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Increased Discontinuation Rates of Anti-TNF Therapy in Elderly Inflammatory Bowel Disease Patients

M. E. de Jong,[a*] L. J. T. Smits,[a*] B. van Ruijven,[a] N. den Broeder,[a] M G. V. M. Russel,[b] T. E. H. Römkens,[c] R. L. West,[d] J. M. Jansen,[e] F. Hoentjen[a]; on behalf of IBDREAM

[a]Inflammatory Bowel Disease Centre, Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands [b]Department of Gastroenterology and Hepatology, Medical Spectrum Twente, Enschede, The Netherlands [c]Department of Gastroenterology and Hepatology, Jeroen Bosch Hospital, 's Hertogenbosch, The Netherlands [d]Department of Gastroenterology and Hepatology, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands [e]Department of Gastroenterology and Hepatology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Corresponding author: Michiel E. de Jong, MSc, Inflammatory Bowel Disease Centre, Department of Gastroenterology and Hepatology, Radboud University Medical Centre, PO Box 9101, code 455, 6500 HB Nijmegen, The Netherlands. Tel.: +31 243611111; Fax: +31 243540103; Email: Michiel.E.deJong@radboudumc.nl

*These authors share first authorship

Abstract

Background and Aims: There is paucity of data on safety and efficacy of anti-tumour necrosis factor [TNF] in elderly inflammatory bowel disease [IBD] patients. We aimed to compare the long-term treatment failure rates and safety of a first anti-TNF agent in IBD patients between different age groups [<40 years/40–59 years/≥60 years].

Methods: IBD patients who started a first anti-TNF agent were identified through IBDREAM, a multicentre prospective IBD registry. Competing risk regression was used to study treatment failure, defined as time to drug discontinuation due to adverse events [AEs] or lack of effectiveness, with discontinuation due to remission as a competing risk.

Results: A total of 895 IBD patients were included; 546 started anti-TNF at age <40 [61.0%], 268 at age 40–59 [29.9%], and 81 at age ≥60 [9.1%]. Treatment failure rate was higher in the two older groups (subhazard rate [SHR] age ≥60 1.46, SHR age 40–59 1.21; $p = 0.03$). The SHR in the elderly [>60] was 1.52 for discontinuation due to AEs and 1.11 for lack of effectiveness. Concomitant thiopurine use was associated with a lower treatment failure rate (SHR 0.78, 95% confidence interval [CI] 0.62–0.98, $p = 0.031$). Serious adverse event [SAE] rate, as well as serious infection rate, were significantly higher in elderly IBD patients [61.2 versus 16.0 and 12.4 per 1000 patient-years, respectively] whereas the malignancy rate was low in all age groups.

Conclusions: Elderly IBD patients starting a first anti-TNF agent showed higher treatment failure rates, but concomitant thiopurine use at baseline was associated with lower failure rates. Elderly IBD patients demonstrated higher rates of SAEs and serious infections.

Key Words: Elderly; safety; anti-TNF

1. Introduction

The global increase in life expectancy as well as inflammatory bowel disease [IBD] incidence is resulting in more elderly IBD patients.[1] IBD therapies in this group of patients can be challenging due to age-specific risks such as infections and malignancies. Current guidelines do not advise different treatment strategies in elderly IBD patients. However, elderly patients are under-represented in clinical studies and there are limited data in elderly patients to guide clinical decision making.[2,3]

Although anti-tumour necrosis factor [TNF] therapy is effective as both induction and maintenance therapy in IBD patients, the immunosuppressive effects are associated with adverse events [AEs].[4,5] These events include [opportunistic] infections, non-melanoma skin cancer, lymphoma, and melanoma, especially in combination with immunosuppressive therapies including thiopurines.[2,6,7] Since the general risk of infections and malignancies increases with age, the safety of anti-TNF therapy in elderly IBD patients is debated and may affect treatment choices in this specific age group.[8]

Current evidence points towards a possible increase in AEs in elderly IBD patients on anti-TNF therapy, although data are scarce.[9] For example, a cohort study reported more severe infections in 95 IBD patients aged >65 years treated with anti-TNF.[10] However, nearly all patients in the latter study used corticosteroids at baseline, which may have influenced infection rates and is not representative of current practice. Furthermore, it is unknown if treatment failure rates [defined as rates of stopping anti-TNF due to AEs or lack of efficacy] are equal in elderly compared with younger IBD patients. Two small retrospective studies from tertiary centres reported higher discontinuation rates in elderly patients on anti-TNF.[11,12] However, results from current studies are difficult to interpret, since stopping anti-TNF due to remission is regarded as anti-TNF discontinuation as well. In fact, when discontinuation rates are used as a proxy for treatment failure, stopping anti-TNF due to 'stable remission' should be regarded as a competing risk instead of an event.

