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Risk of Malignancy with Vedolizumab versus Tumor Necrosis Factor-α Antagonists in Patients with Inflammatory Bowel Diseases

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Abstract

Background and Aims: We conducted a retrospective cohort study comparing the risk of malignancy between patients treated with vedolizumab vs. tumor necrosis factor-α (TNFα) antagonists in patients with inflammatory bowel diseases (IBD).

Methods: Using an administrative claims database, we identified patients with IBD without prior malignancy who were new users of either vedolizumab or TNFα antagonists between 2014–2018, with no prior exposure to either biologic in preceding 1y and had insurance coverage for at least 1y after treatment initiation. We estimated incidence rate of malignancy (solid organ, hematological or skin cancers) in patients treated with vedolizumab and TNFα antagonists, and compared risk using Cox proportional hazard analysis.

Results: We included 4807 patients treated with TNFα antagonists (age, 41±15y, 60% with Crohn's disease [CD]) of whom 65 developed malignancy over 7214 person-year [PY] follow-up

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- Analysis and interpretation of data: SS, HCH
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(incidence rate [IR], 9.0 per 1000-PY), and 759 patients treated with vedolizumab (age, 46±16y, 42% CD) of whom 11 developed malignancy over 950-PY follow-up (IR, 11.6). No difference was observed in the incidence of malignancy between vedolizumab vs. TNFα antagonists (incidence rate ratio, 1.28; 95% CI, 0.61–2.45). After adjusting for age, sex, race, comorbidity burden, disease phenotype and concomitant use of immunomodulators, no difference was observed in time to incident malignancy between vedolizumab vs. TNFα antagonists (HR, 1.15; 95% CI, 0.61–2.19). Similar results were observed on stratified analysis by age and concomitant immunomodulators, and after excluding non-melanoma skin cancers.

Conclusions: In an observational study of patients with IBD, no differences were observed in the risk of incident malignancy in patients treated with vedolizumab vs. TNFα antagonists.

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Keywords

cancer; safety; choice; colitis; biologics

INTRODUCTION

With expanding treatment options for the management of inflammatory bowel diseases (IBD), comparative efficacy and safety are two key considerations in choosing optimal therapy. Tumor necrosis factor-α (TNFα) antagonists are one of the most effective and commonly used biologic agents for the management of patients with moderate to severely active inflammatory bowel diseases (IBD) at high risk of disease-related complications. However, patients and providers are concerned about potential risk of treatment side effects, particularly the risk of malignancy.[1, 2] Studies have variably suggested an increased risk of malignancy with TNFα antagonists, particularly hematological malignancies and possibly melanoma, but not an increased risk of solid organ cancers.[3] More recently, non-TNF-targeting biologics have been introduced with different efficacy and safety profile. Vedolizumab is a gut-targeting anti-integrin agent that blocks lymphocyte interaction with mucosal addressin cell adhesion molecule-1 expressed on the endothelium of mesenteric lymph nodes and gastrointestinal mucosa, impairing the migration of gut-homing lymphocytes.[4] Clinical trials and open-label extension studies have not suggested any increase in the risk of malignancy with this agent, though real-world evidence is lacking.[5, 6]

Head-to-head clinical trials and network meta-analyses have suggested that TNFα antagonists may be more effective than vedolizumab in patients with Crohn's disease, whereas vedolizumab and infliximab may have similar efficacy (and both may be more effective than adalimumab) in patients with ulcerative colitis.[7–9] While vedolizumab may cause lower systemic immune suppression than TNFα antagonists, studies have not confirmed a lower risk of serious infection with vedolizumab.[10–14] To further facilitate treatment selection and inform shared decision-making with patients in choosing vedolizumab and TNFα antagonists, we conducted a real-world observational study comparing the risk of malignancy in patients with IBD treated with vedolizumab vs. patients treated with TNFα antagonists in a de-identified administrative claims database.

METHODS

Data Source

We conducted a retrospective analysis of de-identified medical and pharmacy administrative claims from a large database, OptumLabs® Data Warehouse, which includes data on more than 100 million commercially insured and Medicare Advantage enrollees from geographically diverse regions across the United States, with greatest representation from the South and Midwest.[15] Medical claims include International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-9-CM; ICD-10-CM) diagnosis codes; ICD-9 and ICD-10 procedure codes; Current Procedural Terminology, Fourth Edition (CPT-4) procedure codes; Healthcare Common Procedure Coding System (HCPCS) procedure codes; site of service codes; and provider specialty codes. All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996, and because this study involved analysis of preexisting de-identified data it was exempted from institutional review board approval.

