Inflammatory bowel disease in older patients: from gut feeling towards evidence-based medicine

Asscher, V.E.R.

4

Anti-tumor necrosis factor therapy in patients with inflammatory bowel disease: comorbidity, not patient age, is a predictor of severe adverse events

International Journal of Colorectal Disease 2020

Vera E.R. Asscher
Quirine van der Vliet
Karen van der Aalst
Anniek van der Aalst
Eelco C. Brand
Andrea E. van der Meulen-de Jong
Bas Oldenburg
Marieke J. Pierik
Bas van Tuyl
Nofel Mahmmod
P.W. Jeroen Maljaars
Herma H. Fidder
On behalf of the Dutch Initiative on Crohn and Colitis (ICC)

ABSTRACT

Aim To assess safety and effectiveness of anti-tumor necrosis factor (anti-TNF) therapy in IBD patients ≥60 years.

Methods Ninety IBD patients ≥60 years at initiation of anti-TNF therapy, 145 IBD patients ≥60 years without anti-TNF therapy and 257 IBD patients <60 years at initiation of anti-TNF therapy were retrospectively included in this multicentre study. Primary outcome was the occurrence of severe adverse events (SAE's), serious infections and malignancies. Secondary outcome was effectiveness of therapy. Cox regression analyses were used to assess differences in safety and effectiveness. In safety analyses, first older patients with and without anti-TNF therapy and then older and younger patients with anti-TNF therapy were assessed.

Results In older IBD patients, the use of anti-TNF therapy was associated with serious infections (aHR 3.920, 95% CI 1.185-12.973, p=.025). In anti-TNF exposed patients, cardiovascular disease associated with serious infections (aHR 3.279, 95% CI1.098-9.790, p=.033), and the presence of multiple comorbidities (HR 9.138 (1.248-66.935), p=.029) with malignancies, while patient age did not associate with safety outcomes. Effectiveness of therapy was not affected by age or comorbidity.

Conclusions Older patients receiving anti-TNF therapy have a higher risk of serious infections compared to older IBD patients without anti-TNF therapy, but not compared to younger patients receiving anti-TNF therapy. However, in anti-TNF exposed patients, comorbidity was found to be an indicator with regards to SAE's. Effectiveness was comparable between older and younger patients.

INTRODUCTION

As a consequence of the aging population and the rising prevalence of inflammatory bowel diseases (IBD), the group of older patients with Crohn's disease (CD) or ulcerative colitis (UC) is enlarging. [1] Currently, approximately 10-30% of IBD patients is >60 years old and about 10-15% of new IBD cases is diagnosed in patients >60 years of age. [2-4]

Safety and effectiveness of medication may differ between older and younger patients, as a consequence of comorbidity, polypharmacy, senescence of the immune system or altered clearance of drugs. [5 6] Results from clinical trials cannot be extrapolated to the older patient population with IBD because these patients are generally excluded from trial participation and available data from observational studies on the occurrence of severe adverse events (SAE's) in older IBD patients exposed to anti-TNF therapy are inconsistent. [7-10] Besides this, previous literature has been focussing on patient age, rather than comorbidity as a predictor of safety and effectiveness in patients with IBD receiving anti-tumor necrosis factor (TNF) therapy.

The aim of the present study is therefore to assess safety and effectiveness of anti-TNF therapy in patients with IBD aged 60 years and older while accounting for the presence of comorbidities.

METHODS

Patients

This is a retrospective multicentre cohort study combining data from five hospitals in the Netherlands (University Medical Centre Utrecht (UMCU), St. Antonius Hospital Nieuwegein, Diakonessenhuis Utrecht, Leiden University Medical Centre (LUMC) and Maastricht University Medical Centre (MUMC)) on the effect of patient age on safety and effectiveness of anti-TNF therapy (infliximab (IFX), adalimumab (ADA) or certolizumab pegol (CZP)). Ethical approval has been granted by the medical research ethics committee Leiden The Hague Delft, MREC registration number G20.057 and research was conducted in accordance with the ethical standards as laid down in the declaration of Helsinki. Patients with an established IBD diagnosis were assigned to one of three groups.[11] First, patients exposed to anti-TNF therapy for the first time at ≥60 years, second, patients without any exposure to anti-TNF therapy aged ≥60 years and third, patients <60 years exposed to anti-TNF therapy.

The following data were collected: age, sex, diagnosis, date of diagnosis, duration of follow-up, number of IBD-related hospitalizations and data on anti-TNF therapy and immunosuppressive medication. Oral prednisone treatment was documented if prescribed for a period of at least six months at daily doses of ≥7.5 milligrams. Hepatic comorbidities (steatosis, drug induced liver disease, chronic hepatitis B, chronic hepatitis C and alcoholic

liver disease), gastro-intestinal comorbidities (celiac disease, diverticular disease, ischemic colitis, drug induced colitis and radiation enteropathy), cardiovascular comorbidities (acute mesenteric ischemia, ischemic heart disease, cerebrovascular disease and hypertension), pulmonary comorbidities (asthmatic bronchitis and chronic obstructive pulmonary disease) and the presence of diabetes were recorded.

Outcomes

Primary outcome was safety, defined as the occurrence of any SAE, serious infection or malignancy. Any SAE was defined as any event that resulted in (prolonging) hospitalization, was fatal or life-threatening or led to significant disability. Serious infections were defined similarly. A malignancy was considered a SAE. In addition, serious infections and malignancies were analysed separately as safety outcomes. Hospitalization at start of anti-TNF therapy was not considered a SAE.

Secondary outcome was effectiveness of therapy, defined by treatment response, which was categorized as total sustained clinical benefit (primary clinical benefit or secondary clinical benefit, see below) or no sustained clinical benefit. Patients still receiving anti-TNF therapy at the last day of follow-up or in whom therapy had been discontinued because of remission were assigned to the total sustained clinical benefit group. If anti-TNF therapy had never been switched to another type of TNF-inhibitor, total sustained clinical benefit was scored as primary clinical benefit. Total sustained clinical benefit after one or more switches of anti-TNF therapy was labelled secondary clinical benefit. If anti-TNF therapy was discontinued because of primary non-response, loss of response, occurrence of an adverse event or any other reason, patients were classified as having 'no sustained clinical benefit'. Primary non-response was defined as lack of improvement of clinical signs and symptoms after induction therapy. Loss of response was defined as recurrence of disease activity during maintenance therapy after achieving an appropriate induction response. [12]

Statistical analysis

All analyses were performed using IBM SPSS Statistics version 23.0 (SPSS, Inc, Chicago, IL). For continuous data, descriptive statistics were calculated as means with standard deviations (SD) when data were normally distributed and medians with interquartile ranges (IQR) when not normally distributed. Comparisons between groups were performed using Independent-Samples-T Test or Mann-Whitney U test. Categorical variables were reported using absolute numbers and percentages, comparisons were performed using the $\chi 2$ test or Fisher's exact test. Cox proportional hazards model was used to assess the effect of patient age and comorbidity on primary and secondary outcomes and to assess the effect of therapy as a time dependent variable on primary outcome. To assess whether comorbidity or patient age at start of first anti-TNF therapy affected effectiveness outcomes, Cox proportional hazards model was used. Safety was defined in three different outcomes: any SAE, serious infection and malignancy. For any SAE and malignancy analyses, events occurring until end of follow-up were used. For serious infections, events occurring up until three months

after last administration of medication were used. Effectiveness was defined as duration of anti-TNF therapy.