As evidence is scarce, more real-world data are needed on anti-TNF agents in elderly IBD patients. For this purpose, we used IBDREAM, a large multicentre prospective IBD registry in The Netherlands. The aim of this study was to compare the safety and the treatment failure rates of the first anti-TNF therapy in IBD patients between specific age groups [<40, 40–59, and ≥60 years]. Second, we aimed to identify baseline variables associated with anti-TNF treatment failure due to AEs or lack of effectiveness.

2. Materials and Methods

2.1. Study design

We compared the treatment failure rates of the first treatment with anti-TNF therapy between different age groups in a large multicentre IBD cohort. Risk factors for discontinuation due to AEs or lack of effectiveness were identified.

2.2. Registry and cohort

Data were derived from IBDREAM, a large multicentre prospective IBD registry in The Netherlands. IBDREAM collects medical data in a prospective and systematic fashion from IBD patients in four non-academic hospitals and one academic hospital in The Netherlands [Jeroen Bosch Hospital, s'-Hertogenbosch; Onze Lieve Vrouwe Gasthuis, Amsterdam; Medical Spectrum Twente, Enschede; Franciscus Gasthuis & Vlietland, Rotterdam; and Radboud University Medical Centre, Nijmegen]. After inclusion in IBDREAM, patients' demographic data, disease activity, previous and current medication use, previous serious adverse events [SAEs], hospitalisations, and IBD surgery are registered in IBDREAM. Subsequently, follow-up data are prospectively collected during routine clinical visits.

In the current study, we included all patients with an established diagnosis of Crohn's disease [CD], ulcerative colitis [UC], or IBD unclassified [IBD-U] who used or are using anti-TNF therapy. We defined three groups of IBD patients based on their age at the moment of their first anti-TNF treatment: <40, 40–59, and ≥60 years. We defined 'elderly' as patients aged ≥60 years, as previously published by multiple research groups.[9,13,14]

2.3. Data collection

For this study, data on demographics, medical history, concomitant IBD medication use at start of anti-TNF, reasons for discontinuation, and serious adverse events [SAEs] were extracted from IBDREAM. SAEs included hospital admission due to disease activity or side effects, infections, allergic reactions, IBD-related surgery, or malignancies. Data were retrieved from IBDREAM on August 1, 2018. Follow-up was defined as years from start of first anti-TNF agent until date of data extraction.

2.4. Outcomes

Primary outcomes of this study were the anti-TNF treatment failure rate and the SAE rate during the first anti-TNF therapy. Drug survival was used as proxy for treatment failure; it was calculated by measuring years of anti-TNF treatment until discontinuation due to [serious] AEs or lack of effectiveness, corrected for remission as a competing risk. Lack of effectiveness was defined as either lack of initial clinical response [primary non-response] or loss of response, resulting in a switch of therapy or surgery. Regarding safety, SAE rates including serious infection rates (events per 1000 patient-years [py]) were compared between the age groups. Serious infections were defined as infections requiring hospitalisation. Second, factors associated with treatment failure were identified. We included gender, disease duration, IBD -type [UC versus CD], anti-TNF agent [infliximab or adalimumab], concomitant IBD medication use at baseline [5-aminosalicylic acid, methotrexate, thiopurine, prednisone], malignancy, and previous IBD surgery in our analysis. In addition, we identified factors associated with discontinuation due to AEs alone and discontinuation due to lack of effectiveness alone.

2.5. Statistical methods

We used STATA 11.2's competing risk regression based on Fine and Gray's proportional subhazards model to study time to treatment failure, with discontinuation due to remission as a competing risk. Patients lost to follow-up or stopping anti-TNF for other reasons [e.g. pregnancy] were censored at the moment of cessation of therapy. End of follow-up was defined as date of stopping anti-TNF or date of data extraction. We performed separate competing risk analyses for discontinuation due to AEs alone and discontinuation due to lack of effectiveness alone. For the analysis of discontinuation due to AEs, stopping due to lack of effectiveness was regarded as a competing risk as well. Likewise, stopping due to AEs was regarded as a competing risk in the analysis of discontinuation due to lack of effectiveness. Wald tests were used to determine the significance of

variables included in the competing risks model. Age group was initially treated as a categorical covariate, and was simplified to a linear effect between categories when appropriate.