Study Population

We identified all patients who filled a prescription (or received an infusion) for TNFα antagonists (infliximab, adalimumab, certolizumab pegol and/or golimumab) and/or vedolizumab between January 1, 2014 and December 31, 2018. From this cohort, we included adult patients (18–89 years) with: (a) at least one diagnosis code for IBD (CD: ICD-9 555.x or ICD-10 K50; UC: ICD-9 556.x or ICD-10 K51) prior to index date (date of first filled prescription or infusion for TNFα antagonists or vedolizumab), either from an inpatient or outpatient visit, (b) continuous health plan enrollment with pharmacy benefits, with no prescription for biologic agents used for treating IBD (TNFα antagonists, vedolizumab, or ustekinumab) in the 12 months prior to index date (new-user design), and minimum 12-month enrollment in health plan after index date (patients who received candidate for <12m, and discontinued due to intolerance or non-response, but still remained in the health plan were included). In case a patient received diagnostic codes for both CD and UC, then the patient was classified as having CD if the majority of diagnostic codes were for CD.

We excluded patients with (a) human immunodeficiency virus infection, congenital immunodeficiency, or organ transplantation, (b) diagnosis of any malignancy in baseline 12 months prior to index biologic initiation date (see definition below), or (c) concomitant diagnosis of rheumatoid arthritis, ankylosing spondylitis, psoriasis or psoriatic arthritis within the baseline 12 months period prior to index biologic initiation date. Figure 1 shows the flow of patients for identification of the cohort.

Exposure

The primary exposures of interest were TNFα antagonists and vedolizumab. We considered patients as being continuously exposed from the index date for the duration of their prescription. Patients could contribute to only a single exposure group (TNFα antagonists or vedolizumab); patients who switched from one TNFα antagonist to another TNFα antagonist contributed person-time to TNFα antagonist group for both exposures combined.

Exposures were identified from pharmacy and/or medical claims (for infusions). Patients were followed until occurrence of the outcome of interest (see below), disenrollment from healthcare plan, treatment discontinuation (absence of new prescription or fill for a period of >4 months), or last date of follow-up (December 31, 2019). No minimum duration of biologic exposure was mandated. Since the risk of malignancy can persist briefly after stopping therapy, patients were deemed to be exposed for 3 additional months after treatment discontinuation and contributed to total person-year exposure.

Outcome

The primary outcome of interest was time to incident cancer, identified based on a validated malignancy finding algorithm.[16] Incident cancer was diagnosed based on administrative claims codes (ICD-9 or ICD-10 codes), at first of two cancer codes of the same organ system within 60 days of each other (eTable 1). This algorithm has been validated in Medicare claims against cancer registry data, with a sensitivity between 76–81% and specificity >99.5% for solid organ cancers, and sensitivity between 52–80% and specificity >99.8% for hematological cancers.[16] Non-melanoma skin cancers and melanoma were categorized as skin cancer. In accordance with OptumLabs data sharing policy, we are unable to report absolute numbers of each type of cancer to avoid back-counting small cell size.

To exclude patients with any cancer in the baseline 12m prior initiation of biologic, a more sensitive algorithm based on presence of a single diagnosis code of cancer was used.[16] This definition has a sensitivity of >85% for solid organ cancers, and >73% for hematological cancers.

Covariates

Baseline covariates (at time of biologic exposure or in preceding 12m) included age, sex, race (gathered routinely by the database used), census region, calendar year, comorbidity burden measured using the Elixhauser index (12m baseline period), health care utilization (defined as all-cause inpatient hospitalization or emergency department visits in 12m baseline period for each exposure), and IBD phenotype (CD or UC), abdominal surgery (12m baseline period) and receipt of endoscopy and/or abdominal imaging (12m baseline period). We did not have access to individual patient medical records, endoscopy reports or biochemical parameters.

