distribution was balanced in CD (51% females, 49% men), but the proportion of men was higher in UC (42% females, 58% men). CD patients were younger at time of diagnosis than UC patients (median [q1, q3], CD: 24 [18, 32] years, UC: 28 [21, 39] years; *P* < 0.001) and received their first anti-TNF at younger age (CD: 32 [23, 42] years, UC: 35 [27, 49] years; *P* = 0.002). Median [q1, q3] time from diagnosis to first administration was less than 5 years in both diseases (55 [14, 138] months). Between 1999 and 2009, patients received their first anti-TNF not later in disease course than patients with therapy initiation between 2010 and 2020 (60 [22, 132] months vs 52 [10, 139] months; *P* = 0.142).

The main indication for first anti-TNF therapy was active luminal disease (83%), followed by perianal disease in CD patients (11%), extraintestinal manifestations (5%) and other rare reasons including prophylactic therapy after surgery and one case of pouchitis (1%). Three hundred twenty-one patients (60%) received infliximab as first anti-TNF, 193 patients (36%) received adalimumab, and 24 patients (4%) golimumab.

3.2 | Treatment persistence

In total, 4297 patient-years were evaluated. Median (q1, q3) time of follow-up was 8.1 (4.0, 11.6) years (CD: 9.2 years, UC: 5.8 years). At the end of follow-up, 156 patients (29%) were still on a scheduled anti-TNF treatment with the first anti-TNF (CD: 29%, UC: 26%, *P* = 0.500), whereas treatment has been withdrawn from 382 patients (71%). Median (95% confidence interval) treatment persistence of the first anti-TNF was 2.3 years (28 [22, 38] months) in the total cohort (Figure 1A). With exclusion of all patients being treated shorter than 6 months, median treatment persistence was 4.2 years (50 [42, 60] months). Treatment persistence was 81% after 3 months, 75% after 6 months, 63% after 1 year, 52% after 2 years, 43% after 5 years and 18% after 10 years (Table 2). Male patients remained longer on the first anti-TNF than female patients (male: 37 [25, 48] months, female: 23 [14, 33] months, *P* = 0.002) (Figure 1B) and CD patients longer than UC patients (CD: 39 [30, 50] months, UC: 13 [9, 19] months, *P* < 0.001) (Figure 1C). Nearly 50% of UC patients stopped treatment within the first year. CD patients were treated longer with adalimumab than with infliximab (adalimumab: 67 [55, 95] months, infliximab: 19 [14, 31] months, *P* < 0.001) (Figure 1D). There were no differences concerning drug types in UC (Figure 1E).

3.3 | Reasons for discontinuation

The main reasons for discontinuation of anti-TNF treatment were treatment failure (52%), side effects (25%), remission (14%), patient's wish (4%), pregnancy (2%) and others (4%) (Figure 2).

3.4 | Adverse events

Side effects leading to termination of treatment occurred in 92 patients (25%). There was no significant difference in the frequency of side effects between CD and UC (CD: 25%, UC: 21%; *P* = 0.342). The most common side effects leading to discontinuation were allergic reactions (*n* = 30, 33%), skin reactions (*n* = 28, 30%), infections (*n* = 10, 11%) and malignancies (*n* = 5, 5%). Allergic reactions occurred almost exclusively in the infliximab treatment group.

3.5 | Clinical course of patients

The further therapeutic course after stopping first anti-TNF treatment is shown in Figure 3. Thirty-five per cent of all patients were off biologic therapy at data closure, with 27% not receiving biologics at all after the first anti-TNF treatment. Twenty-six percent of CD patients required one bowel surgery after initiation of first anti-TNF therapy and another 8% more than one surgery. Seventeen per cent of patients with UC required colectomy. At the end of follow-up, 2% of all patients had died. Reasons for death were heterogeneous and