Descriptive statistics were used to describe the number of IBD-related hospitalisations, IBD-related surgeries, and malignancies. Outcomes with a normal distribution were presented as means with standard deviation [SD]; non-normally distributed outcomes were presented as medians with interquartile range [IQR]. Pearson's chi square test was used for binominal variables in the three age groups, and Fisher's exact test if numbers were <5. The Kruskal-Wallis test was used for continuous non-normally distributed variables in the three age groups. To demonstrate the difference between the competing risk model and the overall discontinuation rate [i.e. the cumulative incidence for patients stopping anti-TNF], a Kaplan-Meier [KM] curve [with log-rank test] was used. Thus, in the KM curve, all reasons for discontinuation [including remission] were counted as an event and patients were censored at end of follow-up. Poisson regression analysis was used to compare SAE rates. A p-value <0.05 was considered statistically significant. SPSS Statistics [IBM, version 25] and STATA 11.2 were used for statistical analyses.

2.6. Ethics

This study and the IBDREAM registry were approved by the Radboudumc Medical Ethical Committee [2015–2245]. All participants signed written informed consent.

3. Results

3.1. Patients

A total of 895 IBD patients with a history of at least one anti-TNF agent were identified. Baseline characteristics are shown in Table 1. The majority of IBD patients had CD [679 patients, 75.9%], 200 patients had UC [22.3%], and 16 had IBD-U [1.8%]. Males represented 42.2% of the cohort, and the median age at IBD diagnosis was 26 years [IQR 19–38]. Median follow-up since start of the first anti-TNF was 46 months [IQR 18–97]. In 546 patients [61.0%] the first anti-TNF therapy was started at age <40, 268 patients started at age 40–59 [29.9%], and 81 at age ≥60 [9.1%]. Infliximab was the first anti-TNF therapy in 74.5%, 71.3%, and 66.7% of patients, respectively, per age group, $p = 0.258$. Of the 81 patients who started anti-TNF therapy at age ≥60, 37 [45.7%] patients were ≥60 years at moment of IBD diagnosis. Patients who started the first anti-TNF at age <40 had a median disease duration of 2 years, versus 7.5 years in the older patient groups [p <0.001]. Furthermore, a higher UC versus CD rate was observed in the ≥60 group [32.1% versus 18.5% and 27.2 %, $p = 0.002$]. Co-medication use at baseline was not significantly different between the different age groups, except for thiopurines that were used less in the older patient groups. At the moment of initiation of anti-TNF therapy, immunosuppressive therapy was used in 64.8%, 57.8%, and 63.0% of patients [$p = 0.150$], including thiopurine in 50.2%, 41.0%, 34.6% [$p = 0.005$] and prednisone in 24.2%,

Table 1. Baseline characteristics.