We defined concomitant exposure to immunomodulators as filled prescription for thiopurines or methotrexate ±30 days of index biologic initiation date, which implies intention to treat with combination of biologic and immunomodulators.[17, 18]

Statistical Analysis

We calculated the incidence rate (IR, per 1000 person-years [PY]) and 95% confidence intervals (CI) of all, and major cancer categories, in patients with IBD treated with vedolizumab and TNFα antagonists. Subsequently, we estimated unadjusted incidence rate ratios (IRR) comparing vedolizumab vs. TNFα antagonists and overall risk of cancer, in all patients, and in predefined strata by age (≤60y vs. >60y), disease phenotype (CD vs. UC), and concomitant use of immunomodulators (yes vs. no). Finally, we compared the risk of

malignancy between vedolizumab vs. TNFα antagonists (reference) using Cox proportional hazard models, adjusting for age, sex, race and disease phenotype; concomitant use of immunomodulators was considered as a covariate but due to low exposure rate, this was excluded from final model.

Data Availability Statement

The data underlying this article were provided by OptumLabs® by permission. Data will be shared on request to the corresponding author with permission of OptumLabs®.

RESULTS

We included 4807 patients treated with TNFα antagonists, followed over 7214-PY, of whom 65 developed malignancy, and 759 patients treated with vedolizumab, followed over 950-PY of whom 11 developed malignancy. Baseline characteristics of TNFα antagonists and vedolizumab-treated patients with IBD are shown in Table 1. Among TNFα antagonist-treated patients, 60% had CD, 29.5% were hospitalized and 12.2% underwent abdominal surgery in the 12m prior to initiation of TNFα antagonist; 14.9% patients were treated with immunomodulators concomitantly. Among vedolizumab-treated patients, 42% had CD, 26.2% were hospitalized and 6.2% underwent abdominal surgery in the 12m prior to initiation of vedolizumab; 10.9% patients were treated with immunomodulators concomitantly.

After initiating biologic therapy, 76 patients developed incident cancers, including 31 patients with solid organ cancers and 36 patients with skin cancer; no cases of melanoma were observed. Twenty six patients (34%) were diagnosed with cancer within 6m of initiation of biologic therapy, and 29 (38%) were diagnosed >12m after biologic initiation. The overall rate of incident cancers in vedolizumab- and TNFα antagonist-treated patients was 11.6 (95% CI, 6.4–20.9) and 9.0 (95% CI, 7.1–11.5) per 1000-PY exposure, respectively, corresponding to an IRR of 1.28 (95% CI, 0.61–2.45) (Table 2). No significant differences were observed in the incidence of solid organ, hematological and skin cancers in vedolizumab- and TNFα antagonist-treated patients. On analysis stratified by age, the overall incidence of cancer was 4–5 times higher in adults >60y as compared to adults ≤60y old; however, the risk of cancer with vedolizumab vs. TNFα antagonists was comparable in both age groups. No difference in risk of cancer was observed in patients who were or were not receiving concomitant immunomodulators.

After adjusting for age, sex, race, comorbidity burden, IBD phenotype and concomitant use of immunomodulators, no differences were observed in the risk of malignancy between vedolizumab vs. TNFα antagonist-treated patients (adjusted HR, 1.15; 95% CI, 0.61–2.19). Older age (>60y vs. <30y: HR, 11.0; 95% CI, 4.2–28.8), and ulcerative colitis (HR, 1.59; 95% CI, 1.01–2.51) were associated with increased risk of malignancy.

DISCUSSION

In a large administrative claims database of 5566 biologic-treated patients with IBD, followed over 8164-PY, using a validated malignancy defining algorithm, we observed no

significant difference in the risk of incident cancer in patients treated with vedolizumab and TNFα antagonists, overall, and by several pre-defined clinically important strata of older patients and patients on concomitant immunomodulators. These findings are reassuring, suggesting that, overall, there are no specific malignancy-related safety signals with vedolizumab, and there is no significant difference in the risk of cancer between vedolizumab and TNFα antagonists.

