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Comorbidity influences the comparative safety of biologic therapy in older adults with inflammatory bowel diseases

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Abstract

Background: There is limited data on comparative risk of infections with various biologic agents in older adults with inflammatory bowel diseases (IBD).

Aim: We aimed to assess the comparative safety of biologic agents in older IBD patients with varying comorbidity burden.

Methods: We used data from a large, national commercial insurance plan in the United States to identify patients ≥60 years with IBD who newly initiated tumor necrosis factor-α antagonists (anti-TNF), vedolizumab, or ustekinumab. Comorbidity was defined using the Charlson Comorbidity Index (CCI). Our primary outcome was infection-related hospitalizations. Cox proportional hazards models were fitted in propensity-score weighted cohorts to compare the risk of infections between the different therapeutic classes.

Results: The anti-TNF, vedolizumab and ustekinumab cohorts included 2369, 972, and 352 patients, respectively, with a mean age of 67 years. The overall rate of infection-related hospitalizations was similar to that of anti-TNF agents for patients initiating vedolizumab (HR 0.94, 95% CI 0.84–1.04) and ustekinumab (0.92.,95% CI 0.74–1.16). Among patients with a CCI >1, both ustekinumab (HR: 0.66, 95% CI: 0.46–0.91, p-interaction <0.01) and vedolizumab (HR: 0.78, 95% CI: 0.65–0.94, p-interaction: 0.02) were associated with a significantly lower rate of infection-related hospitalizations compared to anti-TNFs. No difference was found among patients with a CCI ≤1.

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Conflicts of Interest

None of the authors have any relevant conflicts of interest to declare

BK has served on an advisory board for Pfizer, Inc

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Conclusions: Among adults ≥60 years with IBD initiating biologic therapy, both vedolizumab and ustekinumab were associated with lower rates of infection-related hospitalizations than anti-TNF therapy for those with high comorbidity burden.

Keywords

geriatric; Crohn's disease; ulcerative colitis; immunosuppression; multi-morbidity

INTRODUCTION

The number of older adults with inflammatory bowel diseases (IBD) is rapidly rising with nearly 1 million people 60 years and older living with IBD in the United States (US) alone.[1] Globally, IBD is most prevalent among people of older age.[2] Therapeutic options for the treatment of Crohn's disease (CD) and ulcerative colitis (UC) have rapidly proliferated in recent years, however effectively achieving remission may vary by mechanism of immunosuppression.[3, 4] Recent meta-analyses concluded that biologic agents increase the risk of serious and opportunistic infections in older adults with IBD.[5, 6] However, as older adults have a higher baseline risk for infections than younger adults, irrespective of type of treatment, comparisons between older and older patients cannot inform relative positioning within therapeutic algorithms.[7, 8] The comparisons within older adults alone were limited by examination of anti-TNF use versus non-biologic medications and did not stratify by comorbidity burden. Therefore, understanding the comparative safety of biologic agents specifically in older adults with IBD with different comorbidity is an important goal.

Older adults with IBD are disproportionately under-represented in clinical trials of IBD medications.[9] Therefore, real-world studies focused on older adults are needed. There is a paucity of studies on comparative safety of biologic agents focused only on older adults with IBD. The first comparative effectiveness and safety study of anti-tumor necrosis factor (TNF) agents and vedolizumab was a retrospective study based in tertiary care IBD centers with small numbers of patients.[10] A larger study in an administrative claims database, only compared anti-TNF agents to vedolizumab, but did include ustekinumab.[11] Another recent study on the comparative safety of ustekinumab versus adalimumab in patients of all ages with Crohn's disease, underscores the importance of leveraging large scale data to assess the relative safety of ustekinumab in older adults.[12]

Older adults are a heterogeneous population who, with immune senescence, have increased vulnerability to infections. To date, there are no large studies that compared the safety of therapies in older adults with IBD across different therapeutic mechanisms. Existing studies included data from only a few referral centers and have not had sufficient sample size to identify subgroups of older adults where there may be clinically meaningful differences in safety. Serious comorbidity is an important risk factor for infectious complications, particularly in older adults.[13] Yet how such comorbidity interacts with therapies to determine comparative safety has not been determined. Recent clinical practice guidelines suggest incorporating functional status and comorbidity in determining therapy selection, but offer no primary data to guide such decision making.[14] In this study, we aimed to assess the

comparative safety with the contribution of comorbidity of anti-TNF agents, vedolizumab and ustekinumab in older adults with IBD in a large US administrative claims-database.