To assess the influence of anti-TNF therapy on the occurrence of infections and malignancies as a time dependent variable, exposure to anti-TNF therapy was tested as a time-dependent covariate in a Cox proportional hazards model. Exposure time was defined as time from the first anti-TNF infusion until the occurrence of a SAE or end of follow-up. We selected older IBD patients with and without anti-TNF therapy and used duration of follow up since date of diagnosis until end of follow-up as 'time' in the malignancy analysis and follow-up since date of diagnosis until 3 months after the last date of first anti-TNF therapy or end of follow-up in the infection analysis. Hospitalization of any infection or the diagnosis of any malignancy was used as 'status'. In the analyses regarding malignancies, covariates age, comorbidity (categorized in no comorbidity, one comorbidity and two or more comorbidities, or specified in cardiovascular disease and diabetes), use of immunosuppressive therapy (oral prednisone and MTX/thiopurine use), use of budesonide and use of anti-TNF therapy were used. In the analysis regarding serious infections, immunosuppressive therapy was not used as a covariate because a cut off follow-up duration was applied and start and stop dates of immunosuppressive therapy had not been consistently documented. A p-value of <.05 was considered statistically significant.

RESULTS

Study population characteristics

We identified 347 IBD patients currently using anti-TNF therapy, of whom 90 were 60 years or older at initiation of anti-TNF therapy and of whom 257 patients were younger than 60 years at the start of anti-TNF therapy. An additional 145 anti-TNF naive IBD patients of 60 years or older served as controls. The first group of patients was included in the hospitals UMCU (24.4%), St. Antonius Hospital Nieuwegein (16.7%), Diakonessenhuis Utrecht (5.6%), LUMC (17.8%) and MUMC (35.7%). Patients from group 2 were included in the hospitals UMCU (81.7%), Sint Antonius Hospital Nieuwegein (1.9%), Diakonessenhuis Utrecht (4.7%), LUMC (4.3%) and MUMC (7.4%). Patients in group 3 were included in UMCU (99.3%) and LUMC (0.7%). Characteristics of these patients are shown in table 1.

Older patients receiving anti-TNF therapy less often had CD compared to patients receiving anti-TNF therapy at a younger age. The older patients more often had diabetes, gastro-intestinal, cardiovascular and other comorbidities and less often used MTX or thiopurine therapy compared to younger patients with anti-TNF therapy (87.8% versus 96.1%, p<.010). Patients in the anti-TNF naive group were diagnosed at a younger age when compared to the older patients on anti-TNF therapy. Anti-TNF naive patients differed from the older patients on anti-TNF therapy with respect to diagnosis (less CD, more UC) and the use

of immunosuppressive therapy (less thiopurines or MTX). Comorbidity rates were similar between older IBD patients with and without anti-TNF therapy.

Does anti-TNF therapy influence the occurrence of safety outcomes in older patients?

To assess the effect of anti-TNF therapy on safety outcomes in older patients, all older patients were analysed using date of diagnosis as start of follow up, with the use of anti-TNF therapy as a time-dependent covariate.

Twenty-eight serious infections occurred during follow-up. Use of anti-TNF therapy was found to increase risk of serious infections (aHR 3.920, 95% CI 1.185-12.973, p=.025) in multivariable Cox regression. Age at diagnosis, number of comorbidities (table 2) and the presence of cardiovascular disease or diabetes (data not shown) present did not affect the risk of serious infections (table 2).

Twenty-six malignancies occurred during follow-up. Univariable and multivariable Cox regression analysis did not show an association between the use of anti-TNF therapy and the development of malignancies during follow-up (table 3). The presence of the comorbidities diabetes and/or cardiovascular disease was also not associated with occurrence of malignancies (data not shown). Infections and malignancies are presented in supplementary table 1 and 2.

Do patient age or comorbidity affect the safety of anti-TNF therapy?

To assess the effect of patient age and comorbidity on safety outcomes in anti-TNF therapy, all anti-TNF exposed patients were analysed. One hundred and eighteen SAE's (any SAE) occurred after start of first anti-TNF therapy, the majority (46, 40.0%) because of exacerbation of disease and 26 (22.3%) because of IBD-related surgery. Age at start of anti-TNF therapy and comorbidity were not associated with the occurrence of any SAE (supplementary table 3a). The incidence of IBD-related surgery did not differ between older and younger anti-TNF users (5 out of 90 patients (5.6%) versus 21 out of 257 (8.2%), p=0.417).

Twenty serious infections occurred after start of anti-TNF therapy, but age did not affect the risk of occurrence. The presence of cardiovascular disease was independently associated with the occurrence of serious infections (aHR 3.279, 95% CI 1.098-9.790, p=.033), whereas presence of diabetes or the presence of any comorbidity was not (supplementary table 3b).

Eight malignancies were diagnosed after start of anti-TNF therapy, age was not a risk factor (supplementary table 3c).The presence of two or more comorbidities was independently associated with the risk of developing a malignancy (aHR 9.138, 95% CI 1.248-66.935, p=.029, supplementary table 3c). A list of all SAE's occurring after start of first anti-TNF therapy is presented in supplementary tables 4, 5 and 6.

Do patient age or comorbidity affect the effectiveness of anti-TNF therapy?
The clinical effectiveness of anti-TNF therapy did not differ between older and younger anti-TNF users (table 4) or between patients with and without comorbidity. Follow up, defined as the time from first anti-TNF administration until discontinuation of therapy was significantly shorter in the group of older patients compared to younger patients (median duration 70.5 weeks (34.0-155.3) versus 110.0 weeks (41.5-217.0), p=.017, table 4). Follow up did not differ between patients with and without comorbidity (median duration 114.0 weeks (47.0-221.0) versus 92.0 weeks (35.0-200.5), p=.161). When using Cox regression analysis, age at start of anti-TNF therapy, comorbidity and type of anti-TNF therapy did not affect duration of treatment (table 5). The presence of diabetes or cardiovascular disease during follow-up did not significantly affect the duration of treatment as well (data not shown).

The number of older patients discontinuing anti-TNF therapy because of adverse events was significantly higher compared to younger patients (55.9% versus 28.1%, p=.004, table 4) while the number of older patients stopping because of loss of response was significantly lower (26.5% versus 59.5%, p=.001, table 4). The number of patients with comorbidity discontinuing anti-TNF therapy because of adverse events was significantly higher compared to patients without comorbidity (47.1% versus 27.9%, p=.018). The number of patients with comorbidity stopping because of loss of response was lower as compared to patients without comorbidity, although this did not differ significantly (43.1% versus 56.7%, p=.111). Reasons for stopping are presented in supplementary table 7.

