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Older age is associated with higher rate of discontinuation of anti-TNF therapy in patients with Inflammatory Bowel Disease

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Abstract

Background—In increasingly aging populations, awareness of outcomes of older patients treated with biologics is becoming more important. However, few studies to-date have investigated the safety and durability of anti-TNF therapy in this sub-group.

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A Ananthakrishnan	study design, data collection, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

Methods—This was a retrospective single-center study with cases comprising all IBD patients who commenced anti-TNF treatment at age > 60 years. Cases of Crohn's disease (CD) and ulcerative colitis (UC) were identified from medical record review. Our controls consisted of patients younger than age 60 years on anti-TNF treatment and patients > 60 years on treatment with immunomodulators. Kaplan-Meier survival estimates were used to calculate the probability of remaining on anti-TNF therapy.

Results—We identified a total of 54 IBD patients who initiated anti-TNF therapy over the age of 60 years (mean 73, range 61–97 years). Among these, a total of 38 patients (70%) discontinued anti-TNF therapy after a mean of 24.1 months. At 12 months after initiation, 75% of patients older than age 60 years were still on anti-TNF agents compared to 93% among younger users and 82% among older AZA users ($p < 0.05$). Compared to older AZA users, older anti-TNF users remained more likely to require early therapy cessation (HR 2.21, 95% CI 1.29 – 3.78).

Conclusion—The IBD population older than age 60 at the time of initiation of anti-TNF therapy is at higher risk for discontinuation of therapy. They may also be particularly vulnerable to infectious complications requiring hospitalization suggesting need for careful monitoring during therapy.

Keywords

Crohn's disease; ulcerative colitis; age; anti-TNF; infections

INTRODUCTION

The incidence of inflammatory bowel diseases (IBD; Crohn's disease (CD), ulcerative colitis (UC)) is increasing worldwide^{1, 2}, contributing to significant morbidity and healthcare costs. Despite being predominantly a disease of young adulthood, there is a second peak in incidence in the 6th and 7th decades of life^{3, 4}. In addition, the chronic relapsing-remitting nature of the diseases, the unaltered life expectancy, and the aging of the population contribute to an increasing burden of disease among older patients. Also, the diagnosis of IBD is often either delayed or missed in elderly patients⁵, and as a result, this population suffers increased morbidity and mortality compared to younger patients^{3, 4, 6–8}. Anti-tumor necrosis α (anti-TNF) biological therapies have revolutionized therapy for patients with IBD, improving remission rates and quality of life while reducing rates of surgery and hospitalizations⁹. However, the majority of data supporting the use of these therapies stems from clinical trials and large observational cohorts that primarily focus on younger patients, or even exclude patients older than age 65 years^{9–14}. As a result, little data exists to guide treatment decisions regarding these therapies in an older IBD population.

There are several factors that uniquely influence therapeutic decision making in older patients, particularly in regards to biologic therapy. Older IBD patients have more baseline co-morbidities, making biologic agents potentially more dangerous in advanced age. In addition, they are more likely to have had prolonged duration of disease which may negatively influence therapeutic efficacy. Only few studies have examined safety or efficacy of anti-TNF α drugs in the older IBD patient. Cottone *et al.* found greater risk of adverse events in older compared to younger patients, primarily infectious complications¹⁵. Two

other studies, one published in abstract form only, showed age to be a risk factor for infectious complications^{16, 17}. Nevertheless, these studies had several limitations including lack of a corresponding older non-biologic immunomodulator cohort, lack of simultaneous examination of treatment efficacy, or examination of older prevalent users only. This is particularly important as it may bias estimates towards the null given such long-term users are more likely to have tolerated therapy than new users. In addition, while data on the safety of biologic therapy in older rheumatoid arthritis (RA) patients exists, there are limitations to extrapolating such data to the IBD population given differences in co-morbidities, dose of biologic therapy, practice of using concomitant immunomodulators, and different susceptibilities to infections, some of which are specific to IBD patients^{18, 19}. In addition, the RA studies did not include a comparable group of younger patients, or older patients on azathioprine, the most common immunomodulator in IBD patients. Thus, there is an unmet need for additional data regarding biologic therapy in this age group to inform the safe and effective use of these agents in the elderly population.

