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

Andreas Blesl1 | Lukas Binder1 | Christoph Högenauer1,2 | Heimo Wenzl1 | Andrea Borenich3 | Gudrun Pregartner3 | Andrea Berghold3 | Sigrid Mestel1 | Patrizia Kump1 | Franziska Baumann-Durchschein1 | Wolfgang Petritsch1

1Department of Internal Medicine, Division of Gastroenterology and Hepatology, Medical University of Graz, Graz, Austria
2Biotechmed, Graz, Austria
3Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria

Correspondence
Andreas Blesl, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria. Email: andreas.blesl@medunigraz.at

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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.
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.

MATERIALS AND METHODS

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.

Definitions

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, sub-analyses concerning disease types were only performed for patients with CD and UC.

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.

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.

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
|                          | 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)
- Adalimumab: 159 (43)
- Golimumab: 0 (0)

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.
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.
Most long-term studies have excluded patients with only episodic or short treatment (<6 months).\textsuperscript{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).\textsuperscript{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%).\textsuperscript{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.\textsuperscript{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.\textsuperscript{20}

Longer treatment persistence with adalimumab than with infliximab in CD, as observed in this study, is in contrast to previous data.\textsuperscript{13} Retrospective studies and meta-analyses showed equal effectiveness of anti-TNF antibodies for induction and maintenance therapy in CD.\textsuperscript{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.\textsuperscript{14} and by Schultheiss et al. who reported secondary loss of response as main reason for treatment withdrawal.\textsuperscript{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%
of patients. The majority of these side effects were infusion reactions.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16,26-28} This fact may be caused by increased side effects of anti-TNFs in women.\textsuperscript{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.\textsuperscript{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.\textsuperscript{32-34} Smoking is an established risk factor for complicated disease courses in CD.\textsuperscript{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 Univariable | Hazard ratio (95% CI) Multivariable | P-value Multivariable |
|----------------------------------|-----------------------------------|--------------------|-------------------------------------|-----------------------|
| 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 aminosalicylates (yes)   | 1.45 (1.06-2.00)                  | 0.021              | 0.90 (0.48-1.69)                    | 0.753                 |
| Immunomodulators before anti-TNF| 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) | P-value | Hazard ratio (95% CI) | P-value |
| Sex (female)                     | 1.42 (0.98-2.04) | 0.221          | 1.50 (0.94-2.40) | 0.040 |
| Age at first anti-TNF            | 1.01 (0.99-1.02) | 0.95-1.08       | 1.00 (0.98-1.01) | 0.61 (0.34-1.12) |
| Body mass index                  | 0.97 (0.92-1.03) | 1.01 (1.00-1.00) | 0.097 (0.81-1.06) | 0.101 |
| C-reactive protein               | 1.01 (1.00-1.01) | 0.725 (0.32-0.99) | 1.01 (1.00-1.03) | 0.438 |
| Haemoglobin                      | 0.88 (0.80-0.98) | 0.65 (0.39-1.08) | 0.78 (0.42-1.46) | 0.739 |
| Albumin                          | 0.50 (0.32-0.77) | 1.47 (0.85-2.55) | 1.04 (0.63-1.73) | 0.82 (0.50-1.35) |
| Ongoing steroids (yes)           | 1.49 (0.97-2.30) | 0.163 (0.86-1.87) | 1.27 (0.86-1.87) | 0.11 (0.62-1.98) |
| Ongoing immunomodulators (yes)   | 1.24 (0.68-2.26) | 0.047 (0.32-0.77) | 1.24 (0.68-2.26) | 1.31 (0.76-2.25) |
| Ongoing aminosalicylates (yes)   | 0.88 (0.80-0.98) | 1.06 (0.37-1.09) | 0.62 (0.36-1.09) | 1.00 (1.00-1.00) |
| Immunomodulators before anti-TNF | 0.50 (0.32-0.77) | 0.97 (0.45-0.98) | 0.66 (0.45-0.98) | 0.62 (0.36-1.09) |
| Duration of disease              | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) | 1.00 (1.00-1.00) |
| Previous bowel resections (yes)  | 0.53 (0.26-1.08) | 0.479 (0.82-1.43) | 0.53 (0.26-1.08) | 0.479 (0.82-1.43) |
| Smoking (ex)                     | 0.78 (0.50-1.20) | 0.90 (0.28-2.90) | 0.78 (0.50-1.20) | 0.90 (0.28-2.90) |
| Smoking (yes)                    | 0.78 (0.50-1.20) | 0.479 (0.82-1.43) | 0.78 (0.50-1.20) | 0.479 (0.82-1.43) |

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. In acute severe UC, colectomy rates of 20% within 2 years and 40% within 5 years were reported. 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 Liroc trial. Patients suffering from symptomatic strictureing CD who initiated an anti-TNF therapy had resection rates of 32% within a median observation period of 40 months. 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.