The overall incidence of malignancy in our cohort of vedolizumab-treated patients was similar to rates observed in the GEMINI open-label extension study. In the open-label extension study with 2243 vedolizumab-treated patients with IBD, 60 patients developed malignant neoplasms, with an IR of 9.8 per 1000-PY in patients with ulcerative colitis, 8.3 per 1000-PY in patients with Crohn's disease.[5] On indirect comparison with age- and sex-matched reference population with IBD from Optum's Clinformatics™ Data Mart (medication exposure not reported), ratio of observed to expected cancers in vedolizumab-treated patients was unity (1.08; 95% CI, 0.73–1.53).[6] In a post-marketing study from vedolizumab's global safety database, 293 patients developed 299 malignancies (including malignancies within 1 year following vedolizumab initiation), in approximately 208,050-PY of vedolizumab exposure, corresponding to 1.44 events per 1000-PY.[6] This rate was lower than risk observed in our cohort, and in the open-label extension studies, since the global safety database was based on voluntary reporting. The most common malignancies were those of the lower gastrointestinal tract and lymphoma (59 [20%] and 33 [11%] events). Observed rates of malignancy in our cohort was also similar that reported in registry studies of TNFα antagonists. In the TREAT registry of 6,273 patients with Crohn's disease (3,420 treated with infliximab, 3764 treated with conventional therapy, average follow-up 5.2 years), incidence of malignancy in infliximab-treated patients was 6.4 per 1000-PY; IR of lymphoma was 0.5 per 1000-PY, very similar to rates observed in our cohort.[19] In the PYRAMID registry of 5025 patients with Crohn's disease treated with adalimumab with mean follow-up of ~3 years, the incidence of any malignancy (including NMSC) was 8.0 per 1000-PY.[20] These similar rates observed in our studies with other registry studies, and open-label extension studies with adjudication of cancer events, attests to the high accuracy of the malignancy-defining algorithm.[11]

Ours is the first study which compares the risk of incident cancers in patients treated with vedolizumab vs. TNFα antagonists. After adjusting for important covariates including age, sex, race and IBD phenotype, and on analysis stratified by concomitant use of immunomodulators, we confirmed no difference in the overall risk of cancer between vedolizumab- vs. TNFα antagonist-treated patients. We minimized the risk of carryover malignant potential from prior exposures, by adopting a new user design, and excluding patients with prior exposure to biologic therapy in the 1y prior to initiation of biologic agent. Indirect evidence from studies in patients with prior cancer suggest similar findings. In a retrospective cohort study of 96 patients with IBD exposed to vedolizumab, 184 patients exposed to TNFα antagonist, and 183 patients without exposure to immunosuppressive therapy after prior malignancy, Vedamurthy and colleagues observed that neither vedolizumab, nor TNFα antagonists were associated with increased risk of new or recurrent cancer, compared with patients not exposed to immunosuppressive therapy.[21] Though they did not directly compare vedolizumab and TNFα antagonists, IR of new or

recurrent cancer was 2.2 and 4.2 per 1000-PY, respectively. It is important to note that TNFα antagonists were started ~1.3y after cancer diagnosis, and vedolizumab was started ~3.9y after cancer diagnosis; 42% of TNFα antagonist-treated patients continued their therapy without interruption after diagnosis of index cancer. While large registry studies and population-based cohort studies have not shown an increase in risk of solid organ cancers with TNFα antagonists, they have been associated with increased risk of lymphoma, and possibly melanoma.[3, 22, 23] Unfortunately, due to low event rate, we were unable to examine the comparative risk of these specific cancers with vedolizumab.

While we adopted a meticulous approach to observational comparative effectiveness research, we acknowledge several important limitations to our study. First, as an administrative claims database-focused study, we did not have access to subjective or objective measures of disease activity or endoscopy reports and did not have accurate details of disease location and behavior. However, none of these exposures have been shown to significantly influence the risk of cancer, except colorectal cancer. Second, as with any observational study, we cannot rule out unobserved confounders, especially those due to treatment selection; however, our analytical approach, with a new user design and exclusion of patients with any diagnosis cancer in 1y prior to initiation of biologic, provides some protection against bias. It is unclear how long the risk of cancer persists after discontinuation of therapy. We limited this at-risk exposure period to 3 months after drug discontinuation, though acknowledge that increased risk may persist for a longer period of time after stopping therapies. Third, we were unable to compare the risk of malignancy in patients treated with TNFα antagonist or vedolizumab monotherapy or their use in combination with immunomodulators, due to low exposure and event rate especially in patients concomitantly on vedolizumab and immunomodulators. Finally, our median follow-up on therapy was 12–15 months, comparable with claims-based analyses in the United States.[24, 25] Longer term follow-up may allow more comprehensive assessment of cancer risk prolonged exposure, though this has not been observed in open-label extension studies with median 3y follow-up.