Consequently, the aims of our study were (1) to evaluate outcomes among older IBD patients treated with biologic anti-TNF therapy compared to younger IBD patients treated with the same agents; (2) to compare safety and efficacy of anti-TNF therapy in older IBD patients to a comparison group treated with non-biologic immunomodulators, and (3) to describe the adverse events occurring with biologic therapy in a cohort of older anti-TNF users.

METHODS

Study Population

This was a retrospective study at a single academic referral center. All eligible IBD patients who started anti-TNF therapy (infliximab (IFX), adalimumab (ADA), certolizumab pegol (CZP) were identified through a query of the Partners Healthcare Research Practice Data Registry (RPDR), an electronic database of all patients seen at Massachusetts General Hospital (MGH) and affiliated institutions within the Partners Healthcare system. Medical records were reviewed for all patients identified through this query. From 1999 till 2011, a total of 54 patients (47 IFX, 7 ADA) who initiated their first anti-TNF biologic therapy after the age of 60 years comprised our case population. We identified two control populations. The first control group consisted of IBD patients younger than 60 years treated with anti-TNF therapy. This population was obtained through a randomized query of the patients enrolled in the MGH Crohn's and Colitis Center prospective registry. Controls were matched to the case for type of IBD and type of anti-TNF agent. The second control group was identified through the RPDR query as above and consisted of 54 randomly selected patients who were older than age 60 years and on treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) for IBD.

Variables and Outcomes

After identifying patients with IBD, we recorded the current age and age of diagnosis, gender, and duration of disease. Co-morbidity was assessed for each patient using the Charlson co-morbidity index, a validated and widely used measure of co-morbidity²⁰. For

anti-TNF users, we recorded the start date, end date and potential overlap with immunomodulators (combination immunosuppression group) and corticosteroids. Similarly dates and duration of use were identified for the AZA users. For each patient who stopped therapy, we reviewed the medical records for reason for cessation. In addition, we identified the side effects from anti-TNF agents and AZA. Reasons for treatment cessation were categorized as loss of response, infections, other side effects, or death. The side effects were subcategorized as malignancy, lupus/arthritis, dermatologic reactions or intolerance due to an allergic reaction in addition to infections.

Assessment of treatment response was at 6 months after initiation of either anti-TNF therapy or AZA use, and was categorized as complete, partial, or no response. As we did not have sufficient data within the medical records to calculate standardized disease activity measures, global physician impression was used to allocate to each response category. The primary outcome of the study was the time to cessation of treatment. The secondary outcomes were the reasons for cessation of treatment, adverse events and the response at 6 months.

Statistical Analysis

All analysis was performed using Stata 11.0 (StataCorp, College Station, TX). Continuous variables were summarized using means and standard deviations and compared using t-tests while categorical variables were summarized using proportions and compared using the chi-square test with the Fisher's exact modification when appropriate. Kaplan-Meier survival curves were estimated for time to cessation of therapy for each of the three groups. Statistical difference between the curves was estimated using the log-rank test. Cox proportional hazards models were used to determine the independent effect of age-group on time to treatment cessation (primary outcome) as well as to examine the independent predictors of treatment cessation in each group. All variables with $p < 0.05$ in the univariate analysis as well as those which had demonstrated prognostic significance in prior studies were included in the final multivariate model where a similar p -value < 0.05 was indicative of independent statistical significance. The study was approved by the Institutional Review Board of the Massachusetts General Hospital.