TABLE 1 Baseline characteristics

	Crohn's disease (N = 367)	Ulcerative colitis (N = 147)	IBD unclassified (N = 24)
Female sex; yes (%)	188 (51)	62 (42)	12 (50)
Age at disease onset (years)	24 (18, 32)	28 (21, 39)	25 (18, 28)
Age at anti-TNF initiation (years)	32 (23, 42)	35 (27, 49)	31 (20, 47)
Disease duration at anti-TNF initiation (months)	61 (15, 140)	42 (12, 117)	42 (18, 157)
Haemoglobin at anti-TNF initiation (g/L)	130 (118, 143)	129 (119, 142)	122 (107, 136)
C-reactive protein at anti-TNF initiation (mg/L)	9.0 (2.9, 28.0)	6.9 (2.2, 16.9)	7.1 (2.8, 14.8)
Albumin at anti-TNF initiation (g/L)	41 (39, 45)	42 (39, 44)	41 (38, 45)
Body mass index at anti-TNF initiation	22.4 (19.4, 25.9)	24.0 (21.2, 27.3)	22.5 (20.6, 27.6)
Smoking status at anti-TNF initiation; n/yes (%)	302/123 (41)	114/9 (8)	19/4 (21)
Previous bowel resections at anti-TNF initiation; n/yes (%)	367/133 (36)	146/5 (3)	24/2 (8)
Aminosalicylates at anti-TNF initiation; n/yes (%)	329/40 (12)	134/108 (81)	22/9 (41)
Aminosalicylates at stopping first anti-TNF; n/yes (%)	232/10 (4)	98/73 (75)	15/7 (47)
Steroids at anti-TNF initiation; n/yes (%)	331/98 (30)	133/71 (53)	21/13 (62)
Steroids at stopping first anti-TNF; n/yes (%)	233/26 (11)	97/34 (35)	14/5 (36)
Immunomodulators before anti-TNF initiation; n/yes (%)	341/282 (83)	139/100 (72)	23/18 (78)
Immunomodulators at anti-TNF initiation; n/yes (%)	343/176 (51)	140/61 (44)	23/11 (48)
Immunomodulators at stopping first anti-TNF; n/yes (%)	244/104 (43)	105/39 (37)	14/4 (29)
Increased dose before stopping first anti-TNF; n/yes (%)	207/45 (22)	81/28 (35)	13/1 (8)
Disease location Crohn's disease; yes (%)			
L1	65 (18)		
L2	66 (18)		
L3	201 (55)		
L4	32 (9)		
Disease behaviour Crohn's disease; yes (%)			
B1	114 (31)		
B2	75 (20)		
B3	178 (49)		
Perianal disease	134 (37)		
Disease location ulcerative colitis; yes (%)			
E1		7 (5)	
E2		56 (38)	
E3		84 (57)	
Disease location IBD unclassified; yes (%)			
E1			0 (0)
E2			7 (29)
E3			17 (71)
Small bowel involvement; yes (%)			2 (8)
First anti-TNF; yes (%)			
Infliximab	208 (57)	97 (66)	16 (67)
Adalimumab	159 (43)	27 (18)	7 (29)
Golimumab	0 (0)	23 (16)	1 (4)

Disease location was assessed according to the Montreal classification at time of first anti-TNF initiation. Crohn's disease: L1 = ileal, L2 = colonic, L3 = ileocolonic, L4 = upper gastrointestinal involvement, B1 = non-stricturing, non-penetrating, B2 = structuring, B3 = penetrating. Ulcerative colitis and inflammatory bowel disease unclassified: E1 = proctitis, E2 = left-sided colitis, E3 = pancolitis. Data presented as median (q1, q3), yes (%) or n/yes (%) in case of missing data. IBD unclassified, inflammatory bowel disease unclassified.