Table 1. Characteristics of study population

	Older patients with anti-TNF therapy (n=90)	**Older patients without anti-TNF therapy (n=145)**	**Younger patients with anti-TNF therapy (n=257)**
Age at inclusion in years, median [IQR]	68.72 [66.74-73.00]	69.44 [65.01-75.02]	37.43 [27.72-20.24]***
Male, n (%)	49 (54.4)	84 (57.9)	121 (47.1)
Age at diagnosis, mean (±SD)	52.15 (16.10)	46.39 (15.75)**	26.16 (11.27)***
Age at start anti-TNF therapy, mean (±SD)	67.56 (6.00)	n.a.	34.18 (12.94)***
Disease duration in years, median [IQR]	16.67 [5.73-29.48]	21.31 [12.04-34.14]**	10.14 [5.58-18.23]*
Duration of FU in weeks (start first anti-TNF till end FU or stop therapy) median [IQR]	70.50 [34.00-155.25]	n.a.	110.00 [41.50-217.00]*

Table 1. Continued.

	Older patients with anti-TNF therapy (n=90)	**Older patients without anti-TNF therapy (n=145)**	**Younger patients with anti-TNF therapy (n=257)**
Duration of FU in months (date diagnosis till malignancy or end FU), median [IQR]	194.00 [66.00-322.50]	249.00 [144.00-396.00]	n.a.
Duration of total anti-TNF therapy in years, median [IQR]	1.72 [0.81-4.04]	n.a.	3.34 [1.44-5.41]***
Type of IBD, n (%)			
CD	56 (62.2)	67 (46.2)**	206 (80.2)**
UC	30 (33.3)	71 (49.0)**	44 (17.1)**
IBD-U/IC	4 (4.4)	7 (4.8)	7 (2.7)
Montreal Classification, n(%)			
CD Location L1/L2/ L3/L4	11 (19.6)/ 18 (32.1)/ 26 (46.2)/ 1 (1.8)	14 (21.2)/ 25 (37.9)/ 27 (40.9)/ 0 (0.0)	30 (14.6)/ 61 (29.6)/ 112 (54.4)/ 3 (1.5)
CD Behaviour B1/ B2/B3	19 (34.5)/ 26 (47.3)/ 10 (18.2)	36 (53.7)/ 17 (25.4)/14 (20.9)*	81 (39.5)/ 68 (33.2)/ 56 (27.3)
Perianal disease	21 (41.1)	10 (15.2)**	85 (43.4)
UC extension E1/ E2/E3	0 (0.0)/ 14 (45.2)/ 17 (54.8)	2 (2.9)/29 (42.6)/ 37(54.4)	1 (2.2)/ 12 (26.7)/ 32 (71.1)
Comorbidity, n (%)			
Hepatic	6 (6.7)	14 (9.7)	8 (3.1)
Gastrointestinal	19 (21.1)	28 (19.3)	6 (2.3)***
Cardiovascular	35 (38.9)	74 (51.0)	34 (13.2)***
Pulmonary	10 (11.1)	18 (12.4)	18 (7.0)
Diabetes Mellitus	14 (15.7)	18 (12.4)	12 (4.7)**
Comorbidity, n (%)			
No comorbidity	35 (38.9)	47 (32.4)	191 (74.3)***
One comorbidity	33 (36.7)	55 (37.9)	54 (21.0)
Two or more comorbidities	22 (24.4)	43 (29.7)	12 (4.7)
Type of TNF-inhibitor, n (%)			
IFX	67	n.a.	220*
ADA	44		129
CZP	0 (0.0)		5

Table 1. Continued.

	Older patients with anti-TNF therapy (n=90)	**Older patients without anti-TNF therapy (n=145)**	**Younger patients with anti-TNF therapy (n=257)**
Immunosuppressant, n (%)			
Thiopurines/MTX	79 (87.8)	51 (35.4)***	247 (96.1)**

Older Inflammatory Bowel Disease (IBD) patients (≥60 years) at initiation of anti-tumor necrosis factor (anti-TNF) therapy were compared to older IBD patients (≥60 years) without any anti-TNF therapy and with younger IBD patients aged <60 years at initiation of anti-TNF therapy. Significant differences are shown. *** p<.001, **p<.01, *p<.05.

IQR=interquartile range, SD=standard deviation, FU=follow-up, CD=Crohn's disease, UC=ulcerative colitis, IBD-U=IBD Unclassified, IC=Indeterminate Colitis, IFX=Infliximab, ADA=Adalimumab, CZP=Certoluzimab pegol, MTX=Methotrexate.

L4 was reported when only upper Gastrointestinal (GI) disease was present, CD Location was missing in N=1 (group 3), CD Behaviour was missing in N=1 (group 1) and N=1 (group 2), Perianal disease was missing in N=5 (group 1), N=10 (group 2) and N=1 (group 3), UC Extension was missing in N=3 (group 1), N=6 (group 2) and N=10 (group 3). The use of MTX was missing in N=1 in the group with older IBD patients without anti-TNF therapy.

Table 2. Univariable and multivariable analysis on the occurrence of serious infections in older anti-TNF users and older non-users, using follow-up time from date of diagnosis until 3 months after last administration of anti-TNF therapy or end of follow-up

	Univariable Analysis			**Multivariable analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
anti-TNF therapy	5.131	1.679-15.684	0.004	3.920	1.185-12.973	0.025
Age at diagnosis	1.026	0.997-1.057	0.078	1.018	0.987-1.049	0.264
Comorbidity*						
1	1.308	0.550-3.112	0.544	1.164	0.487-2.785	0.733
2 or more	1.202	0.445-3.247	0.717	0.999	0.363-2.751	0.998

HR=Hazard Ratio, CI=Confidence Interval, TNF=Tumor Necrosis Factor *reference is zero comorbidities.