RESULTS

Characteristics of the study population

Our study included 54 patients who initiated anti-TNF therapy above the age of 60 years (mean age 73 years, range 61 – 97 years) (Table 1). The comparison group including younger anti-TNF users had a mean age of 33 years while the mean age of older immunomodulator users was 73 years. The mean age at diagnosis of IBD for the three groups was 54, 21 and 58 years respectively (Table 1). A similar proportion of older and younger anti-TNF users had been on immunomodulators (primarily AZA) previously (79.6% and 83.3% respectively, $p=0.62$). However, there were fewer older anti-TNF patients currently on combination immunosuppression with AZA compared to younger anti-TNF users (31.5% vs. 66.7% respectively, $p<0.001$). Approximately half of the older anti-TNF users were on corticosteroids in overlap with anti-TNF agents (57.4%), while the

corresponding proportions among younger anti-TNF users and older AZA users were 35.2% and 72.2% respectively ($p=0.001$).

Durability of anti-TNF use

A total of 38 patients (70%) older than 60 years discontinued anti-TNF therapy after a mean duration of 24.1 months. Figure 1 presents the proportion of patients able to continue anti-TNF therapy or AZA. At 12 months after initiation, 75% of patients older than age 60 years were still on anti-TNF agents compared to 93% among younger users and 82% among older AZA users ($p < 0.05$). At 24 months after initiation, 53% of older anti-TNF users continued therapy compared to 90% among younger users. On univariate analysis, older anti-TNF users were three times more likely to stop therapy (Hazard ratio (HR) 3.23, 95% confidence interval (CI) 1.81 – 5.78) compared to younger users. In addition, compared to older AZA users, older anti-TNF users remained more likely to require early therapy cessation (HR 2.21, 95% CI 1.29 – 3.78). However, there was no difference in durability of AZA use in older users compared to anti-TNF use in younger patients (HR 1.44, 95% CI 0.77 – 2.68). On multivariate analysis, adjusting for type of IBD, disease duration, co-morbidity, gender, concomitant immunosuppression, and corticosteroid use, older anti-TNF users were four-fold more likely to stop therapy early (HR 4.35, 95% CI 2.03 – 9.31) compared to younger anti-TNF users.

Treatment response and reason for cessation of therapy

Table 2 presents the likelihood of treatment response at 6 months after initiation of therapy among the older and younger anti-TNF users. Older anti-TNF users were less likely to be treatment responders at 6 months compared to younger users (unadjusted odds ratio (OR) 0.31, 95% CI 0.13 – 0.77). Adjusting for duration of disease, IBD type, gender, and use of concomitant immunosuppression did not significantly alter this association (OR 0.30, 95% CI 0.09 – 0.97). Among younger anti-TNF users who stopped therapy, loss of response was numerically more common (59%) than among older users (42%) ($p=0.24$). In contrast, infections were a more common reason for treatment cessation in older (21%) compared to younger users (6%, $p=0.16$). However, because of the small sample size, these differences did not meet statistical significance.

We then examined predictors of anti-TNF cessation in older users (Table 3). The only significant predictor of early therapy cessation among older anti-TNF users was the use of combination immunosuppression with a two-fold increase in likelihood (HR 2.20, 95% CI 1.12 – 4.32) (Figure 2). This association persisted even after adjusting for use of steroids. However, the reason for therapy cessation among older anti-TNF users did not differ based on whether the user was on combination immunosuppression or steroids (data not shown). IBD type, gender, duration of disease, Charlson co-morbidity or type of anti-TNF agent did not influence need to stop therapy. However, among all anti-TNF users, increasing co-morbidity was associated with an increase in likelihood of treatment cessation (HR 1.15, 95% CI 1.01 – 1.33).