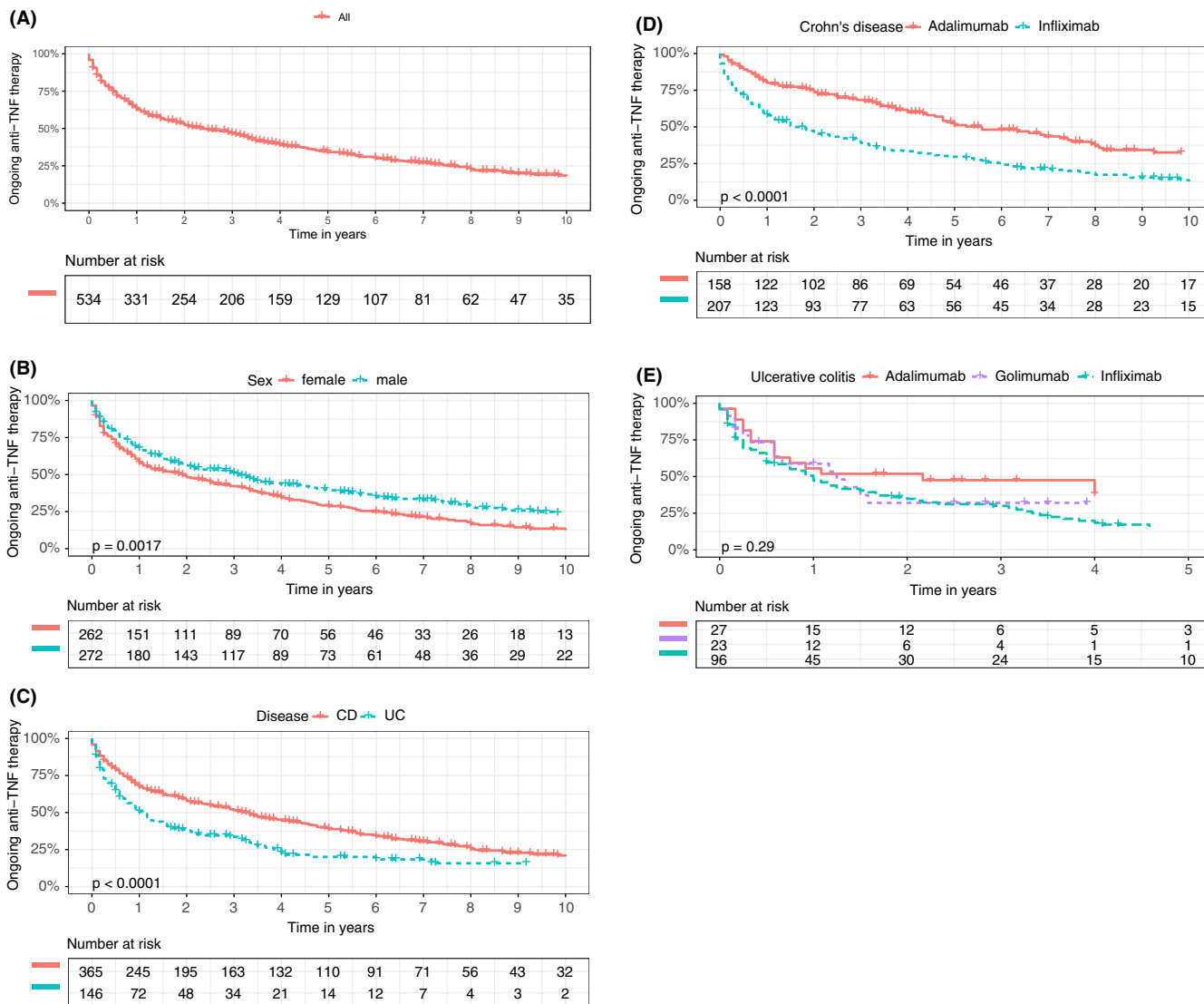


FIGURE 1 A-E: Kaplan-Meier curves of treatment persistence. A, All patients included in the study, including inflammatory bowel disease unclassified. Data of four patients missing due to uncertain time of stopping first anti-TNF treatment. B, Data separated by sex, inflammatory bowel disease unclassified included. C, Data separated by disease type (CD = Crohn's disease, UC = ulcerative colitis), patients with inflammatory bowel disease unclassified were excluded. D, E, Data separated by type of anti-TNF medication for Crohn's disease (D) and ulcerative colitis (E). Comparisons were done using the log-rank test

included malignancy, sepsis, complications of short bowel syndrome, liver cirrhosis and intracranial haemorrhage as well as suicide and murder.