METHODS

Study Design and Data Source

We conducted an observational study with a cohort design using unidentifiable claims data from a commercial U.S. health insurance plan. The database includes claims from 2008 to 2019 covering 85,972,617 individuals from every US state as well as Puerto Rico, Virgin Islands, and Washington DC. This database also includes some claims through the Medicare Advantage program. Members' demographics, dates of enrollment, medical and pharmacy claims during enrollment were extracted. This cohort has been previously used in other pharmacoepidemiologic studies in IBD.[15, 16]

Study Population and Cohort Definitions

Patients 60 years and older with IBD were identified as those having ≥1 claim with an International Classification of Diseases (ICD) 9th or 10th edition code for CD (ICD-9 555.x, ICD-10 K50.x) or UC (ICD-9 556.x, ICD-10 K51.x). For each of the three treatment cohorts – anti-TNF, vedolizumab and ustekinumab – we identified patients who had ≥1 claim for the treatment. The use of 1 IBD diagnosis code and 1 IBD-specific medication to identify patients with IBD in administrative claims databases is a widely accepted definition.[17, 18] Treatment claims were identified using national drug codes (NDC) and brand names in the pharmacy claims and healthcare common procedure coding system codes (HCPCS) in the medical claims. Anti-TNF agents included adalimumab, infliximab, golimumab, or certolizumab pegol. The date of the earliest treatment claim was defined as the index date to ensure the index date corresponds to the time of treatment initiation. We excluded patients who had <180 days of continuous enrollment prior to the index date to establish a baseline period.

Patients who had vedolizumab or ustekinumab during the 6-month baseline period who were switching to anti-TNF therapy were excluded from the anti-TNF cohort. The on-treatment follow-up period spanned from the index date to the date of treatment discontinuation, defined as the date of the last claim for the treatment during enrollment over a period with no gaps in treatment plus 90 days. A gap was defined as a period of >90 days between claims for the treatment. Patients with no follow-up duration or missing sex were excluded.

Study Outcomes

The primary outcome was the time from treatment initiation to an infection-related hospitalization, which has been defined previously as a serious infection in studies of biologic agents.[19] Infection-related hospitalizations were identified during the follow-up period by medical claims with an inpatient or emergency room place of service and an infection-related primary ICD-code. The secondary outcome was time from treatment initiation to any infection, defined analogously except using any claim with an infection-related diagnosis code. Infection related codes are listed in Supplemental Table 1. These

codes have been used in multiple prior studies of comparative safety in IBD and have demonstrated validity when compared to chart review.[15, 16, 20, 21]

Covariates

Age at index date was calculated based on date of birth. Sex was extracted from demographic records in the database. IBD sub-type was classified as CD or UC based on the majority of IBD-related claims that were incurred prior to the index date. Duration of IBD diagnosis under enrollment was defined as the number of days from the date of the first IBD-related claim during enrollment to the index date. Prior IBD medications were identified based on medical and pharmacy claims in the baseline period. IBD-related hospitalizations were identified based on inpatient claims with a primary diagnosis code for CD or UC during the baseline-period. The Charlson Comorbidity Index (CCI) is a weighted index that is widely used to summarize the total comorbidity burden of patients based on administrative data. We calculated the CCI using medical claims incurred during the baseline period that were associated with an ICD-9 or 10 code for each of the constituent conditions.[22, 23]