Adverse events on anti-TNF therapy among older users

Four patients (7.5%) required hospitalizations for infectious complications (Table 4). There was 1 death secondary to *Listeria* bacteremia in a 94 year old with UC who received IFX while hospitalized for a severe flare. Twelve patients (22%) experienced adverse reactions soon after administration of the biologic agent including nausea (5 patients, 9%), allergic reactions (5 patients, 9.2%), and severe pain (3 patients, 6%). Other adverse events that occurred on anti-TNF therapy but did not result in hospitalization include psoriasis (4 patients, 7.5%), anemia (3 patients, 6%), and lupus (2 patients, 4%).

DISCUSSION

Safety and efficacy of biologic therapy in older IBD patients is an important concern^{3, 4, 6, 8}. Yet this remains an area where there is scant information to guide clinical practice with most clinical trials and observational cohorts biased towards younger patients. In this case-control study examining safety, efficacy and durability of anti-TNF agents in older IBD patients, we demonstrate that (1) older anti-TNF users were more likely to stop therapy early compared to younger users; (2) older patients were also more likely to stop biologic therapy compared to use of immunomodulators; and (3) infections remain an important concern in older anti-TNF users.

There is limited high quality data examining the safety and durability of anti-TNF therapy in older IBD patients. In an elegant study, Cottone *et al.* collected data from users of IFX or ADA from 16 centers in Italy¹⁵. Over a 9 year period, they were able to accrue 95 patients (3% of their anti-TNF cohort) who were older than 65 years of age who were treated with biologic agents. Such patients were compared to a control group younger than 65 years who were on anti-TNF therapy, and a group of older controls not on treatment with biologics. In their study, serious infections and death were significantly more common in older patients (11% vs. 0.5%). While our primary study outcome, namely therapy cessation, was broader than their outcome which was primarily serious infections or death, our findings are consistent with their results in demonstrating that older anti-TNF users are more likely to require early therapy cessation than younger users. Our study is also distinct from theirs in that we only included anti-TNF users who were over the age of 60 years at the time of initiation of biologic therapy. This minimizes the potential for 'prevalent bias' i.e. patients who may have already been on long-term use by the time they reached our age cut-off, and thus have demonstrated themselves to be at lower risk for therapy cessation than 'new users'. Thus our estimates of treatment durability likely have greater applicability for decision making among new anti-TNF users.

The reason for therapy cessation was similar between the two groups, but acknowledging the limitations of the small sample size, loss of response was a more common reason for cessation among younger users with a trend towards infections being more common in older patients. This supports the findings of Cottone *et al.* and indeed other studies that have similarly demonstrated a higher risk for infections in older patients^{15–17, 21}. Two studies from the Mayo Clinic similarly suggested a significant increase in the risk of infections in older patients^{16, 17}. Neither study was adequately powered to demonstrate increase in risk of specific infections. Nevertheless, these findings suggest a strong need for vigilance for

infectious complications in older anti-TNF users. As pneumonia remains a common infectious complication but may be prevented through appropriate vaccinations, it is essential to ensure appropriate healthcare maintenance among older users as they may be most likely to derive an absolute benefit from such measures²². We did not find that co-morbidity itself was predictive of need for treatment cessation in the older cohort, but this finding could stem from the relative homogeneity in co-morbidity within that subgroup. Expanding our analysis to all anti-TNF users, we found an increase in the Charlson co-morbidity index was associated with an increase in likelihood of therapy cessation suggesting that it is important to factor in co-morbidity in therapeutic decision making for individual patients as significant co-morbidity may be a relative contraindication for the use of biologic therapies or may increase the likelihood of complications associated therein.

Another finding from our study was that AZA appeared to be better tolerated among the older patients with a lower rate of therapy cessation. Clinical trials such as the SONIC study suggest a higher efficacy for IFX over AZA over 1 year²³. However, as such studies have been conducted primarily in younger patients, caution must be used in extrapolating such results to the older patients who may also be more vulnerable to adverse effects. Thus, there is an unmet need for comparative studies of efficacy and safety of biologic and non-biologic therapies in older patients.