3.6 | Predictors of treatment failure

To assess predictors of treatment failure, univariable and multivariable analyses were conducted using Cox regression. Overall, no independent predictors could be observed upon multivariable analysis in the total cohort (Table 3). When separating disease types, female sex (HR 1.73 [1.02-2.92], $P = 0.040$) was identified as independent risk factor for treatment failure in UC patients. Albumin levels at anti-TNF initiation (HR 0.57 [0.32-0.99], $P = 0.047$) predicted treatment failure in CD (Table 4).

4 | DISCUSSION

Our present study spans 20 years of anti-TNF therapy in inflammatory bowel diseases with over 500 patients with a median follow-up of more than 8 years and about 4300 patient-years in total. To the best of our knowledge, this is the longest observation period concerning long-term treatment persistence of anti-TNF therapy in inflammatory bowel diseases published yet. We could demonstrate treatment withdrawal from 71% of patients within follow-up. Median treatment persistence was more than 2 years (28 months) in the total cohort, and male patients were treated longer than females. Patients with CD remained longer on treatment with the first anti-TNF than patients with UC, and patients with adalimumab therapy longer than patients with infliximab in CD. Main reasons for treatment discontinuation were treatment failure and side effects.

TABLE 2 Treatment persistence assessed with Kaplan-Meier analysis

Characteristics	Treatment persistence; % (95% CI)						Median treatment persistence; months (95% CI)
	3 months	6 months	1 year	2 years	5 years	10 years	
Overall treatment persistence	81 (78, 85)	75 (71, 78)	63 (59, 67)	52 (48, 57)	34 (30, 39)	18 (14, 23)	28 (22, 38)
Disease							
Crohn's disease	85 (81, 89)	79 (75, 83)	67 (63, 72)	58 (53, 63)	39 (34, 45)	20 (16, 26)	39 (30, 50)
Ulcerative colitis	73 (66, 81)	64 (57, 73)	51 (43, 60)	38 (31, 47)	20 (14, 29)	16 (9, 26)	13 (9, 19)
IBD unclassified	74 (58, 94)	70 (53, 91)	65 (48, 88)	55 (37, 80)	43 (25, 72)	11 (2, 65)	27 (12, NA)
Sex							
Female	77 (73, 83)	70 (65, 76)	58 (52, 64)	48 (42, 55)	29 (23, 35)	12 (8, 19)	23 (14, 33)
Male	85 (81, 89)	79 (74, 84)	68 (62, 73)	56 (51, 63)	39 (34, 46)	24 (18, 31)	37 (25, 48)
Age (years)							
<40	80 (76, 84)	73 (69, 78)	61 (57, 67)	51 (46, 56)	35 (30, 41)	18 (14, 24)	25 (18, 39)
>40	84 (78, 89)	77 (71, 84)	66 (59, 73)	55 (48, 63)	32 (25, 41)	18 (12, 27)	36 (22, 43)
First anti-TNF							
Infliximab	76 (71, 81)	68 (63, 73)	55 (50, 61)	43 (38, 49)	26 (22, 32)	12 (8, 17)	18 (12, 24)
Adalimumab	91 (87, 95)	86 (82, 91)	76 (70, 83)	70 (64, 77)	49 (41, 58)	30 (22, 40)	60 (48, 87)
Golimumab	75 (59, 94)	70 (54, 91)	56 (39, 81)	31 (16, 59)	31 (16, 59)	NA	15 (7, NA)
First anti-TNF (Crohn's disease)							
Infliximab	79 (73, 85)	71 (65, 77)	58 (52, 65)	46 (39, 53)	30 (24, 37)	13 (9, 19)	19 (14, 31)
Adalimumab	93 (89, 97)	89 (84, 94)	80 (74, 87)	74 (67, 81)	51 (43, 61)	33 (24, 44)	67 (55, 95)
First anti-TNF (ulcerative colitis)							
Infliximab	69 (61, 79)	60 (50, 70)	47 (38, 59)	35 (26, 46)	16 (9, 26)	14 (8, 24)	12 (7, 20)
Adalimumab	81 (68, 98)	74 (59, 93)	56 (40, 78)	52 (36, 75)	38 (21, 69)	19 (4, 86)	26 (7, NA)
Golimumab	78 (63, 97)	73 (57, 94)	59 (41, 84)	32 (17, 61)	32 (17, 61)	NA	15 (7, NA)

Abbreviations: CI, confidence interval; NA, not applicable.