	All patients [n = 895]	1st anti-TNF < 40 [n = 546]	1st anti-TNF 4059 [n = 268]	1st anti-TNF ≥ 60 [n = 81]	p-value
Age at start 1st anti-TNF, median [IQR]	34.2 [24.1–48.3]	26.4 [11.5]	48.8 [9.2]	67.1 [8.3]	-
Disease duration in years, median [IQR]	3.0 [1.0–10.0]	2.0 [5.0]	7.5 [19.0]	7.5 [23.3]	**0.000***
Follow-up since start 1st anti-TNF, months, median [IQR]	46 [18–97]	55 [23–103]	36 [17–87]	19 [9–48]	**0.000***
Gender: male, n [%]	378 [42.2]	209 [38.3]	139 [51.9]	30 [37.0]	**0.001***
IBD type, n [%]					
- Crohn's disease	679 [75.9]	436 [79.9]	190 [70.9]	53 [65.4]	**0.001***
- Ulcerative colitis	200 [22.3]	101 [18.5]	73 [27.2]	26 [32.1]	**0.002***
- IBD-U	16 [1.8]	9 [1.6]	5 [1.9]	2 [2.5]	0.735
1st anti-TNF, n [%]					
- Infliximab	652 [72.8]	407 [74.5]	191 [71.3]	54 [66.7]	0.258
- Adalimumab	243 [27.2]	139 [25.5]	77 [28.7]	27 [33.3]	0.258
Medical history, n [%]					
- PSC	8 [0.9]	7 [1.3]	0 [0.0]	1 [1.2]	0.178
- Prior IBD-surgery	154 [17.2]	72 [13.2]	64 [23.9]	18 [22.2]	**0.000***
- Prior malignancy	13 [1.5]	2 [0.4]	2 [0.7]	9 [11.1]	**0.000***
- BCC/SCC	8 [0.9]	0 [0.0]	5 [1.9]	3 [3.7]	**0.000***
Mesalamine at baseline, n [%]					
- 5-ASA oral	123 [13.7]	69 [12.6]	41 [15.3]	13 [16.0]	0.486
Immunosuppressives at baseline, n [%]					
- Prednisone	210 [23.5]	132 [24.2]	56 [20.9]	22 [27.2]	0.420
- Prednisone alone[a]	91 [10.2]	55 [10.1]	23 [8.6]	13 [16.0]	0.147
- Budesonide	72 [8.0]	39 [7.1]	22 [8.2]	11 [13.6]	0.143
- Methotrexate	31 [3.5]	15 [2.7]	12 [4.5]	4 [4.9]	0.261
- Thiopurine	412 [46.0]	274 [50.2]	110 [41.0]	28 [34.6]	**0.005***
- No immunosuppressives[b]	335 [37.4]	192 [35.2]	113 [42.2]	30 [37.0]	0.150

Bold entries are significant p-values. IQR, interquartile range; n, number; TNF, tumour necrosis factor; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease unclassified; PSC, primary sclerosing cholangitis; BCC, basal-cell carcinoma; SCC, squamous cell carcinoma; 5-ASA, 5-aminosalicylic acid.

[a]No thiopurine or methotrexate.

[b]No thiopurine, methotrexate, prednisone, or budesonide.

*A p-value <0.05 was considered statistically significant

20.9%, and 27.2%, of patients aged <40, 40–59, and ≥60, respectively [$p = 0.420$].

3.2. Reasons for discontinuation

Of 895 IBD patients, 450 discontinued therapy [50.3%] during follow-up. The drug survival after 6 months was 84.3%, 81.6%, and 71.8% in patients aged <40, 40–59, and ≥60, respectively, and 76.4%, 72,8%, and 66.3% after 12 months. Remission was the reason for stopping in 15.1%, 13.5%, and 3.0% of patients aged <40, 40–59, and ≥60 years, respectively. The main reasons for stopping anti-TNF in elderly patients were AEs in 39.4% and lack of effectiveness in 42.4% of patients who discontinued [Table 2]. In patients aged <40 and 40–59, the main reason for discontinuation was lack of effectiveness [40.5% and 47.4%, respectively]. In these patient groups, AEs were the reason for stopping in respectively 27.1% and 28.6% of patients who discontinued anti-TNF.

3.3. Competing risk models

3.3.1. Treatment failure

We analysed the probability of treatment failure by a competing-risks regression analysis, with discontinuation due to AEs or lack of effectiveness as the outcome of interest and discontinuation due to remission as a competing event. Overall, age was associated with a higher discontinuation rate [$p = 0.03$ Figure 1], with a subhazard rate [SHR] for discontinuation of 1.23 (95% confidence interval [CI] 0.96–1.56) in the 40–59 group and 1.46 [95% CI 0.94–2.20] in the ≥60 group, both compared with the <40 group. Thiopurine use at baseline was associated with a lower rate of treatment failure, regardless of age [SHR 0.78, 95% CI 0.62–0.98, $p = 0.031$]. Neither prednisone use nor methotrexate use was associated with a higher rate of treatment failure in the entire cohort. However, the subgroup of patients who only used prednisone in addition to anti-TNF, but without thiopurines or methotrexate at baseline, did have a higher risk of treatment failure [SHR 1.45, 95% CI 1.02–2.04, $p = 0.037$; Supplementary Table A, available as Supplementary data at *ECCO-JCC* online].

Supplementary Figure A, available as Supplementary data at *ECCO-JCC* online, demonstrates the analysis without competing risk [thus, remission was included as a reason for discontinuation instead of a competing risk for treatment failure]. In this analysis, no statistically significant difference in time to drug discontinuation was detected between age groups [log-rank test].