In summary, in a large administrative claims database study with over 8000-PY exposure to biologic agents, between 2014 to 2018, we observed that no difference in the incidence and risk of malignancy, particularly solid organ and non-melanoma skin cancer, in patients treated with vedolizumab or TNFα antagonists. These findings are very reassuring and directly inform discussions around comparative safety of these two therapies, including in older patients. Future prospective registry and real-world observational studies with longer duration of follow-up are warranted to confirm these findings and specifically, examine the risk of hematological malignancies and melanoma with vedolizumab.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

- Siddharth Singh reports research grants from AbbVie, Janssen
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- Lindsey Sangaralingham – None to declare
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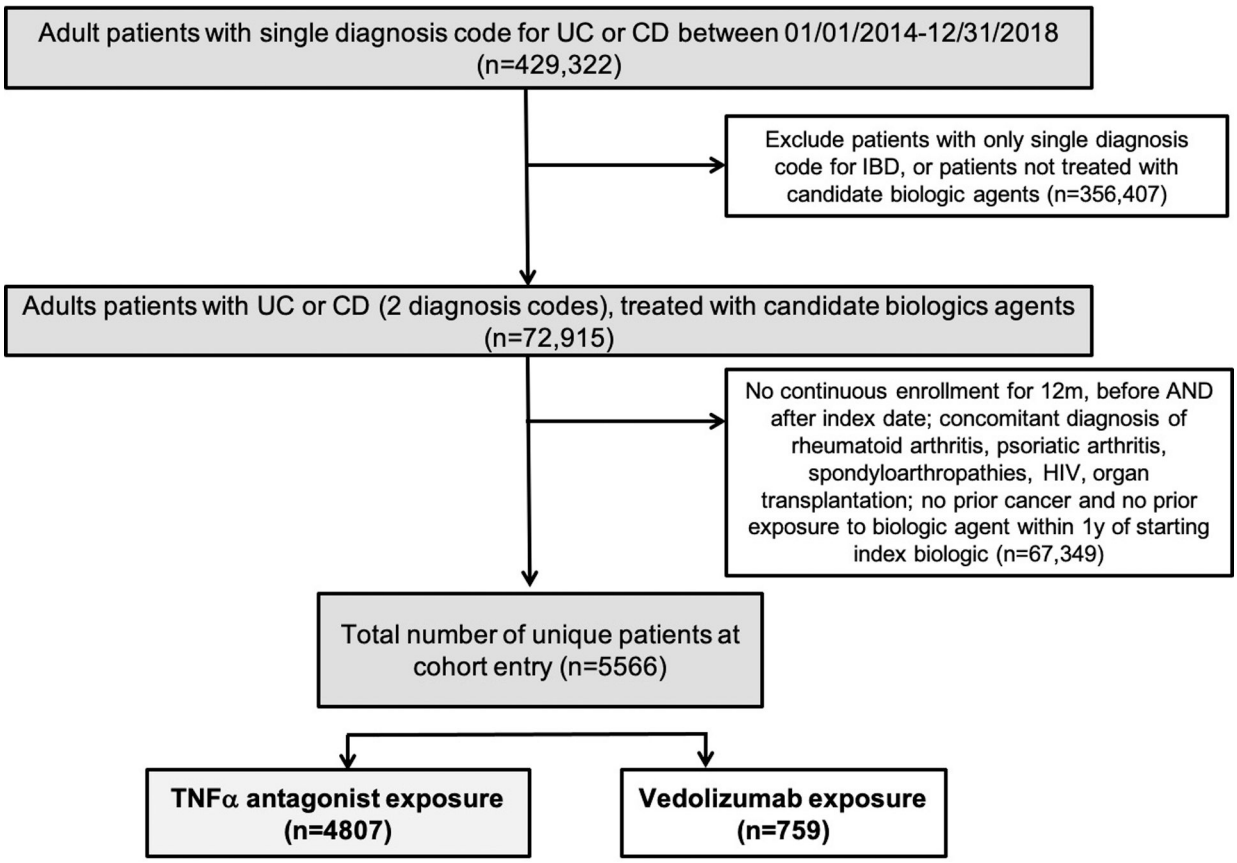

Figure 1.