Statistical Analysis

Propensity score (PS) weighting was used to balance the vedolizumab and ustekinumab cohorts with the anti-TNF cohort in terms of baseline covariates. Two sets of PS weights were estimated to enable separate pairwise comparisons between vedolizumab and ustekinumab versus anti-TNF. Propensity scores were estimated using separate multivariable logistic regressions regressing treatment initiation with vedolizumab and ustekinumab versus anti-TNF on age, sex, IBD duration under enrollment, prior corticosteroid use, prior immunomodulator use, prior IBD hospitalization, and CCI as covariates. Standardized differences in the covariates comparing the vedolizumab and ustekinumab cohorts with the anti-TNF cohort, before and after weighting, are reported to assess the degree of covariate balance.

To compare the primary and secondary outcomes between the treatment cohorts, we fitted separate weighted Cox proportional hazard models comparing vedolizumab and ustekinumab versus anti-TNF. The models included indicators for older age (70-79 years and ≥80 years) and high comorbidity (CCI >1) to assess their independent associations. Adjusted hazard ratios (HR) for vedolizumab and ustekinumab versus anti-TNF were estimated, with 95% confidence intervals (CIs) and p-values estimated by bootstrapping[24]. To assess for treatment effect heterogeneity across patients with different comorbidity burden, we fit extended models that included interactions between CCI ≥ 2 and treatment. These extended models were then used to estimate the stratum-specific adjusted hazard ratios for vedolizumab and ustekinumab versus anti-TNF by comorbidity index status. These analyses were also repeated to assess for treatment effect heterogeneity between IBD subtypes among those initiating vedolizumab or anti-TNF. The analyses were performed using R version 3.4.1.

RESULTS

We identified 2,369 patients with IBD initiating anti-TNF agents, 972 patients initiating vedolizumab and 352 patients initiating ustekinumab at age ≥60 years. Prior to weighting, the mean age in the 3 cohorts ranged from 67 to 68 years. Over one third of patients in each cohort had corticosteroid use in the baseline period. In the vedolizumab cohort, 24% had prior anti-TNF use in the previous 6 months and 1% had prior ustekinumab. In the ustekinumab cohort, 25% had prior anti-TNF use and 14% had prior vedolizumab use. During the baseline period, 16% in the anti-TNF cohort, 18% in the vedolizumab cohort and 20% in the ustekinumab cohort had an IBD-related hospitalization. Further descriptive characteristics of the cohort are provided in Table 1. After propensity score weighting, only differences between type of IBD remained significant.

There were 8,576, 3,060 and 506 infection-related claims in the anti-TNF, vedolizumab and ustekinumab cohort over 2,378, 816 and 161 person-years of follow-up respectively. Overall incidence rates for any infection during follow-up were similar: 3,606/1,000 person-years (p-y) with anti-TNF agents, 3,748/1,000 p-y with vedolizumab and 3,139/1,000 p-y with ustekinumab. In patients hospitalized for infections after initiation of therapy, pneumonia was the most common diagnosis, followed by septicemia for hospitalization. In patients who had any infection, urinary tract infections (UTIs), upper respiratory infections (URIs) and fungal infections of the nail were the most commonly detected infections (Figure 1).

Among the overall cohort, there were no significant differences in the rate of infection-related hospitalizations with vedolizumab (HR: 0.94, 95% CI: 0.84 – 1.04) or ustekinumab (HR: 0.92, 95% CI: 0.75 – 1.16) compared with anti-TNF agents (Table 2). Patients 70-79 years had higher rates of infection-related hospitalizations than those <70 years among initiators of vedolizumab and anti-TNF agents (HR: 1.27, 95% CI: 1.12 – 1.43). Patients ≥80 years had higher rates than those <70 years among initiators of ustekinumab and anti-TNF agents (HR: 1.48, 95% CI: 1.04 – 2.12). Those with a CCI ≥2 also had higher rates of infection-related hospitalizations than those with a lower CCI among those initiating vedolizumab and anti-TNF agents (HR: 1.38, 95% CI: 1.23 – 1.55) and those initiating ustekinumab and anti-TNF agents (HR: 1.25, 95% CI: 1.04 – 1.47). Similar trends are noted for all infections as detailed in Table 3.