Table 3. Univariable and multivariable analysis on the occurrence of malignancies in older anti-TNF users and older non-users, using follow-up time from date of diagnosis until end of follow-up

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Anti-TNF therapy	2.617	0.770-8.894	0.123	1.422	0.284-7.128	0.668
Age at diagnosis	1.046	1.010-1.082	0.011	1.025	0.989-1.063	0.178
Comorbidity*						
1	3.248	1.058-9.971	0.040	2.706	0.844-8.683	0.094
2 or more	4.036	1.238-13.156	0.021	2.869	0.809-10.183	0.103
Budesonide	1.681	0.771-3.663	0.191	1.746	0.758-4.018	0.190
Oral prednisone	0.721	0.287-1.815	0.488	1.012	0.365-2.802	0.982
MTX and/or thiopurine use	0.700	0.321-1.527	0.270	0.630	0.245-1.621	0.338

HR=Hazard Ratio, CI=Confidence Interval, TNF=Tumor Necrosis Factor, MTX= Methotrexate *reference is zero comorbidities

Table 4. Treatment response in older and younger anti-TNF users

	Older anti-TNF patients (n=90)	**Younger anti-TNF patients (n=257)**	**P-value**
First anti-TNF therapy, n (%)			
IFX	59 (65.6)	199 (77.4)	0.035
ADA	31 (34.4)	58 (22.6)	
First anti-TNF treatment duration in weeks, median [IQR]	70.50 [34.00-155.25]	110.00 [41.50-217.00]	0.017
Stop date of first anti-TNF therapy n (%)*			0.004
year <2005	0 (0,0)	14 (11.0)	
year 2005-2009	6 (17.1)	46 (36.2)	
year ≥2010	29 (82.9)	67 (52.8)	
Total sustained clinical benefit,	73 (81.1)	201 (78.2)	0.653
n (%)	55 (61.1)	133 (51.8)	0.141
Primary clinical benefit, n (%)	18 (20.0)	68 (26.5)	0.257
Secondary clinical benefit, n (%)			
Stop reasons for first anti-TNF treatment , n (%)			
Primary non-responder	1 (2.9)	5 (4.7)	1.000
Secondary loss of response	9 (26.5)	72 (59.5)	0.001
Adverse event	19 (55.9)	34 (28.1)	0.004
Other	5 (14.7)	10 (8.3)	0.323

Treatment response compared between patients on anti-TNF therapy aged ≥60 years and aged <60 years. Stop date of first anti-TNF therapy: the year in which the first anti-TNF therapy was stopped. Total sustained clinical benefit: still receiving anti-TNF therapy at last day of FU or anti-TNF therapy discontinuation because of remission. Primary clinical benefit: no switch to other anti-TNF therapy during FU and still receiving anti-TNF therapy at last day of FU or discontinuation of remission of disease. Secondary clinical benefit: clinical benefit after one or more switches of anti-TNF therapy. Primary non-responder: lack of improvement of clinical signs and symptoms after induction therapy. Secondary loss of response: recurrence of disease activity during maintenance therapy after achieving an appropriate induction response. Percentages per stop reason were calculated as percentage of all stop reasons per group. TNF= Tumor Necrosis Factor, IQR=Interquartile Range, IFX=Infliximab, ADA=Adalimumab, FU=Follow-Up

Table 5. Univariable and multivariable analysis on duration of first anti-TNF treatment

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	0.999	0.991-1.008	0.906	1.000	0.990-1.010	0.966
Comorbidity*						
1	0.739	0.501-1.088	0.126	0.731	0.484-1.104	0.137
2 or more	1.130	0.676-1.887	0.642	1.130	0.635-2.012	0.678
Type of anti-TNF therapy±	1.087	0.753-1.568	0.657	1.114	0.767-1.620	0.570

HR=Hazard Ratio, CI=Confidence Interval, TNF=Tumor Necrosis Factor *reference is zero comorbidities, ±reference is infliximab therapy (certolizumab pegol was not used as first anti-TNF therapy)

DISCUSSION

In this multicentre study we found that the presence of comorbidity was a better indicator of serious infections and malignancies in anti-TNF exposed patients than patient age. Effectiveness of anti-TNF therapy was comparable between older and younger patients. Reasons for cessation of therapy did differ, being more often due to adverse events in older patients and patients with comorbidity.

In our study, exposure to anti-TNF treatment increased the risk of serious infections in older patients with IBD. In the Treat registry an increase in serious infections was observed in anti-TNF treated IBD patients. [13] Lobaton et al. found a higher incidence of serious infections in patients aged ≥65 years on anti-TNF therapy as compared to older patients using immunosuppressive medication and/or corticosteroids. [8]

More recently, two meta-analyses were published assessing safety risks of biologics in older patients with IBD. Both Piovani et al. (RR 2.70, 95% CI 1.56-4.66, serious infections) and Borren and Ananthakrishnan (OR 11.22; 95% CI 3.60-34.99, any infection) found that the risk of infections was substantially increased when comparing older anti-TNF users to older non-users.[14 15]

When comparing younger to older patients, we used age at start of follow-up as a factor in multivariate analysis instead of using an arbitrary cut-off at 60 or 65 years of age. As ageing is a gradual process with a steady reduction of physiologic reserves, this strategy may be a better way to evaluate the role of ageing on occurrence of serious infections and malignancies. In our study, patient age did not affect the occurrence of SAE's, serious infections and malignancies. However, presence of cardiovascular disease did increase the risk of serious infections, and the presence of multiple comorbidities increased the risk of developing a malignancy.

These findings are in contrast to those of the Borren and Ananthakrishnan meta-analysis, in which older patients had a higher risk of malignancy (OR, 3.47; 95% CI, 1.71–7.03) and

infection (OR, 3.48; 95% CI, 1.98–6.14). This may be due to the fact that the patients in a number of these studies were older [16 17] and may have had more comorbidities.

Especially this latter factor may be important as studies on toxicity of chemotherapy found that comorbidity increases the risk for toxicity and is a better indicator for toxicity risk than patient age.[16 17] Previous studies found that presence of comorbidities increased the risk for adverse events in response to immunosuppressive treatments. [18 19]

Desai et al. concluded that older IBD patients were less likely to respond to anti-TNF therapy and had a shorter drug survival as compared to younger patients. Among both patient groups, comorbidity (Charlson Comorbidity Index (CCI) >0) was associated with anti-TNF therapy discontinuation. This could be due to polypharmacy combined with altered drug absorption, distribution and elimination [20] or due to an increased opportunity for drug interactions because of polypharmacy for multiple morbidities. [21]

In line with a recent study on persistence of anti-TNF therapy in older patients with IBD by Porcari et al. [22] we observed a shorter treatment duration in older patients compared to younger patients. However, when analysing both patient groups together using Cox regression analysis and correcting for confounders, age at start of therapy did not affect treatment duration. Older patients did discontinue therapy more frequently due to adverse events, and less often due to loss of response, as compared with younger patients. This has also been described by Desai et al.[7] Both our results and the study by Porcari et al. did not find comorbidity to affect time to cessation of anti-TNF therapy while Desai et al. found increasing comorbidity to be associated with treatment cessation.[7] Regarding effectiveness, Lobaton et al. only found a reduced short-term response to anti-TNF therapy in older patients, but this difference disappeared after six months. [8]

Our study has some limitations, in addition to those inherent to any study with a retrospective design. Clinical activity scores were not available, as a result of which data on clinical treatment response were based on comments in medical reports instead of disease activity scores. Comorbidity scores were based on the sum of comorbidities because information to calculate a comorbidity score such as the CCI was not fully available. However, because data in all patients were obtained from medical reports, reporting bias would have affected all patients equally. Furthermore, younger patients exposed to anti-TNF therapy were mostly (93.4%) included in referral centres and the older non anti-TNF users were included in referral hospitals only. One could argue this could have affected comparability of patients, although we assume that in all hospitals international guidelines considering anti-TNF therapy are maintained, especially concerning reasons to stop therapy. The older non anti-TNF users, although included in a referral centre, had a milder disease compared to older anti-TNF users, as expressed by the infrequent use of immunomodulatory medication in this group during follow-up.