3.3.2. Discontinuation due to AEs

The difference in discontinuation rates due to AEs between the three age groups did not reach statistical difference, with an SHR of 1.07 [95% CI 0.73–1.58] in the 40–59 group and 1.52 [95% CI 0.83–2.76] in the ≥60 group, compared with the youngest group [Figure 2a]. Concomitant prednisone use was not associated with a higher rate of discontinuation due to AEs, except for the subgroup of patients who only used prednisone in addition to anti-TNF, but without thiopurines or methotrexate at baseline [SHR 2.09, 95% CI 1.31–3.32, $p = 0.002$]. Female gender [SHR 1.48, 95% CI 1.03–2.12, $p = 0.036$] was associated with discontinuation due to AEs as well.

3.3.3. Discontinuation due to lack of effectiveness

Discontinuation rates due to lack of effectiveness were not significantly different between age groups [Figure 2b], with an SHR of 1.24 [95% CI 0.91–1.68] and 1.11 [95% CI 0.63–1.95] in the age groups 40–59 and ≥60, respectively. The only risk factor for discontinuation due to lack of effectiveness was use of adalimumab, compared with infliximab [SHR 1.54, 95% CI 1.15–2.07, $p = 0.004$].

3.4. SAEs

All SAEs from start of anti-TNF therapy until 1 month after discontinuation are shown in Table 3. The incidence rate of different SAEs compared with the rate in the youngest age group, expressed as incidence rate ratios [IRR], are shown in Table 4. The overall SAE incidence rate in the ≥60 compared with the <40 age group was significantly higher [IRR 2.06, 95% CI 1.42–3.00, $p < 0.001$]. SAEs in the elderly patients are specified in Table 5.

Serious infections were documented in 42 patients. The serious infection rate [infections per 1000 py] was significantly higher in the elderly patient group [61.2 versus 16.0 and 12.4 per 1000 py, $p < 0.001$]. Concomitant immunosuppressive comedication use at baseline did not result into a higher serious infection rate [IRR 0.95, 95% CI 0.52–1.74, $p = 0.857$].

During anti-TNF therapy, five patients developed a malignancy. In the youngest group, one parotid tumour and one squamous cell carcinoma were detected. Two patients aged between 40 and 59

Table 2. Reasons for anti-TNF discontinuation per age group.

Reason for discontinuation,	All patients [*n* = 450]	1st anti-TNF < 40 [*n* = 284]	1st anti-TNF 40–59 [*n* = 133]	1st anti-TNF ≥ 60 [*n* = 33]	*p*-value
AE, *n* [%]	128 [28.4]	77 [27.1]	38 [28.6]	13 [39.4]	0.330
infection	22	11	9	2	
infusion reaction	25	19	4	2	
dermatological side effect	19	15	3	1	
rheumatological side effect	19	12	6	1	
antidrug antibodies	11	3	5	3	
other AEs	32	17	11	4	
Lack of effectiveness, *n* [%]	192 [42.7]	115 [40.5]	63 [47.4]	14 [42.4]	0.417
Remission, *n* [%]	62 [13.8]	43 [15.1]	18 [13.5]	1 [3.0]	0.066
Patients' request, *n* [%]	11 [2.4]	9 [3.2]	2 [1.5]	0 [0.0]	0.564
Pregnancy, *n* [%]	14 [3.1]	14 [4.9]	0 [0.0]	0 [0.0]	**0.007***
Other, *n* [%]	43 [9.6]	26 [9.2]	12 [9.0]	5 [15.2]	0.782

Bold entries are significant *p*-values. TNF, tumour necrosis factor; AE, adverse event; n, number.

*A *p*-value <0.05 was considered statistically significant.

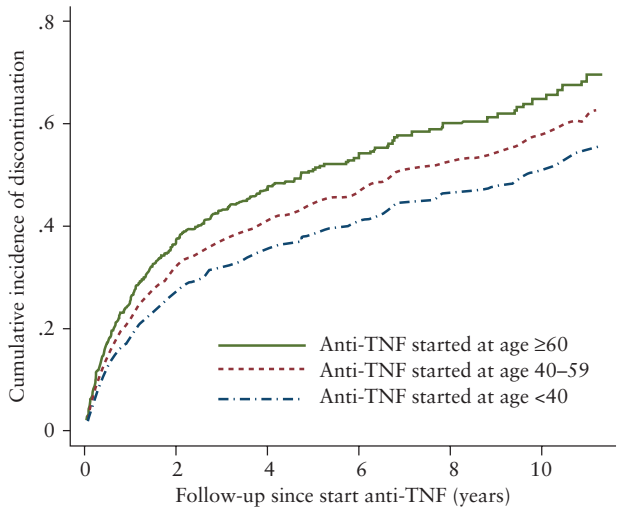

Figure 1. Cumulative incidence function of discontinuation due to adverse events or lack of effectiveness in patients who started anti-tumour necrosis factor [TNF] at age <40/40–59/≥60 as estimated by the competing risk regression model.

were diagnosed with breast cancer, and one elderly patient developed a squamous cell carcinoma.