Most long-term studies have excluded patients with only episodic or short treatment (<6 months).^{13,14} This is the reason why our reported persistence rates seem to be shorter than in previous studies at first sight (2.3 years vs 3.3 and 3.1 years).^{13,14} But when we excluded patients with treatment duration of fewer than 6 months in our cohort, persistence was enhanced to 4.2 years. One study even excluded all patients with a treatment duration of fewer than 12 months, resulting therefore in even longer treatment persistence (females: 4.5 years, males: 7.3 years) and lower rates of discontinuation within the observation period (46%).¹⁶ In our cohort, less than one-third of patients remained on anti-TNF treatment. The reason for this divergence is caused by the fact that nearly 40% of patients withdrew from therapy within the first year in our study. Similar withdrawal rates were reported in two other studies after 1 year.^{18,19} As patients with acute severe colitis were not excluded from our analysis, the high rate of treatment discontinuation in UC within the first year may be caused by the lower response rates to anti-TNF treatment in this demanding clinical situation and may have contributed to the short treatment persistence in UC patients. A retrospective British cohort study for adalimumab also associated the diagnosis UC and concomitant prednisolone intake with increased risk for treatment discontinuation.²⁰

Longer treatment persistence with adalimumab than with infliximab in CD, as observed in this study, is in contrast to previous data.¹³ Retrospective studies and meta-analyses showed equal effectiveness of anti-TNF antibodies for induction and maintenance therapy in CD.²¹⁻²³ An explanation for the longer treatment persistence of adalimumab in CD in our cohort may be the usage of adalimumab in less severe cases.

The most common reason for discontinuation was treatment failure (52%). This is in accordance with results reported by Pouillon et al.¹⁴ and by Schultheiss et al. who reported secondary loss of response as main reason for treatment withdrawal.¹⁶ But when interpreting our data, one has to keep in mind that 14% of patients withdrew from treatment with the first anti-TNF due to remission. Another 6% stopped due to pregnancy or patient's wish which may also implicate satisfactory disease control in most of these patients. Therefore, treatment discontinuation of first anti-TNF should not be interpreted solely as indicating insufficient anti-TNF treatment effect or occurrence of side effects.

Adverse events were the second common cause for treatment discontinuation (25%) and were dominated by allergic reactions, skin manifestations and infections. Previously, discontinuation of infliximab treatment in CD due to side effects was reported in 13%

FIGURE 2 Timepoints of discontinuation of first anti-TNF therapy and according reasons including all disease and medication types