In addition, while immunomodulator therapy was better tolerated than biologic therapy, use of combination immunosuppression with AZA and anti-TNF agents was associated with a two-fold increase in therapy cessation. This finding among our older cohort is in contrast to some clinical trials and observational studies (albeit among young patients) where combination therapy either resulted in a superior treatment response or had no effect on durability of anti-TNF therapy^{12, 23–25}. While we did not observe a statistically significant difference in the reason for therapy cessation, prior studies have demonstrated that infectious complications were more common in patients on combination therapy²¹. In addition, while no malignancy was seen in our small cohort, there is the theoretical concern of a numerically higher rate of lymphoma with combination therapy, along with increasing risk of lymphoma in older individuals²⁶. Thus, our findings suggest cautious use of combination therapy in older patients.

Finally, we also observed lower rate of response to anti-TNF therapy at 6 months in older patients. This is consistent with clinical trials where response to anti-TNF agents is inversely proportional to duration of disease²⁷. The mean duration of disease in our older cohort was nearly 19 years compared to 12 years in our younger anti-TNF users. However, adjusting for duration of disease did not significantly attenuate the efficacy estimates suggesting that there may be other biologic factors behind the difference in treatment response between younger and older anti-TNF users.

There are a few important implications to our findings. To our knowledge, there have been few prior published studies comparing treatment response, adverse events, and long-term durability of biologic therapy in older IBD patients in parallel with a cohort of younger anti-TNF users and older non-biologic immunomodulator users within the same hospital. If our findings of higher rates of therapy cessation and lower tolerance to therapy among older

users are duplicated in other cohorts, this can inform clinical practice and assessment of risks/benefits of therapy among older IBD patients with moderate-to-severe CD or UC. Nevertheless, factoring into the decision to initiate anti-TNF therapy in older individuals is not only the likelihood of infectious complications with such therapies, but also consequence of untreated disease and potential risks associated with alternative treatments such as surgery and the likelihood of post-operative complications^{3, 8, 28}.

There are several limitations to our study. First, it was a single center study restricted to an academic referral center. Larger, multicenter studies including those that are population-based are essential to accurately estimate effect size as well as examine the impact of age on specific infections, malignancy, and treatment response. Second, as our study was retrospective, it is possible that our assessment of adverse events was incomplete. Similarly, assessment of treatment response was based on global physician impression rather than standardized disease activity indices as several patients were assessed in our clinic prior to more routine use of standardized disease activity scores. However, time to therapy cessation, our primary outcome, is a hard endpoint and is less likely to be influenced by the retrospective design. The relatively small sample size may result in inadequate power to examine weaker associations. Finally, our control population was selected from our patient registry rather than from the bigger pool within the Partners Healthcare system. However, this allowed for availability of more complete data regarding efficacy and safety of infliximab. In addition, the performance of infliximab was similar to what has been described in other observational studies further supporting the representativeness of the controls.

In conclusion, we demonstrate that anti-TNF users with initiation of therapy beyond the age of 60 years are three-fold more likely to require therapy cessation compared to younger users, and two-fold more likely than older users of immunomodulators. Infectious complications remain an important adverse outcome in such patients. In particular, combination therapy appears to be associated with a higher likelihood of therapy cessation, thus advocating caution in the use of such combined treatments in older patients. With the increasing prevalence of IBD among older individuals, there is an urgent and unmet need for larger, prospective studies of treatment response and adverse outcomes in such patients.