3.5. Follow-up treatment

A total of 139/450 [30.9%] patients started a second anti-TNF agent within 1 year after discontinuation, respectively in 35.2%, 23.3%, and 24.2% of patients aged <40, 40–59, and ≥60 [p = 0.044].

4. Discussion

In this large multicentre cohort study, we found that older age [≥60] at the moment of starting a first anti-TNF agent was associated with more SAEs and serious infections, and increasing age was associated with a higher rate of treatment failure. In contrast, thiopurine use at start of anti-TNF was associated with a lower treatment failure rate.

Our results demonstrating higher treatment failure rates of anti-TNF therapy in elderly IBD patients are in line with previous studies in small cohorts. Two retrospective single-centre studies reported higher discontinuation rates in elderly IBD patients who started anti-TNF compared with younger IBD patients.[11,12] In our cohort, AEs were an important reason for anti-TNF treatment failure in elderly patients. Moreover, there was a clear trend towards higher discontinuation rates due to AEs in elderly patients compared with younger patients, although this did not reach statistical significance.

In our cohort, elderly patients had a higher serious infection rate [61.2 versus 16.0 and 12.4 per 1000 py]. Likewise, higher serious infection rates [92 versus 31 per 1000 py] were reported in elderly IBD patients on anti-TNF therapy in a retrospective cohort study.[11] The higher infection rate in the elderly on anti-TNF may be explained by the fact that older age itself is an independent risk factor for opportunistic infections [OI] and OI-related AEs in UC.[15,16] The overall serious infection rate of 17 per 1000 py in our total cohort is in line with a French population-based study and the Treat registry, which reported rates of respectively 19 and 22 per 1000 py.[17,18] The serious infection rate was not affected by concomitant co-medication use, in line with the results of the SONIC trial.[19] In addition, we observed only a limited number of malignancies during anti-TNF treatment. Indeed, several studies previously reported no increased risk of