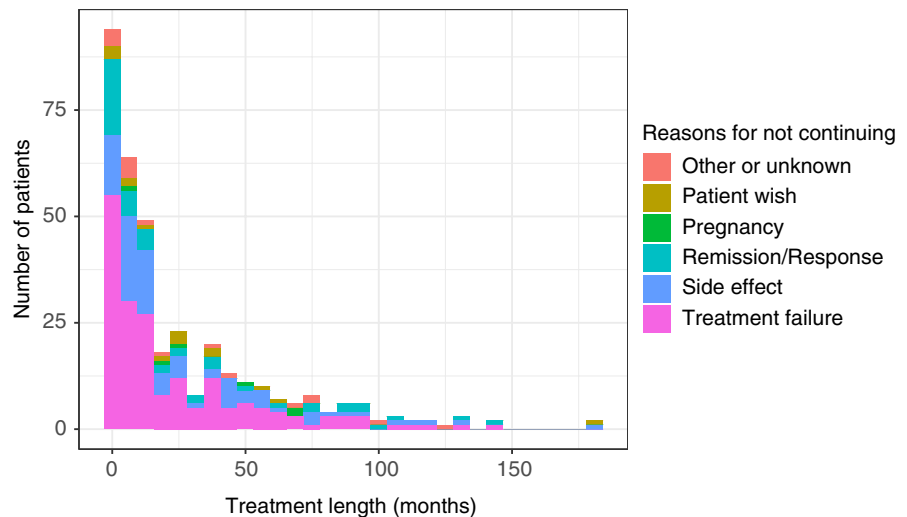
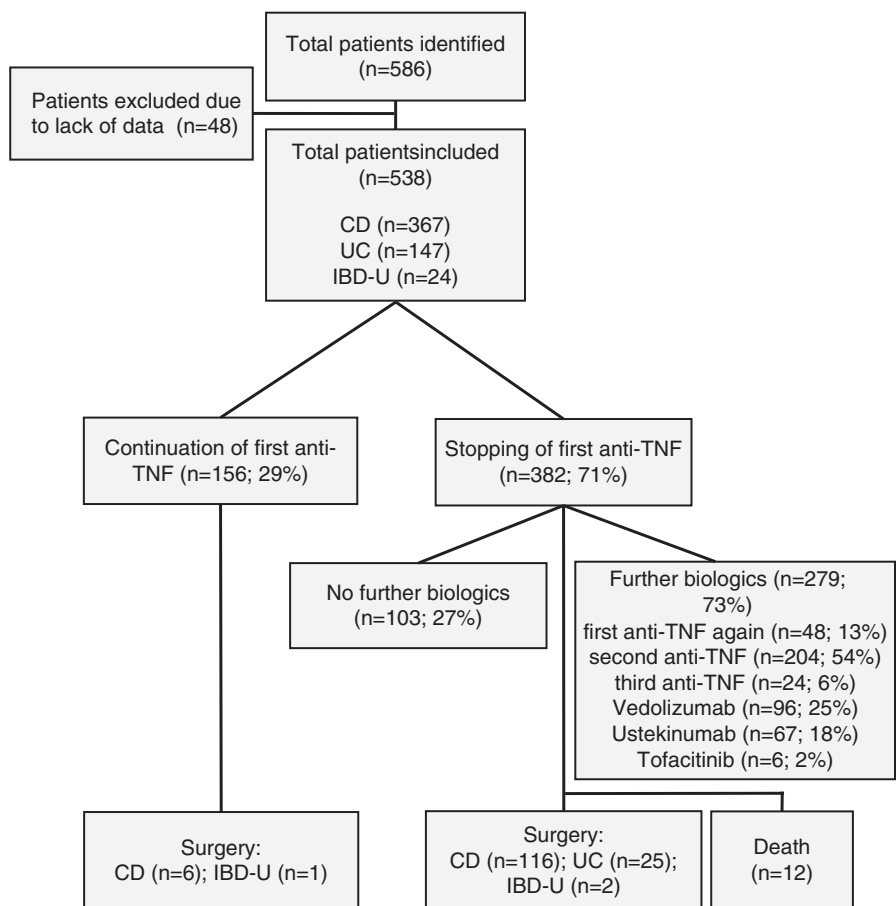


FIGURE 3 Clinical course of patients over the observation period. From the included patients, 29% remained on the first anti-TNF, whereas treatment had been withdrawn from 71% of patients. Within the group of patients stopping first anti-TNF, 27% did not receive treatment with biologics again. Thirty-four per cent of patients with CD needed surgery after initiation of the first anti-TNF. Seventeen per cent of patients with UC required colectomy. In total, 2% of all patients died. Percentage from further biologics calculated from the total number of patients stopping first anti-TNF. Abbreviations: CD, Crohn's disease; UC, ulcerative colitis; IBD-U, inflammatory bowel disease unclassified



of patients. The majority of these side effects were infusion reactions.²⁴ For adalimumab, a recent analysis concerning safety including 16 trials showed that adverse events leading to discontinuation of the drug occurred in 19% (CD) and 22% (UC) of patients.²⁵

Anti-TNF treatment was stopped earlier in females than in males, and female sex was identified as independent predictor for treatment failure in UC. Female sex as risk factor for anti-TNF discontinuation was reported earlier not only for inflammatory bowel diseases

but also for rheumatoid arthritis, psoriasis and ankylosing spondylitis.^{16,26-28} This fact may be caused by increased side effects of anti-TNFs in women.¹⁶ Factors as augmented body fat in women, lower hepatic clearance and the influence of sex hormones have been discussed as reasons for this increase.²⁹⁻³¹ Age and body mass index were not found to be risk factors for treatment failure in our study, but are described in literature.³²⁻³⁴ Smoking is an established risk factor for complicated disease courses in CD.³⁵ Smoking rates were