Importantly, a significant interaction was noted by comorbidity for infection related hospitalizations (Table 2). Among patients ≥60 years with IBD and a CCI >1, those treated with vedolizumab (HR: 0.78, 95% CI: 0.65 – 0.94) and ustekinumab (HR: 0.66, 95% CI: 0.46 – 0.91) had significantly lower rates of infection-related hospitalization than patients treated with anti-TNF agents. In contrast, among older adults without significant comorbidity, both vedolizumab (HR: 1.04, 95% CI: 0.90 – 1.19) and ustekinumab (HR: 1.14, 95% CI: 0.88 – 1.46) users had a similar rate of infection-related hospitalizations compared with anti-TNF users. Tests for interaction between treatment and comorbidity status indicated that the effect of vedolizumab and ustekinumab relative to anti-TNF varied by comorbidity status ($p=0.02$ and $p<0.01$, respectively).

There were no significant differences in the effect of vedolizumab versus anti-TNF agents by type of IBD for infection-related hospitalizations. However, there was a significant difference in the effect on any infection between UC and CD patients. Older adults with UC treated with vedolizumab experienced a lower rate of any infection compared with anti-TNF agents (HR: 0.68, 95% CI: 0.46 – 0.96), whereas there were no significant differences among patients with CD (HR: 1.16, 95% CI: 0.81 – 1.59).

DISCUSSION

We present data from a large, national cohort of adults ≥60 years with IBD who are treated with biologic agents to assess comparative safety. Despite the rapidly increasing number of older adults with moderate to severe IBD managed in clinical practice, there is a dearth of data to guide clinical management decisions and patient counseling.[25] We found that while there is no overall difference in the rate of serious infections for older adults treated with anti-TNF agents, vedolizumab and ustekinumab, for older adults with IBD and greater comorbidity, vedolizumab and ustekinumab confer a lower rate for an infection-related hospitalization than anti-TNF agents. This novel observation may help inform relative positioning of biologic therapies for older adults with IBD.

In a single-center study of IBD patients of all ages, Asscher et al reported that co-morbidity, not age, was significantly associated with an increased risk of hospitalizations in patients treated vedolizumab and ustekinumab.[26] Similarly, another study in IBD patients of all ages demonstrated that frailty conferred a significantly increased risk of infections after immunosuppression.[27] Taken together these findings highlight the importance of using constructs beyond chronologic age to risk stratify patients at higher risk for infections. Older patients with IBD are much less likely to be treated with effective, guideline recommended, immunosuppression for moderate to severe IBD.[28] Advanced age, co-morbidity, frailty and disability are all overlapping, but distinct, constructs, that need to be untangled in older patients with IBD to improve access to modern therapeutic options and strategies.[29]

Pharmacoepidemiologic studies are essential to informing the management of sub-populations, especially in rare disease conditions, such as IBD. However, to our knowledge, there are no pharmacoepidemiologic studies comparing all approved classes of biologic agents in older adults with IBD. We previously demonstrated that ustekinumab was associated with a lower rate of infections compared with anti-TNF agents in adults of all ages.[15] A study of biologic agents in older adults enrolled in Medicare claims concluded that vedolizumab was associated with a lower rate for serious infections than anti-TNF agents; however, despite adjusting for comorbidity, they did not test for interactions with treatment.[11] Ustekinumab and vedolizumab are less immunogenic agents that do not necessitate concomitant immunomodulatory therapy.[30] Therefore, in situations where there may be comparable effectiveness, agents with a lower risk of infections, such as vedolizumab and ustekinumab may be preferred for older adults with greater comorbidity burden.