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. 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.

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.

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. 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.

ORCID

Andreas Blesl https://orcid.org/0000-0002-9338-4140

Christoph Högenauer https://orcid.org/0000-0003-4566-0806

REFERENCES

1. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn’s disease. Lancet. 2017;389:1741–1755.
2. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet. 2017;389:1756–1770.
3. Derkx B, Taminiau J, Radema S, et al. Tumour-necrosis-factor antibody treatment in Crohn’s disease. Lancet. 1993;342:173–174.
4. https://www.ema.europa.eu/en/medicines/human/EPAR/remicade.
5. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–2476.
6. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142:257–265.e1–3.

7. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146:85–95; quiz e14–5.

8. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146:96–109.e1.

9. Colombel J-F, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132:52–65.

10. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359:1541–1549.

11. Seminario JL, Loftus EV Jr, Colombel JF, Thapa P, Sandborn WJ. Infliximab for Crohn's disease: the first 500 patients followed up through 2009. *Dig Dis Sci*. 2013;58:797–806.

12. García-Bosch O, Aceituno M, Ordás I, et al. Long-term follow-up of patients treated with infliximab for ulcerative colitis: predictive factors of response-an observational study. *Dig Dis Sci*. 2016;61:2051–2059.

13. Olivera P, Thiriet L, Luc A, Baumann C, Danese S, Peyrin-Biroulet L. Treatment Persistence for Infliximab Versus Adalimumab in Crohn's Disease: A 14-Year Single-Center Experience. *Inflamm Bowel Dis*. 2017;23:976–985.

14. Pouillon L, Baumann C, Rousseau H, et al. Treatment persistence of infliximab versus adalimumab in ulcerative colitis: a 16-year single-center experience. *Inflamm Bowel Dis*. 2019;25:945–954.

15. Inokuchi T, Takahashi S, Hiraoka S, et al. Long-term outcomes of patients with Crohn's disease who received infliximab or adalimumab as the first-line biologics. *J Gastroenterol Hepatol*. 2019;34:1329–1336.

16. Schultheiss JPD, Brand EC, Lamers E, et al. Earlier discontinuation of TNF-α inhibitor therapy in female patients with inflammatory bowel disease is related to a greater risk of side effects. *Aliment Pharmacol Ther*. 2019;50:386–396.

17. Maaser C, Sturm A, Vavricka SR, et al. ECCO-ESGAR guideline for diagnostic assessment in IBD Part 1: initial diagnosis, monitoring of known IBD, detection of complications. *J Crohns Colitis*. 2019;13:144–164.

18. Targownik LE, Tennakoon A, Leung S, et al. Factors associated with discontinuation of anti-TNF inhibitors among persons with IBD: a population-based analysis. *Inflamm Bowel Dis*. 2017;23:409–420.

19. Eberhardsson M, Söderling JK, Neovius M, et al. Anti-TNF treatment in Crohn's disease and risk of bowel resection-a population-based cohort study. *Aliment Pharmacol Ther*. 2017;46:589–598.

20. Gendelman O, Weitzman D, Rosenberg V, Shalev V, Chodick G, Amital H. Characterization of adherence and persistence profile in known IBD, detection of complications. *Am J Gastroenterol*. 2018;84:786–795.

21. Narula N, Kainz S, Petritsch W, et al. The efficacy and safety of either infliximab or adalimumab in 362 patients with anti-TNF-α naïve Crohn's disease. *Aliment Pharmacol Ther*. 2016;44:170–180.

22. Cholapranee A, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. *Aliment Pharmacol Ther*. 2017;45:1291–1302.

23. Hazlewood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology*. 2015;148:344–354.e5; quiz e14–5.

24. Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut*. 2009;58:492–500.

25. Colombel J-F, Sandborn WJ, Reinisch W, et al. Long-term safety of adalimumab in clinical trials in adult patients with Crohn's disease or ulcerative colitis. *Aliment Pharmacol Ther*. 2018;47:219–228.