The strength of our study lies in the large number of patients included and the multicentre aspect; patients were included from three referral hospitals and two general hospitals. We believe that our study therefore provides reliable and generalizable data on the effect of anti-TNF compounds in older patients with IBD.

In conclusion, this study shows that the presence of comorbidities, and not an increasing age, is a risk factor for SAE's in IBD patients on anti-TNF therapy. Older patients receiving anti-TNF therapy have a higher risk of serious infections compared to older IBD patients without anti-TNF therapy, but not compared to younger IBD patients receiving anti-TNF therapy. Effectiveness of therapy was comparable between older and younger patients but older patients tend to stop therapy more often because of adverse events and less often due to loss of response compared to younger patients. Careful monitoring of the older IBD patient with multiple comorbidities receiving anti-TNF therapy is recommended.

REFERENCES

1. Cosnes J, Gower-Rousseau C, Seksik P, et al. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology* 2011;140(6):1785-94. doi: 10.1053/j.gastro.2011.01.055 [published Online First: 2011/05/03]
2. del Val JH. Old-age inflammatory bowel disease onset: a different problem? *World J Gastroenterol* 2011;17(22):2734-9. doi: 10.3748/wjg.v17.i22.2734
3. Hadithi M, Cazemier M, Meijer GA, et al. Retrospective analysis of old-age colitis in the Dutch inflammatory bowel disease population. *World J Gastroenterol* 2008;14(20):3183-7.
4. Loftus EV, Jr., Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. *Gut* 2000;46(3):336-43.
5. Hamaker ME, Jonker JM, de Rooij SE, et al. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol* 2012;13(10):e437-44. doi: 10.1016/S1470-2045(12)70259-0 [published Online First: 2012/10/03]
6. Fulop T, Witkowski JM, Pawelec G, et al. On the immunological theory of aging. *Interdiscip Top Gerontol* 2014;39:163-76. doi: 10.1159/000358904
7. Desai A, Zator ZA, de Silva P, et al. Older age is associated with higher rate of discontinuation of anti-TNF therapy in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19(2):309-15. doi: 10.1002/ibd.23026 [published Online First: 2012/05/19]
8. Lobaton T, Ferrante M, Rutgeerts P, et al. Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2015;42(4):441-51. doi: 10.1111/apt.13294 [published Online First: 2015/06/25]
9. Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;9(1):30-5. doi: 10.1016/j.cgh.2010.09.026 [published Online First: 2010/10/19]
10. Colombel JF, Loftus EV, Jr., Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004;126(1):19-31.
11. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1989;170:2-6; discussion 16-9. [published Online First: 1989/01/01]
12. Yanai H, Hanauer SB. Assessing response and loss of response to biological therapies in IBD. *Am J Gastroenterol* 2011;106(4):685-98. doi: 10.1038/ajg.2011.103
13. Lichtenstein GR, Feagan BG, Cohen RD, et al. Infliximab for Crohn's Disease: More Than 13 Years of Real-world Experience. *Inflamm Bowel Dis* 2018;24(3):490-501. doi: 10.1093/ibd/izx072 [published Online First: 2018/02/21]
14. Piovani D, Danese S, Peyrin-Biroulet L, et al. Systematic review with meta-analysis: biologics and risk of infection or cancer in elderly patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2020 doi: 10.1111/apt.15692 [published Online First: 2020/03/15]
15. Borren NZ, Ananthakrishnan AN. Safety of Biologic Therapy in Older Patients with Immune-Mediated Diseases: A Systematic Review and Meta-Analysis. *Clin Gastroenterol Hepatol* 2019 doi: 10.1016/j.cgh.2018.12.032 [published Online First: 2019/01/08]
16. Zauderer M, Patil S, Hurria A. Feasibility and toxicity of dose-dense adjuvant chemotherapy in older women with breast cancer. *Breast Cancer Res Treat* 2009;117(1):205-10. doi: 10.1007/s10549-008-0116-0 [published Online First: 2008/07/16]
17. Edwards MJ, Campbell ID, Lawrenson RA, et al. Influence of comorbidity on chemotherapy use for early breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat* 2017;165(1):17-39. doi: 10.1007/s10549-017-4295-4 [published Online First: 2017/05/22]

18. Cohen S, Radominski SC, Gomez-Reino JJ, et al. Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2014;66(11):2924-37. doi: 10.1002/art.38779 [published Online First: 2014/07/23]
19. Ananthakrishnan AN, Cagan A, Cai T, et al. Diabetes and the risk of infections with immunomodulator therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther* 2015;41(11):1141-8. doi: 10.1111/apt.13195 [published Online First: 2015/04/14]
20. Bressler R, Bahl JJ. Principles of drug therapy for the elderly patient. *Mayo Clin Proc* 2003;78(12):1564-77. doi: 10.4065/78.12.1564 [published Online First: 2003/12/10]
21. Zhang M, Holman CD, Price SD, et al. Comorbidity and repeat admission to hospital for adverse drug reactions in older adults: retrospective cohort study. *BMJ* 2009;338:a2752. doi: 10.1136/bmj.a2752 [published Online First: 2009/01/09]
22. 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;May;37(5):383-392 doi: 10.1007/s40266-020-00744-3 [published Online First: 2020/02/06]

Supplementary table 1. List of malignancies occurring during follow-up from date of diagnosis in older anti-TNF users and older non-users

Patient ID	Age at start follow-up	Time after diagnosis in months	Event type
441	16,13	404	Colorectal carcinoma
363	16,96	486	Colorectal cancer
347	20,26	433	Breast cancer
16	23,81	156	Pleomorphic adenoma of the parotid gland
442	24,18	502	Prostate cancer
416	28,96	345	Urothelial carcinoma
448	29,28	285	Colorectal carcinoma
17	30,33	324	Prostate cancer
48	31,81	322	Prostate cancer
444	32,64	244	Endometrial cancer
428	37,19	434	Non-Hodgkin lymphoma
326	37,75	233	Prostate cancer
440	38,41	300	Colorectal carcinoma
325	42,33	248	Pancreatic carcinoma
360	43,04	288	Colorectal cancer
382	43,49	208	Prostate cancer
402	44,42	271	Oesophageal carcinoma
61	46,8	254	Breast cancer
438	51,63	313	Colorectal carcinoma
6	52,29	162	Pancreatic carcinoma
394	52,65	176	Prostate cancer
310	56,22	24	Lung cancer
348	61,89	0	Colorectal cancer
72	62,71	32	Prostate cancer
322	67,85	96	Breast cancer
53	70,82	97	Renal cell cancer

Supplementary table 2. List of infections occurring after date of IBD diagnosis until 3 months after last administration of anti-TNF therapy or until end of follow up in older users and older non-users