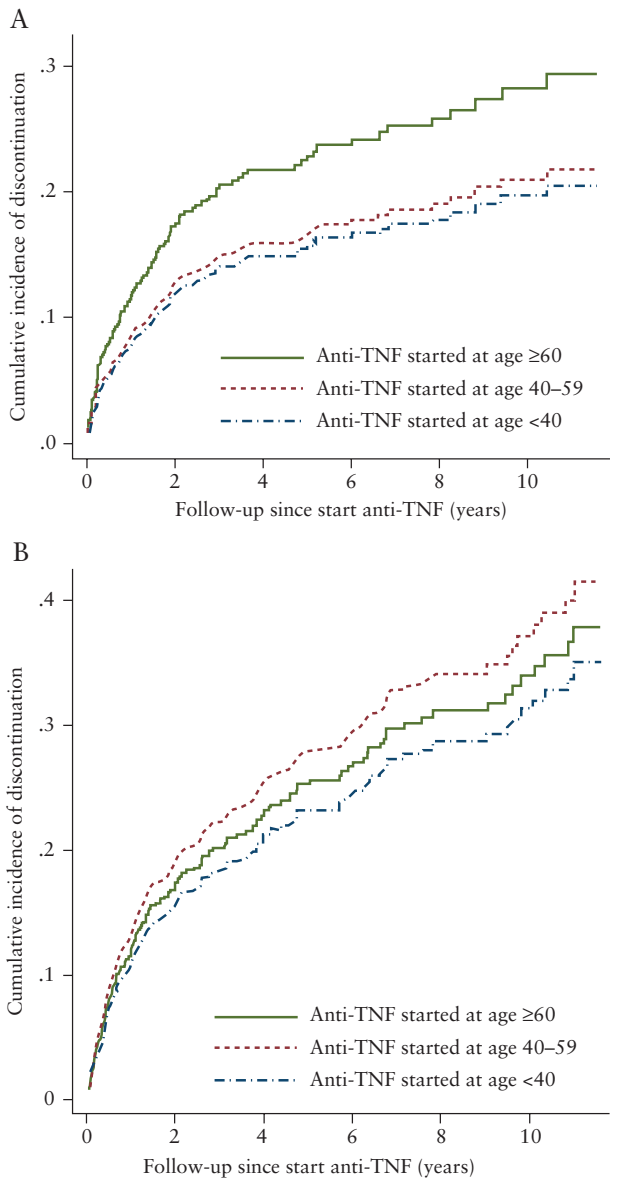

Figure 2. a: Cumulative incidence function of discontinuation due to adverse events in patients who started anti- tumour necrosis factor [TNF] at age <40/40–59/≥60 as estimated by the competing risk regression model. b: Cumulative incidence function of discontinuation due to lack of effectiveness in patients who started anti-TNF at age <40/40–59/≥60 as estimated by the competing risk regression model.

malignancies in anti-TNF treated patients in general.[20] However, the required follow-up for detection of malignancies may be longer than the follow-up time in our study [mean 46 months].

Concomitant thiopurine use was associated with a reduced risk of treatment failure. Previous studies reported conflicting results regarding the impact of co-medication on anti-TNF continuation. Several studies reported co-medication to be associated with successful continuation of anti-TNF,[19,21,22] and two studies found azathioprine combination therapy to be associated with anti-TNF cessation.[12,23] Potential explanations for the lower risk of anti-TNF treatment failure in patients with combination therapy may be the suppression of immunogenicity, and the improved control of inflammation with combination versus monotherapy.[19] The only predictor for discontinuation due to lack of effectiveness was adalimumab use,

Table 3. SAEs during anti-TNF use per age group.

SAE	All [*n* = 895]	1st anti-TNF < 40 [*n* = 546] Follow-up years = 1770		1st anti-TNF 40–59 [*n* = 268] Follow-up years = 687		1st anti-TNF ≥ 60 [*n* = 81] Follow-up years = 147	
	Number	Number	SAE rate /1000 py	Number	SAE rate /1000 py	Number	SAE rate /1000 py
Infection	42	22	12.4	11	16.0	9	61.2
Disease activity	96	65	36.7	25	36.4	6	40.8
Malignancy	6	3	1.7	2	2.9	1	6.8
Allergic reaction	7	5	2.8	0	0.0	2	13.6
Other	47	27	15.3	15	21.8	5	34.0
Hospitalisation	92	65	36.7	18	26.2	9	61.2

TNF, tumour necrosis factor; SAE, serious adverse event; py, patient-years; n, number.

Table 4. SAE incidence rate ratios in age group 40–59 and ≥60 compared with age group <40.

SAE	1st anti-TNF 40–59 [*n* = 268]		1st anti-TNF ≥ 60 [*n* = 81]	
	IRR + 95%CI	*p*-value	IRR + 95% CI	*p*-value
Total	0.98, 0.74–1.28	*p* = 0.871	**2.06, 1.42–3.00**	***p* <0.001***
Infection	1.29, 0.62–2.66	*p* = 0.494	**4.92, 2.27–10.69**	***p* <0.001***
Disease activity	0.99, 0.62–1.57	*p* = 0.967	1.11, 0.48–2.56	*p* = 0.805
Malignancy	1.72,0.29–10.27	*p* = 0.554	4.01,0.42–38.56	*p* = 0.229
Allergic reaction	-	*p* = 0.992	4.81, 0.93–24.81	*p* = 0.060
Other	1.43, 0.76–2.69	*p* = 0.266	2.23, 0.86–5.79	*p* = 0.100
Hospitalisation	0.61, 0.36–1.03	*p* = 0.065	1.43, 0.71–2.87	*p* = 0.316

Bold entries are significant *p*-values. TNF, tumour necrosis factor; SAE, serious adverse event; IRR, incidence rate ratio; n, number; CI, confidence interval.
*A *p*-value <0.05 was considered statistically significant

Table 5. SAEs in IBD patients aged ≥60.