TABLE 3 Univariable and multivariable cox regression analysis to identify predictors of treatment failure for all disease types (including inflammatory bowel disease unclassified) combined

Variables	Hazard ratio (95% CI) Univariable	P-value Uni-variable	Hazard ratio (95% CI) Multivariable	P-value Multi-variable
Sex (female)	1.34 (1.01-1.79)	0.044	1.43 (0.95-2.16)	0.087
Age at first anti-TNF	1.00 (0.99-1.02)	0.375		
Disease type (Ulcerative colitis)	2.00 (1.48-2.70)	0.001	1.62 (0.80-3.25)	0.177
Body mass index	1.00 (0.96-1.04)	0.979		
C-reactive protein	1.00 (1.00-1.01)	0.098	1.00 (1.00-1.01)	0.359
Haemoglobin	0.89 (0.83-0.97)	0.006	1.01 (0.89-1.15)	0.829
Albumin	0.57 (0.41-0.79)	0.001	0.67 (0.42-1.07)	0.092
Ongoing steroids (yes)	1.51 (1.10-2.07)	0.010	1.13 (0.75-1.71)	0.562
Ongoing immunomodulators (yes)	1.06 (0.79-1.43)	0.700		
Ongoing aminosaliculates (yes)	1.45 (1.06-2.00)	0.021	0.90 (0.48-1.69)	0.753
Immunomodulators before anti-TNF (yes)	1.06 (0.72-1.57)	0.765		
Duration of disease	1.00 (1.00-1.00)	0.140		
Previous bowel resections (yes)	0.56 (0.39-0.80)	0.002	0.70 (0.41-1.18)	0.181
Smoking (ex)	0.61 (0.36-1.06)	0.081	0.77 (0.41-1.44)	0.418
Smoking (yes)	0.68 (0.47-0.98)	0.041	0.92 (0.55-1.52)	0.739

All variables were assessed at time of first anti-TNF treatment initiation.

Abbreviations: CI, confidence interval.

TABLE 4 Univariable and multivariable cox regression analysis to identify predictors of treatment failure for Crohn's disease and ulcerative colitis

Variables	Crohn's disease			Ulcerative colitis		
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P-value
	Univariable	Multivariable	Multi-variable	Univariable	Multivariable	Multi-variable
Sex (female)	1.42 (0.98-2.04)	1.44 (0.80-2.59)	0.221	1.50 (0.94-2.40)	1.73 (1.02-2.92)	0.040
Age at first anti-TNF	1.01 (0.99-1.02)			1.00 (0.98-1.01)		
Body mass index	0.97 (0.92-1.03)			1.01 (0.95-1.08)		
C-reactive protein	1.01 (1.00-1.01)	1.00 (1.00-1.01)	0.496	1.01 (1.00-1.03)	1.01 (1.00-1.03)	0.101
Haemoglobin	0.88 (0.80-0.98)	1.03 (0.86-1.24)	0.725	0.92 (0.81-1.06)		
Albumin	0.50 (0.32-0.77)	0.57 (0.32-0.99)	0.047	0.65 (0.39-1.08)	0.78 (0.42-1.46)	0.438
Ongoing steroids (yes)	1.49 (0.97-2.30)	1.47 (0.85-2.55)	0.163	1.04 (0.63-1.73)		
Ongoing immunomodulators (yes)	1.27 (0.86-1.87)			0.82 (0.50-1.35)		
Ongoing aminosaliculates (yes)	1.11 (0.62-1.98)			0.61 (0.34-1.12)		
Immunomodulators before anti-TNF (yes)	1.24 (0.68-2.26)			1.31 (0.76-2.25)		
Duration of disease	1.00 (1.00-1.00)			1.00 (1.00-1.00)		
Previous bowel resections (yes)	0.66 (0.45-0.98)	0.62 (0.36-1.09)	0.097	1.02 (0.25-4.21)		
Smoking (ex)	0.53 (0.26-1.08)	0.75 (0.34-1.65)	0.479	1.02 (0.43-2.40)		
Smoking (yes)	0.78 (0.50-1.20)	0.82 (0.47-1.43)	0.479	0.90 (0.28-2.90)		

All variables were assessed at the time of first anti-TNF treatment initiation.