Patient ID	Age at start follow-up	Time after diagnosis in months	Event type
1	25,80	156	Perianal abscess
17	30,33	235	Fever
26	59,93	3	Perianal abscess
28	46,58	153	Drainage of abscess
29	18,34	577	Fever due to bacterial translocation
32	24,75	114	Incision abdominal abscess
42	37,19	292	Drainage abdominal abscess
43	30,70	455	Cholangitis (suspect)
44	42,75	229	Perianal abscess next to pouch
47	46,60	6	Drainage perianal abscesses
52	31,13	317	CMV pouchitis and ileitis
58	29,63	264	Drainage of abscess
70	29,99	124	Incision and drainage perianal abscess
71	71,35	0	Fever and cold shivers
323	20,47	264	Abdominal abscess
341	53,15	82	Abscess right lower abdomen
365	43,38	335	Septic abdomen
375	66,38	14	Abscess
381	54,11	138	Abscess
382	43,49	35	Abscess
388	43,03	124	Incision and drainage perianal abscess
395	56,54	230	Intraabdominal abscess
402	44,42	119	Abdominal pain and fever
410	50,48	13	Gastroenteritis
412	53,87	13	Abscess
451	42,00	110	Douglas abscess
480	70,24	50	Abscess
491	64,68	2	Herpes zoster infection

Supplementary table 3a. Univariable and multivariable analysis on the occurrence of any SAE in older and younger IBD patients on anti-TNF therapy

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	0.988	0.988-1.008	0.629	0.992	0.980-1.003	0.154
Diabetes	1.740	0.977-3.098	0.060	1.783	0.990-3.211	0.054
Cardiovascular Disease	1.311	0.853-2.016	0.217	1.503	0.912-2.477	0.110

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	0.988	0.988-1.008	0.629	0.994	0.983-1.006	0.313
Comorbidity*						
1	0.961	0.620-1.491	0.860	1.042	0.655-1.658	0.862
2 or more	1.435	0.811-2.541	0.215	1.678	0.879-3.206	0.117

HR=Hazard Ratio, CI=Confidence Interval *reference is zero comorbidities

Supplementary table 3b. Univariable and multivariable analysis on the occurrence of serious infections in older and younger IBD patients on anti-TNF therapy

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	1.008	0.984-1.033	0.513	0.992	0.964-1.020	0.559
Diabetes	1.992	0.572-6.938	0.279	1.684	0.473-6.000	0.421
Cardiovascular disease	2.882	1.1727.085	0.021	3.279	1.098-9.790	0.033

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	1.008	0.984-1.033	0.513	1.002	0.975-1.029	0.907
Comorbidity*						
1	2.004	0.790-5.087	0.144	1.962	0.724-5.318	0.185
2 or more	1.552	0.336-7.166	0.573	1.492	0.282-7.893	0.638

HR=Hazard Ratio, CI=Confidence Interval *reference is zero comorbidities

Supplementary table 3c. Univariable and multivariable analysis on the occurrence of malignancies in older and younger IBD patients on anti-TNF therapy

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	1.061	1.015-1.109	0.009	1.050	0.995-1.107	0.076
Diabetes	6.506	1.535-27.571	0.011	3.970	0.929-16.961	0.063
Cardiovascular disease	4.250	1.059-17.049	0.041	1.593	0.338-7.519	0.556

	Univariable Analysis			**Multivariable Analysis**		
	HR	95% CI	P-value	HR	95% CI	P-value
Age at start therapy	1.061	1.015-1.109	0.009	1.035	0.979-1.095	0.223
Comorbidity*						
1	1.406	0.127-15.534	0.781	0.837	0.065-10.734	0.892
2 or more	19.545	3.741-102.101	0.000	9.138	1.248-66.935	0.029

HR=Hazard Ratio, CI=Confidence Interval *reference is zero comorbidities

Supplementary table 4. List of any serious adverse events after start of anti-TNF therapy up until end of follow-up

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	SAE category	SAE
281	11,4	14	Exacerbation	Exacerbation
306	12,31	382	Exacerbation	Exacerbation
243	14,23	3	Exacerbation	Exacerbation
222	15,27	49	IBD Surgery	Ileocecal resection
187	15,73	15	Exacerbation	Exacerbation
213	16,11	215	Exacerbation	Exacerbation
97	17,37	6	Exacerbation	Exacerbation
221	17,73	23	IBD related complication or symptom	Hematoma, abscess right lower abdomen and perihepatic abscess
207	18,13	80	Exacerbation	Exacerbation
147	18,62	28	IBD Surgery	Ileocecal resection
287	18,66	23	IBD related complication or symptom	Abdominal pain
194	18,71	316	Exacerbation	Exacerbation
120	18,86	144	Exacerbation	Exacerbation
226	19,09	132	Exacerbation	Exacerbation
98	20,11	89	IBD Surgery	Subtotal colectomy
85	20,56	169	Exacerbation/ Infection	Exacerbation or urinary tract infection
160	20,91	399	IBD Surgery	Subtotal colectomy
138	21,1	213	Medication complication	Sensibility loss of the lower legs
181	22,35	180	IBD related complication	Ileocecal abscess
174	22,38	329	Exacerbation	Exacerbation
252	22,6	38	IBD Surgery	Ileocecal resection
275	22,86	41	IBD related complication or symptom	Perianal abscess
141	22,9	135	IBD related complication or symptom	Ileitis
122	23,02	38	IBD related complication or symptom	Therapy refractory disease
105	23,29	34	Exacerbation	Exacerbation
121	23,56	113	IBD related complication or symptom	Extended perianal fistulae
90	23,88	107	Exacerbation	Exacerbation
305	24,04	36	IBD related complication or symptom	Pyoderma gangrenosum

Supplementary table 4. Continued.

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	SAE category	SAE
268	24,09	66	IBD Surgery	Proctocolectomy
175	24,36	24	Exacerbation	Exacerbation
303	24,58	46	Exacerbation	Exacerbation
162	25,22	4	Exacerbation	Exacerbation
215	25,61	223	IBD related complication or symptom	Rectal blood loss
307	26,26	37	IBD Surgery	Ileocecal resection
135	26,86	208	IBD Surgery	Proctocolectomy
134	26,89	8	Exacerbation	Exacerbation
152	27	177	IBD Surgery	Subtotal colectomy
113	27,71	51	IBD related complication or symptom	Protein losing enteropathy
273	27,77	147	IBD related complication or symptom	Abdominal pain
262	28,34	250	IBD related complication or symptom	Electrolyte disorder
237	28,71	152	Exacerbation	Exacerbation
115	28,9	375	IBD related complication or symptom	Diarrhoea and vomiting
286	29,13	45	Exacerbation	Exacerbation
283	29,4	14	Exacerbation	Exacerbation
119	29,46	290	Exacerbation	Exacerbation
225	29,68	19	Exacerbation	Exacerbation
255	30,1	79	IBD related complication or symptom	Stenosis lineal flexure
117	30,18	45	IBD Surgery	Ileocecal resection
278	31,16	140	IBD related complication or symptom	Ileus
267	31,45	34	Exacerbation	Exacerbation
302	33,51	121	Exacerbation	Exacerbation
233	33,67	64	Infection	Viral enteritis
288	34,18	19	Exacerbation	Exacerbation
197	34,97	72	Exacerbation	Exacerbation
201	36,13	5	IBD related complication or symptom	Stenosis ileum
171	36,38	1	IBD Surgery	Right hemicolectomy
92	36,4	64	IBD Surgery	Ileocecal resection

Supplementary table 4. Continued.