26. Souto A, Maneiro JR, Gómez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. *Rheumatology (Oxford)*. 2016;55:523–534.

27. Iannone F, Lopriore S, Bucci R, et al. Long-term clinical outcomes in 420 patients with psoriatic arthritis taking anti-tumor necrosis factor drugs in real-world settings. *J Rheumatol*. 2016;43:911–917.

28. Pavelka K, Forejtová S, Stolfa J, et al. Anti-TNF therapy of ankylosing spondylitis in clinical practice. Results from the Czech national registry ATTRA. *Clin Exp Rheumatol*. 2009;27:958–963.

29. Meibomh B, Beerle I, Derendorf H. How important are gender differences in pharmacokinetics? *Clin Pharmacokinet*. 2002;41:329–342.

30. Rademaker M. Do women have more adverse drug reactions? *Am J Clin Dermatol*. 2001;2:349–351.

31. Nicolson TJ, Mellor HR, Roberts RR. Gender differences in drug toxicity. *Trends Pharmacol Sci*. 2010;31:108–114.

32. Porcari S, Viola A, Orlando A, et al. Persistence on anti-tumour necrosis factor therapy in older patients with inflammatory bowel disease compared with younger patients: data from the Sicilian Network for Inflammatory Bowel Diseases (SN-IBD). *Drugs Aging*. 2020;37:383–392.

33. Harper JW, Sinanan MN, Zisman TL. Increased body mass index is associated with earlier time to loss of response to infliximab in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2013;19:2118–2124.

34. Kurnool S, Nguyen NH, Proudfoot J, et al. High body mass index is associated with increased risk of treatment failure and surgery in biologic-treated patients with ulcerative colitis. *Aliment Pharmacol Ther*. 2018;47:1472–1479.

35. Wintjens D, Bergey F, Saccenti E, et al. Disease activity patterns of Crohn's disease in the first 10 years after diagnosis in the population-based IBD South Limburg cohort. *J Crohns Colitis*. 2021;15:391–400.

36. Targownik LE, Singh H, Nugent Z, Bernstein CN. The epidemiology of colectomy in ulcerative colitis: results from a population-based cohort. *Am J Gastroenterol*. 2012;107:1228–1235.

37. Aratari A, Papic C, Clemente V, et al. Colectomy rate in acute severe ulcerative colitis in the infliximab era. *Dig Liver Dis*. 2008;40:821–826.

38. Laharie D, Bourreille A, Branche J, et al. Long-term outcome of patients with steroid-refractory acute severe UC treated with ciclosporin or infliximab. *Gut*. 2018;67:237–243.

39. Stevens TW, Haasnoot ML, D’Haens GR, et al. Laparoscopic ileocecal resection versus infliximab for terminal ileitis in Crohn's disease: retrospective long-term follow-up of the LIRIC trial. *Lancet Gastroenterol Hepatol*. 2020;5:900–907.

40. Rodríguez-Lago I, Hoyo J, Pérez-Girbés A, et al. Early treatment with anti-tumor necrosis factor agents improves long-term effectiveness in symptomatic strictureing Crohn's disease. *United Eur Gastroenterol J*. 2020;8:1056–1066.

41. Reenaers C, Mary J-Y, Nachury M, et al. Outcomes 7 years after withdrawal of anti-TNF therapy in patients with inflammatory bowel disease: a real-life cohort from northern India. *Indian J Gastroenterol*. 2020;39:388–397.
43. Bots SJ, Kuin S, Ponsioen CY, et al. Relapse rates and predictors for relapse in a real-life cohort of IBD patients after discontinuation of anti-TNF therapy. *Scand J Gastroenterol*. 2019;54:281–288.

44. Fernandes SR, Bernardo S, Simões C, et al. Proactive infliximab drug monitoring is superior to conventional management in inflammatory bowel disease. *Inflamm Bowel Dis*. 2020;26:263–270.

45. Papamichael K, Rakowsky S, Rivera C, Cheifetz AS, Osterman MT. Association between serum infliximab trough concentrations during maintenance therapy and biochemical, endoscopic, and histologic remission in Crohn’s Disease. *Inflamm Bowel Dis*. 2018;24:2266–2271.

46. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn’s disease. *Aliment Pharmacol Ther*. 2017;45:933–940.

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