Abbreviation: CI, confidence interval.

high in our cohort (41%), but we could not identify smoking as a risk factor for treatment failure.

In our cohort, colectomy was necessary for nearly a fifth of UC patients (17%), and one-third of CD patients (34%) required at least one surgery after initiation of first anti-TNF. A colectomy risk of 15% after 20 years from time of UC diagnosis was reported previously.³⁶ In acute severe UC, colectomy rates of 20% within 2 years and 40% within 5 years were reported.^{37,38} In CD with isolated terminal ileitis, nearly 50% of all prior anti-TNF treated patients needed resection within an observation period of over 5 years in the Liric trial.³⁹ Patients suffering from symptomatic stricturing CD who initiated an anti-TNF therapy had resection rates of 32% within a median observation period of 40 months.⁴⁰ Eberhardson et al. reported surgery rates of 28% 7 years after initiation of the first anti-TNF independent from continuation or discontinuation of the drug throughout the first year in Sweden.¹⁹

Twenty-seven per cent of patients did not receive biologic therapy again after stopping first anti-TNF in our study population. Twenty-one per cent of CD patients did not need restart of biologics 7 years after withdrawal in the STORI trial, and quiescent disease course was reported in 28% of patients in another CD cohort.^{35,41} In recent published Indian and Dutch cohorts, relapse rates after discontinuation of anti-TNF treatment (median observation time: 26 and 47 months) of around 50% were reported.^{42,43}

Our results should be interpreted in the context of some limitations. By its nature as a retrospective single-centre study, we had to use existing data of different quality, and the design makes the study vulnerable to a regional bias. Not all assessed parameters were leviable for all included patients, and no data on achievement of clinical or endoscopic remission during anti-TNF therapy were available. Furthermore, the study was carried out in a tertiary referral centre, and therefore, the proportion of severe cases may be higher. Nowadays, measuring drug levels of anti-TNFs is routinely performed in most IBD centres to optimize treatment, which may lead to better outcomes and lower surgery rates.⁴⁴⁻⁴⁶

Our data also have some strengths. As a single-centre long-term outcome study, it reflects real-world experiences in daily routine without the bias of a shorter, multicentre trial with strict inclusion and exclusion criteria. Reduced heterogeneity of treatment strategies is an additional benefit of the single-centre design. Moreover, this is the first study, which analysed the overall outcome of first anti-TNF treatment over 20 years with a respectable number of patients for both disease types.

5 | CONCLUSION

In summary, treatment persistence of anti-TNF therapy in inflammatory bowel diseases was limited, mainly due to treatment failure and side effects, but also due to remission. Longer persistence could be observed in males, in patients with CD and for adalimumab

treatment in CD. Despite the use of anti-TNF antibodies, surgery rates remained high in patients with CD and UC.

The results of our study should be taken into account for a personalized approach and an individual treatment decision for patients suffering from inflammatory bowel diseases. For the future, more evidence about benefits and disadvantages of available treatment options needs to be generated.

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AUTHORSHIP

Guarantor of the article: None.

Author contributions: AB (Andreas Blesl) planned the study, acquired data, analysed data, interpreted data and drafted the manuscript. LB, CH, HW, SM, PK and FBD acquired data and critically reviewed the manuscript. AB (Andrea Borenich), GP and AB (Andrea Berghold) did the statistical workup and graphic design and critically reviewed the manuscript. WP planned the study, acquired data, analysed data, interpreted data and critically reviewed the manuscript.

ETHICS APPROVAL

The study was approved by the research ethics committees at the Medical University of Graz (EK 31-089 ex 18/19) and was registered at clinicaltrials.gov (NCT04575701).

DATA AVAILABILITY STATEMENT

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

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