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	SAE category	SAE
308	37,25	321	Other	Clinical evaluation of Crohn's disease after six weeks treatment with oral prednisone
304	37,86	106	IBD Surgery	Part of jejunum resection
294	38,15	105	Infection	Bacterial meningitis
139	38,31	19	IBD Surgery	Part of jejunum resection
195	39,55	184	Exacerbation	Exacerbation
188	39,94	22	Exacerbation	Exacerbation
227	39,98	43	Other	Clinical injection adalimumab because of previous allergic reaction
190	40,12	208	Exacerbation	Exacerbation
251	40,22	148	Exacerbation	Exacerbation
154	40,54	39	IBD Surgery	Ileocecal resection
186	40,82	270	IBD related complication or symptom	Clinical colonoscopy because of dysplasia and crohn's disease
108	41,56	108	IBD Surgery	Subtotal colectomy
127	42,7	12	Exacerbation	Exacerbation
89	43,48	69	IBD related complication or symptom	Pancreatitis and primary sclerosing cholangitis
191	43,99	42	IBD Surgery	Right hemicolectomy
232	44,17	368	Exacerbation	Exacerbation
78	44,66	328	Malignancy	Urothelial cell carcinoma
218	44,69	28	Exacerbation	Exacerbation
246	44,81	3	IBD related complication or symptom	Constipation
256	47,08	153	Malignancy	Breast cancer
295	47,48	82	Infection	CMV infection
276	47,7	193	IBD Surgery	Ileocecal resection
236	48,02	144	IBD related complication or symptom	Abdominal pain
462	49,83	4	IBD related complication or symptom	Stenosis
457	51,26	544	IBD related complication or symptom/ Infection	Fever and perianal abscess
456	51,55	1	IBD Surgery	Incision and drainage of perianal abscess
196	52,39	60	Exacerbation	Exacerbation

Supplementary table 4. Continued.

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	SAE category	SAE
142	53,69	176	Exacerbation	Exacerbation
467	54,11	205	IBD related complication or symptom	Perianal abscess
470	54,22	9	Medication complication	Nausea and vomiting during azathiopurine treatment
460	54,75	6	IBD related complication or symptom	Anemia
466	56,6	213	IBD related complication or symptom	Ileus
472	56,77	28	IBD Surgery	Colectomy
478	57,46	177	Infection	Fever
82	58,43	4	IBD Surgery	Subtotal colectomy
487	59,46	6	Exacerbation	Exacerbation
54	60,76	11	IBD Surgery	Subtotal colectomy
6	61,63	43	IBD Surgery	Subtotal colectomy
70	61,74	10	Exacerbation	Exacerbation
44	61,77	6	IBD related complication or symptom	Perianal abscess
29	62,13	207	IBD related complication or symptom	Stenosis ileum
19	62,93	176	Exacerbation	Exacerbation
41	64,12	50	IBD related complication or symptom	Ileus
38	64,16	41	Exacerbation	Exacerbation
15	64,57	6	IBD Surgery	Subtotal colectomy
7	64,64	80	IBD Surgery	Subtotal colectomy
32	64,83	15	Infection	Cryptosporidium infection
40	65,14	77	IBD related complication or symptom	Ileus
11	65,66	41	Exacerbation	Exacerbation
64	65,71	68	IBD related complication or symptom	Constipation
476	65,77	24	IBD Surgery	Sigmoid resection
33	66,21	254	IBD related complication or symptom	Rectal blood loss and anemia

Supplementary table 4. Continued.

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	SAE category	SAE
43	67,18	10	IBD related complication or symptom	Stenosis
51	67,59	42	Exacerbation	Exacerbation
26	68,4	65	Infection	Pneumonia
62	69,52	77	Infection	Listeria bacteraemia
14	71,73	46	Exacerbation	Exacerbation
28	72,58	10	Exacerbation	Exacerbation
12	73,94	262	Exacerbation	Exacerbation
10	74,09	1	Exacerbation	Exacerbation
53	76,85	108	Malignancy	Renal cell tumor

Supplementary table 5. List of serious infections after start of anti-TNF therapy until 12 weeks after last administration of anti-TNF medication

Patient ID	Age at start anti-TNF therapy in years	Time after start therapy in weeks	Infection
221	17,73	23	Perihepatic and right lower abdomen abscess
85	20,56	169	Exacerbation or urinary tract infection
252	22,6	19	Cecal abscess
275	22,86	41	Perianal abscess
159	24,2	15	Drainage of abscess
303	24,58	250	Drainage of abscess
233	33,67	64	Viral enteritis
92	36,4	11	Drainage of abscess
294	38,15	105	Bacterial meningitis
251	40,22	519	Perianal abscess
295	47,48	82	CMV infection
457	51,26	544	Perianal abscess
456	51,55	1	Incision and drainage perianal abscess
467	54,11	205	Perianal abscess
472	56,77	196	Gastro-enteritis
478	57,46	181	Fever
487	59,46	457	Pneumonia
44	61,77	6	Perianal abscess
32	64,83	15	Cryptosporidium infection
43	67,18	78	Cholangitis

Supplementary table 6. List of malignancies after start of anti-TNF therapy until end of follow-up

Patient ID	Age at start anti-TNF therapy	Time after start therapy in weeks	Malignancy
89	43,48	298	Biliary adenocarcinoma
78	44,66	328	Urothelial carcinoma
218	44,69	582	Renal cell carcinoma
256	47,08	153	Breast cancer
487	59,46	0	Renal cell carcinoma
6	61,63	221	Pancreatic cancer
61	65,83	113	Breast cancer
53	76,85	108	Renal cell carcinoma

Supplementary table 7. List of stop reasons for first anti-TNF therapy

Patient ID	Age at start anti-TNF therapy	Time until stop therapy in weeks	Category	Stop reason
281	11,40	150	Adverse event	Allergic reaction
238	11,55	285	Loss of response	
123	15,12	219	Loss of response	
222	15,27	87	Loss of response	
187	15,73	17	Loss of response	
86	16,31	8	Adverse event	None specified
207	18,13	9	Loss of response	
110	18,32	36	Loss of response	
179	18,51	32	Loss of response	
194	18,71	260	Loss of response	
120	18,86	97	Loss of response	
266	18,97	8	Non response at first admission	
226	19,09	202	Loss of response	
98	20,11	8	Adverse event	Allergic reaction with antibodies
160	20,91	133	Adverse event	None specified
138	21,1	160	Loss of response	
203	21,35	297	Adverse event	None specified
249	21,64	69	Adverse event	Alopecia
177	21,73	17	Loss of response	
157	21,86	25	Loss of response	
100	22,15	53	Other	Patients wish; tiredness after admissions
181	22,35	26	Loss of response	
174	22,38	331	Loss of response	Loss of response
275	22,86	43	Loss of response	
141	22,9	164	Other	Pregnancy wish

Supplementary table 7. Continued.