A study assessing overall risk of infection in older patients with IBD reported that pneumonia was the most common infection noted in that cohort.[31] We found that pneumonia

was the most common infection resulting in hospitalization, but not the most common infection overall in older IBD patients treated with biologic agents. These studies emphasize the importance of promoting vaccinations, especially against respiratory infections, for older patients with IBD. Uptake of recommended vaccinations is low among patients with IBD, though it is higher for the influenza vaccine. In one cohort of patients with IBD of all ages, uptake for pneumococcal vaccination was as low as 10%.[32] Arguably, uptake of the pneumococcal vaccination is higher in older adults than younger adults, however, overall uptake of the pneumococcal vaccine among eligible older adults is not high.[33]

This study has a number of strengths, including a large sample size of older adults treated with a biologic agent for IBD from a national cohort. Our study has several limitations as well. As with all studies in administrative claims databases, we cannot ascertain granular details of IBD behavior, disease activity, medication doses and laboratory values. Specifically, we assessed patients with IBD together although there are likely differential risks of infections between those with Crohn's disease and ulcerative colitis. Additionally, characterizing comorbidity through an index does not allow for assessing the impact of specific comorbidities. Nevertheless, the CCI is widely used as a surrogate for serious comorbidity in studies of IBD and allows for meaningful analyses given the available sample size. As in all administrative claims studies, the cohorts have differential follow up; in the ustekinumab arm, this may have resulted in greater uncertainty in the estimates of the incidence rates. Finally, although the data source included some claims from members enrolled in Medicare Advantage programs, there is still the possibility of missing complete capture of biologic agents. However, the majority of Americans ≥65 years and older have some form of commercial insurance coverage and therefore biologic capture is unlikely to be universal even in Medicare claims databases.[34] The impact on comparative safety may not be strong unless there was differential ascertainment of outcomes. In spite of robust statistical methodology to account for confounders, there is always a potential for unmeasured confounding, especially confounding by indication. Despite the limitations, pharmacoepidemiologic studies are still essential to understanding medication safety in special populations where prospective randomized trials would not be practical to conduct.

To our knowledge, this is the first pharmacoepidemiologic study comparing all approved classes of biologic agents to treat IBD focused on older adults. We demonstrate that comorbidity is a mediator of infections requiring hospitalizations. These data can help counsel older adults who are about to initiate a biologic agent in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STUDY HIGHLIGHTS

What is known?

- Increasing number of older adults with inflammatory bowel diseases (IBD) require immunosuppression with biologic agents
- Older adults with IBD requiring biologic agents experience a greater risk for infections than younger adults

What is new here?

- Overall, anti-tumor necrosis factor (TNF) agents, vedolizumab and ustekinumab are associated with similar rates of infections and infection-related hospitalization
- However, in older adults with a greater burden of co-morbidities, vedolizumab and ustekinumab are associated with lower rates of infection-related hospitalizations than anti-tumor necrosis factors (TNF) agents