Flow of patients for identification of TNFα antagonist- or vedolizumab-treated patients with inflammatory bowel diseases.

Table 1.

Baseline demographic characteristics, healthcare utilization and IBD-related medication use in the 12 months prior to initiation of index biologic, in the entire cohort.

Variable	TNFα antagonists (n=4807)	Vedolizumab (n=759)
Demographic variables		
Mean age ± SD, years	41 ± 15	46 ± 16
Sex (% males)	50.8	48.1
Race/Ethnicity, (% Caucasians)	71.9	74.4
IBD phenotype • Crohn's disease (%) • Ulcerative colitis (%)	 60.3 39.8	 41.6 58.4
Total person-year follow-up • Mean (± SD) follow-up after starting biologic, months	7214 15.1 ± 13.8	950 12.1 ± 11.1
Healthcare utilization and comorbidities (in 12 months prior to starting candidate biologic)		
Emergency room visits (% pts with ≥1)	48.5	44.8
Inpatient hospitalization (% pts with ≥1)	29.5	26.2
Abdominal Imaging (% of pts with ≥1)	56.3	44.7
Endoscopic procedures (% pts with ≥1)	74.9	71.9
Abdominal surgery (% pts with ≥1)	12.2	6.2
Elixhauser score • Elixhauser score 0–1 • Elixhauser score 2 or more	 55.6 44.4	 48.8 51.2
Major comorbidities [*] • Chronic obstructive lung disease • Diabetes with or without complication • Hypertension with or without complication • Obesity	 12.6 9.3 22.0 8.3	 13.0 12.9 26.1 11.2
IBD-related medication use (in 3 or 12 months prior to starting candidate biologic) [†]		
Oral corticosteroids	73.9	74.2
Immunomodulators • Prior use (in baseline 12m), % • Concomitant use (within ±30d), %	 16.1 14.9	 11.7 10.9
Opiates (in baseline 12m), %	42.6	37.3

[*] Patients diagnosed with cancer in 1y prior to starting index biologic were excluded

[†] Patients exposed to TNFa antagonists or vedolizumab in 1y prior to starting index biologic were excluded

[Abbreviations: n=number of patients, SD=standard deviation, TNF=tumor necrosis factor]

Table 2.

Incidence rate of malignancy by treatment exposure during follow-up, overall, by major cancer types, and pre-defined strata. Note, we are unable to report absolute numbers of each type of cancer to avoid back-counting small cell size per OptumLabs policy.

	Incidence rate (95% CI), per 1000 person-years		Incidence rate ratios (95% CI), vedolizumab vs. TNFα antagonists
	Vedolizumab	TNFα antagonists	
Overall	11.6 (6.4–20.9)	9.0 (7.1–11.5)	1.28 (0.61–2.45)
Cancer type • Solid organ • Hematological • Skin cancer	5.3 (2.2–12.6) 1.1 (0.1–7.5) 5.3 (2.2–12.7)	3.6 (2.5–5.3) 0.6 (0.2–1.5) 4.3 (3.0–6.1)	1.46 (0.44–3.86) 1.90 (0.04–19.18) 1.23 (0.37–3.18)
Age at biologic initiation • ≤60y • >60y	7.6 (3.4–17.0) 30.4 (12.7–73.0)	6.3 (4.6–8.6) 34.2 (22.9–51.0)	1.21 (0.42–2.87) 0.89 (0.26–2.38)
Disease phenotype • Crohn’s disease • Ulcerative colitis	7.6 (2.4–23.5) 14.4 (7.2–28.8)	7.6 (5.5–10.6) 11.4 (8.0–16.4)	1.00 (0.20–3.16) 1.26 (0.50–2.81)
Concomitant IMM • Yes • No	0 13.0 (7.2–23.4)	5.5 (2.7–11.0) 9.9 (7.6–12.8)	NA 1.31 (0.62–2.52)
Elixhauser index • <2 • ≥2	6.1 (2.0–18.9) 18.1 (9.0–36.0)	6.1 (4.2–9.0) 13.3 (9.7–18.2)	0.99 (0.19–3.23) 1.35 (0.55–2.94)

[Abbreviations: CI=confidence interval, n=number of patients, p-y=person-years, TNF=tumor necrosis factor]