Patient ID	Age at start anti-TNF therapy	Time until stop therapy in weeks	Category	Stop reason
296	22,91	8	Non response at first admission	
122	23,02	43	Loss of response	
137	23,02	2	Non response at first admission	
81	23,09	104	Adverse event	None specified
105	23,29	70	Other	Painful injection sites
121	23,56	492	Loss of response	
136	23,58	104	Other	Logistic reasons
90	23,88	47	Loss of response	
305	24,04	14	Loss of response	
268	24,09	13	Adverse event	Allergic reaction
159	24,2	56	Loss of response	
175	24,36	25	Adverse event	None specified
303	24,58	243	Loss of response	
146	25,01	16	Adverse reaction	Allergic reaction with antibodies
162	25,22	305	Other	None specified
104	25,43	69	Loss of response	
215	25,61	192	Other	Discontinuation at patients own initiative
106	25,87	39	Loss of response	
214	26,23	340	Loss of response	
307	26,26	200	Adverse event	Back pain
135	26,86	76	Loss of response	
134	26,89	13	Loss of response	
152	27	10	Adverse event	Non specified
113	27,71	306	Loss of response	
273	27,77	15	Adverse event	Itching injection site
242	28,73	2	Loss of response	
115	28,9	180	Loss of response	
291	29,08	50	Loss of response	
286	29,13	0,57	Adverse event	Infiltrate at site of injection
165	29,35	690	Adverse event	None specified
283	29,4	47	Loss of response	
119	29,46	70	Other	Discontinuation at patients own initiative
220	29,6	5	Other	Surgical intervention

Supplementary table 7. Continued.

Patient ID	Age at start anti-TNF therapy	Time until stop therapy in weeks	Category	Stop reason
225	29,68	4	Other	No reason for treatment discontinuation found
247	29,79	40	Loss of response	
255	30,1	133	Loss of response	
117	30,18	12	Loss of response	
184	30,41	2	Adverse event	None specified
130	31,05	14	Loss of response	
300	31,11	1	Adverse event	Delayed hypersensitivity reaction
278	31,16	39	Adverse event	Allergic reaction
267	31,45	26	Loss of response	
211	32,61	156	Loss of response	
166	32,76	140	Loss of response	
302	33,51	4	Non response at first admission	
87	33,71	63	Loss of response	
197	34,97	131	Adverse event	None specified
308	37,25	6	Non response at first admission	
253	37,47	26	Loss of response	
99	37,48	115	Loss of response	
167	37,68	189	Loss of response	
304	37,86	49	Adverse event	Hyperpigmentation
299	38,01	184	Loss of response	
173	38,24	20	Loss of response	
176	39,05	6	Loss of response	
114	39,48	52	Loss of response	
188	39,94	86	Loss of response	
227	39,98	1	Adverse event	Allergic reaction
190	40,12	95	Adverse event	None specified
251	40,22	513	Loss of response	
124	40,31	52	Loss of response	
154	40,54	39	Loss of response	
186	40,82	52	Loss of response	
289	41,16	6	Adverse event	Skin reaction
108	41,56	57	Loss of response	
208	42,33	24	Loss of response	
127	42,7	49	Adverse event	None specified
89	43,48	61	Loss of response	
189	43,56	297	Loss of response	
191	43,99	26	Loss of response	

Supplementary table 7. Continued.

Patient ID	Age at start anti-TNF therapy	Time until stop therapy in weeks	Category	Stop reason
78	44,66	115	Adverse event	Herpes simplex virus keratitis and patients wish to stop medication
218	44,69	71	Loss of response	
246	44,81	74	Loss of response	
206	45,88	53	Loss of response	
490	46,47	387	Loss of response	
297	47,07	40	Loss of response	
133	48,5	8	Adverse event	Allergic reaction
204	49,38	37	Loss of response	
280	49,4	253	Loss of response	
205	49,74	35	Loss of response	
462	49,83	115	Adverse event	Hypersensitivity reaction
301	49,95	52	Loss of response	
309	50,89	199	Loss of response	
240	52,15	1	Adverse event	Delayed hypersensitivity reaction
185	53,04	15	Adverse event	None specified
142	53,69	26	Other	Arthralgia
470	54,22	0	Adverse event	Fainting
465	54,29	32	Adverse event	Flue-like symptoms
469	56,06	160	Loss of response	
455	57,17	50	Adverse event	Herpes zoster infection
144	57,39	47	Adverse event	Hypersensitivity reaction
478	57,46	365	Loss of response	
475	58,62	95	Loss of response	
461	58,92	2	Adverse event	Allergic reaction
463	58,99	59	Loss of response	
16	60,46	1	Adverse event	Allergic reaction (skin reaction and itching)
489	61,12	21	Adverse event	Itching
6	61,63	43	Loss of response	
70	61,74	11	Other	Subtotal colectomy
1	61,8	6	Adverse event	None specified
29	62,13	213	Loss of response	
17	62,61	100	Adverse event	Pericarditis and kidney failure

Supplementary table 7. Continued.

Patient ID	Age at start anti-TNF therapy	Time until stop therapy in weeks	Category	Stop reason
19	62,93	8	Adverse event	Skin reaction, muscle and joint complaints
18	63,2	12	Adverse event	Itching
56	63,55	123	Loss of response	
41	64,12	65	Adverse event	Antibodies
38	64,16	47	Loss of response	
7	64,64	81	Loss of response	
40	65,14	63	Adverse event	None specified
11	65,66	21	Loss of response	
64	65,71	72	Other	No venous access
50	65,79	104	Adverse event	Other
61	65,83	46	Loss of response	
58	66,92	156	Other	Stop reason not specified
51	67,59	51	Adverse event	Hypertension, dyspnoea, nausea
31	67,89	35	Adverse event	Muscle complaints
26	68,4	43	Adverse event	Skin reaction
474	68,91	26	Other	Wait gain, night sweating
59	69,42	26	Adverse event	Pneumonia
62	69,52	0,14	Adverse event	Listeria meningitis
72	69,8	120	Adverse event	Fever, cold shivers, hypotension
12	73,94	52	Adverse event	None specified
10	74,09	1	No response at first admission	
65	76,75	126	Loss of response	
53	76,85	14	Adverse event	Fever, cold shivers
68	80,65	42	Loss of response	
34	81,6	367	Adverse event	None specified
73	81,92	87	Adverse event	Allergic reaction (dyspnoea)
25	83,82	143	Adverse event	Fever