SAEs in patients aged ≥60	Number
Infection	
- pneumonia	3
- PJP	1
- urinary sepsis	3
- cholecystitis	1
- bacteraemia during active disease	1
Disease activity	
- partial colectomy	1
- resection neoterminal ileum	1
- dehydration, high-output stoma	1
- abdominal pain	2
Malignancy	
- squamous cell carcinoma	1
Allergic reaction	
- Hypersensitivity reaction with antidrug antibodies	1
- Anaphylaxis	1
Other	
- diverticulitis	1
- foraminotomy L5	1
- inguinal hernia	1
- total hip prosthesis	1
- small cerebral infarction	1

SAE, serious adverse events; IBD, inflammatory bowel disease; PJP, pneumocystis jirovecii pneumonia.

compared with infliximab use. It was previously described that the median time to secondary loss of response was longer in infliximab- versus adalimumab-treated CD patients.[24] In addition, a more recent systematic review reported infliximab to be superior to adalimumab in UC patients in inducing mucosal healing.[25] Unfortunately, no head-to-head trials are available between infliximab and adalimumab to further explore these observations.

Our results provide more insight into the real-world experience of elderly patients on anti-TNF, and may have important implications for clinical practice. The higher rate of discontinuation due to treatment failure as well as the higher serious infection rate underline the need for close monitoring for early detection and management of [S]AEs in this patient category. Nevertheless, in clinical practice, not only the potential risks of AEs associated with anti-TNF treatment but also the risks associated with alternative treatments such as other biologics or surgery should be considered.

The strengths of our study include the large number of patients on anti-TNF [*n* = 895], the multicentre setting including both an academic and four non-academic centres, and the long-term follow-up. In addition, this is the first study specifically evaluating treatment failure defined as discontinuation due to AEs or lack of effectiveness in patients in different age categories, while correcting for competing risks. The importance of the correct statistical method is illustrated by the fact that higher age was associated with discontinuation due to treatment failure in the competing risk model, whereas we did not observe differences in discontinuation rates when stopping due to remission was not regarded as a competing risk [Supplementary Figure 1]. Competing risks should be considered in future analyses of treatment discontinuation, as discontinuation due to remission is a distinct clinical strategy in current guidelines.[26–28]

This study also comes with limitations. First, there might be selection bias in patients who received anti-TNF, especially in the

elderly. Since previous studies reported higher AE risks in elderly, clinicians might be inclined to only treat the elderly with the most severe IBD with anti-TNF. Indeed, it is known that anti-TNF is used relatively less in the elderly IBD patients.[29,30] Second, this cautious attitude of clinicians is reflected in the relatively small number of elderly patients on anti-TNF in our cohort compared with younger patients. This imbalance could potentially have impacted on outcomes. It may have contributed to the fact we did not observe a significantly higher discontinuation rate due to AEs in elderly patients compared with younger patients. However, we still observed that an increasing age was significantly associated with a higher risk of treatment failure. Third, we did not match elderly IBD patients to younger IBD patients on several potential confounding characteristics such as disease duration and previous surgery.[31,32] However, we did not observe an association between disease duration or surgery with treatment failure rates.

In conclusion, in this large multicentre cohort, we found that patients aged ≥60 years starting a first anti-TNF agent are at increased risk of stopping anti-TNF due to AEs or lack of effectiveness, compared with patients <60 years. Elderly IBD patients had a higher SAE and serious infection rate. Furthermore, concomitant thiopurine use was associated with a reduced risk of treatment failure. These findings support tight monitoring and timely management of [S]AEs when starting anti-TNF in elderly IBD patients.

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Conflict of Interest

FH has served on advisory boards, or as speaker, or consultant for Abbvie, Celgene, Janssen Cilag, MSD, Takeda, Celltrion, Teva, Sandoz, and Dr Falk, and has received unrestricted grants from Dr Falk, Janssen-Cilag, Abbvie. JJ has served on advisory boards, or as speaker, or consultant for Abbvie, Amgen, Ferring, Fresenius, Janssen, MSD, Pfizer, Takeda. RW has participated in advisory boards, or as a speaker, or consultant for the following companies: Abbvie, Janssen.

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Author Contributions

No additional writing assistance was used for this manuscript. MJ, LS, BR, NB, MR, TR, RW, JJ, and FH all contributed to the design of the study. MJ, FH, MR, TR, RW, and JJ included patients in IBDREAM. LS and MJ collected data; MJ, LS, and BR analysed the data. NB assisted in statistical analysis. LS and MJ drafted the manuscript. FH, NB, MR, TH, RW, and BR critically revised the manuscript for important intellectual content. All authors have approved the final version of this manuscript.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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