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Figure 1.
Durability of therapy among the study population, stratified by age and treatment

Figure 2.
Influence of combination immunosuppression on durability of anti-TNF therapy in older users (age > 60 years)

Table 1

Characteristics of the study population

Characteristic	Older anti-TNF users (n = 54) [N (%)]	Younger anti-TNF users (n = 54) [N (%)]	Older azathioprine users (n = 54) [N (%)]	p-value
Mean age (in years) (SD)	72.7 (8.0)	32.9 (8.1)	72.9 (5.5)	< 0.001 [†]
Sex				0.046
Male	18 (33.3)	30 (55.6)	28 (51.9)	
Female	36 (66.7)	24 (44.4)	26 (48.2)	
Mean Charlson co-morbidity (SD)	1.3 (1.6)	0.1 (0.9)	2.1 (2.7)	< 0.001 [†]
Type of IBD				0.037
UC	17 (31.5)	15 (27.8)	27 (50.0)	
Crohn's disease	37 (68.5)	39 (72.2)	27 (50.0)	
Mean age at diagnosis (in years) (SD)	53.7 (19.2)	21.2 (7.4)	58.1 (15.0)	< 0.001 [†]
Mean disease duration (in years) (SD)	19 (16.3)	11.7 (7.2)	14.9 (13.8)	0.003 [†]
Prior IMM use	43 (79.6)	45 (83.3)	-	0.62
Type of anti-TNF				1.00
Infliximab	45 (83.3)	45 (83.3)	-	
Adalimumab	9 (16.7)	9 (16.7)	-	
Concomitant IMM	17 (31.5)	36 (66.7)	-	< 0.001 [†]
Concomitant steroid	31 (57.4)	19 (35.2)	39 (72.2)	0.001

SD – standard deviation; IBD – inflammatory bowel disease; UC – ulcerative colitis; TNF – tumor necrosis factor; IMM – immunomodulator

[†] - p-value for difference between older and younger anti-TNF users

Table 2

Response and reason for cessation of anti-TNF therapy

	Older anti-TNF users [N (%)]	Younger anti-TNF users [N (%)]	p-value
Response			0.01
Partial or complete response	33 (61.1%)	45 (83.3%)	
No response / therapy stopped before 6 months	21 (38.9%)	9 (16.47%)	
Reason for therapy cessation			0.349
Loss of response	16 (42.1)	10 (58.8)	
Infections	8 (21.1%) ⁺	1 (5.9%)	
Other adverse events	12 (31.6%)	6 (35.3%)	
Death	2 (5.3%)*	0 (0%)	

⁺ 2/8 patients (25%) with infectious complications were on combination therapy with immunomodulators and 4 (50%) were on corticosteroids.

* Both patients who died were on combination therapy with steroids and 1 was on an immunomodulator.

Table 3

Predictors of anti-TNF therapy cessation among users 60 years and older

Predictor	Hazard ratio	95% confidence interval
Sex		
Male	1.0 (Reference)	
Female	0.75	0.28 – 1.50
Charlson co-morbidity	0.98	0.82 – 1.18
IBD type		
Crohn's disease	1.0 (Reference)	
Ulcerative colitis	1.49	0.72 – 3.11
Duration of disease	1.00	0.98 – 1.02
Type of anti-TNF		
Infliximab	1.0 (Reference)	
Adalimumab	1.54	0.62 – 3.80
Combination immunosuppression		
No	1.0 (Reference)	
Yes	2.20	1.12 – 4.32
Concurrent steroid use		
No	1.0 (Reference)	
Yes	1.39	0.70 – 2.76

IBD – inflammatory bowel disease

Table 4

Infectious and non-infectious complications among anti-TNF users 60 years and older

Complication type	Number of events	Requiring hospitalization
Infectious complications*		
Pneumonia	4	2
Abscess	1	1
Listeria sepsis	1	1
Urinary tract infection	1	0
Cellulitis	1	0
Non-infectious complications		
<i>Malignancy</i>		
Lung Cancer	2	2
Skin Cancer	1	1
Breast Cancer	1	0
Thyroid Cancer	1	0
<i>Infusion/Injection Reactions</i>		
Nausea	5	0
Allergic/Anaphylactoid reactions	5	0
Severe Pain	3	0
<i>Other</i>		
Psoriasis	4	0
Anemia	3	0
Lupus	2	0
Arrhythmia	2	0
Arthralgia	1	0
Osteonecrosis	1	0