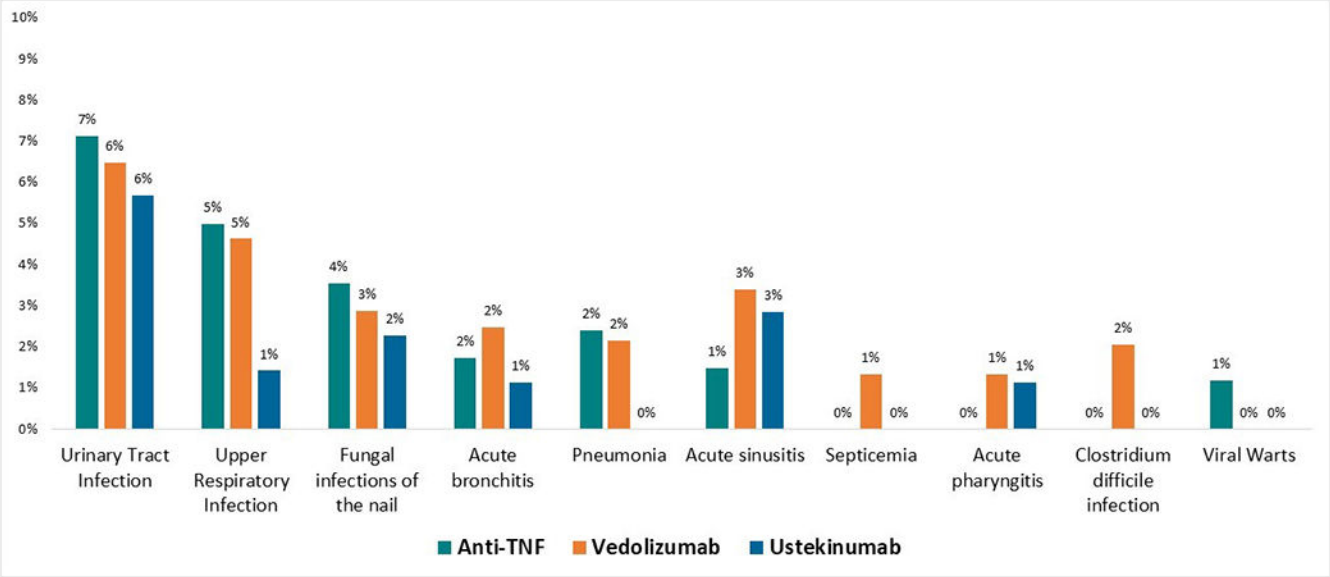

Figure 1: Frequency of infections in patients ≥60 years with inflammatory bowel diseases (IBD) after initiation of anti-tumor necrosis factor (TNF) infections, vedolizumab or ustekinumab

anti-TNF agents: infliximab, adalimumab, certolizumab-pegol and golimumab

Table 1:

Characteristics of patients ≥60 years with inflammatory bowel diseases (IBD) initiating a biologic agent in a national United States administrative claims cohort

	Anti-TNF	Vedolizumab	Ustekinumab
n	2369	972	352
Mean age [*] in years (SD)	67 (±6)	68 (±7)	67 (±6)
% Female	54	49	68
% Crohn's disease	55	44	84
% Prior IBD hospitalization	16	18	20
% Corticosteroid use at baseline [^]	38	35	36
% Immunomodulator use at baseline [^]	12	6	10
Mean Charlson comorbidity index	1.3	1.5	1.6
Mean follow up in days (SD)	366 (±320)	307 (±300)	167 (±155)

TNF: Tumor Necrosis Factor

[*] At treatment initiation

[^] Baseline is defined as a 180-day period prior to biologic initiation

Table 2:

Hazard ratio comparing rates of infection-related hospitalizations for patients ≥60 years with IBD treated with a biologic agent

Infection-related hospitalization	Hazard Ratio	95% Confidence Interval	p-interaction
Vedolizumab vs anti-TNF agents	0.94	0.84 – 1.04	
Charlson comorbidity index ≤1	1.04	0.90 – 1.19	0.02
Charlson comorbidity index >1	0.78	0.65 – 0.94	
Ustekinumab vs anti-TNF agents	0.92	0.75 – 1.13	
Charlson comorbidity index ≤1	1.14	0.88 – 1.46	<0.01
Charlson comorbidity index >1	0.66	0.46 – 0.91	

Table 3:

Hazard ratio comparing rates of any infection in patients ≥60 years with IBD treated with a biologic agent

Any Infection	Hazard Ratio	95% Confidence Interval	p-interaction
Vedolizumab vs anti-TNF agents	0.86	0.66 – 1.07	
Charlson comorbidity index ≤1	0.81	0.51 – 1.15	0.65
Charlson comorbidity index >1	0.90	0.65 – 1.22	
Ustekinumab vs anti-TNF agents	0.82	0.43 – 1.32	
Charlson comorbidity index ≤1	0.94	0.31 – 1.82	0.59
Charlson comorbidity index >1	0.71	0.29 – 1.26	