Tofacitinib Treatment Safety in Moderate to Severe Ulcerative Colitis: Comparison of Observational Population Cohort Data From the IBM MarketScan® Administrative Claims Database With Tofacitinib Trial Data

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Background: Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). We aimed to estimate the overall incidence of safety events in patients with UC in a real-life population cohort for comparison with the tofacitinib UC clinical trial program.

Methods: Clinical trial-like criteria were applied to an IBM MarketScan® claims database population-based cohort (n = 22,967) of patients with UC (October 2010 to September 2015) to identify a UC trial-like cohort treated with tumor necrosis factor inhibitors (TNFi; n = 6366) to compare with the tofacitinib UC clinical trial cohort (n = 1157).

Results: Incidence rates (events per 100 patient-years; [95% confidence interval]) in the UC trial-like cohort were as follows: serious infections, 3.33 (2.73–4.02); opportunistic infections (OIs; excluding herpes zoster [HZ]), 1.45 (1.06–1.93); HZ, 1.77 (1.34–2.29); malignancies (excluding nonmelanoma skin cancer [NMSC]), 0.63 (0.43–0.90); NMSC, 1.69 (1.35–2.10); major adverse cardiovascular events (MACE), 0.51 (0.31–0.79); pulmonary embolism (PE), 0.54 (0.30–0.89); deep vein thrombosis (DVT), 1.41 (1.00–1.93); and gastrointestinal perforations, 0.31 (0.16–0.54). Compared with the UC trial-like cohort, tofacitinib-treated patients had numerically lower incidence rates for serious infections (1.75 [1.27–2.36]), OIs (excluding HZ; 0.16 [0.04–0.42]), NMSC (0.78 [0.47–1.22]), PE (0.16 [0.04–0.41]), and DVT (0.04 [0.00–0.23]), and a higher rate for HZ (3.57 [2.84–4.43]); rates for malignancies (excluding NMSC), MACE, and gastrointestinal perforations were similar.

Conclusions: When acknowledging limitations of comparing claims data with controlled clinical trial data, incidence rates for HZ among TNFi-treated patients in the UC trial-like cohort were lower than in the tofacitinib UC clinical trial cohort; rates for serious infections, OIs, NMSC, PE, and DVT were numerically higher.

Key Words: ulcerative colitis, indirect comparison, safety

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Abbreviations: CI, confidence interval; COX, cyclo-oxygenase; CPT, Current Procedural Terminology; DVT, deep vein thrombosis; GI, gastrointestinal; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HZ, herpes zoster; ICD-9, International Classification of Diseases, 9th Revision; IV, intravenous; MACE, major adverse cardiovascular events; N_E, number of treatment episodes; NMSC, nonmelanoma skin cancer; NSAID, nonsteroidal anti-inflammatory drug; OI, opportunistic infection; OLE, open-label, long-term extension; PE, pulmonary embolism; PY, patient-years; SEER, Surveillance, Epidemiology, and End Results; TNFi, tumor necrosis factor inhibitor; UC, ulcerative colitis.

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INTRODUCTION

For patients with ulcerative colitis (UC), existing data suggest an increased prevalence of many types of infection and certain malignancies.[1, 2] These are important safety considerations for patients, due to immunosuppression associated with the disease itself[3, 4] and the immunosuppressant therapies[5, 6] used to treat UC, which include biologic therapies (such as tumor necrosis factor inhibitors [TNFi], anti-integrins, and interleukin-12/23 antagonists). Accordingly, there is a need for representative epidemiological data with which to compare and contrast safety outcomes from controlled clinical trials of new UC therapies, particularly in the absence of head-to-head comparative clinical studies.[1, 2] Contextualization of safety data for new UC therapies with safety data of therapies that represent the current standard of care (ie, TNFi) is of particular importance.

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of UC. The tofacitinib UC clinical trial program reported the efficacy and safety of tofacitinib in patients with moderate to severe UC in a randomized controlled setting as induction therapy[7, 8] (one 8-week phase 2 study [A3921063, NCT00787202] and two 8-week phase 3 studies [OCTAVE Induction 1 and 2, NCT01465763 and NCT01458951]), and as maintenance therapy (a 52-week phase 3 study for clinical responders in OCTAVE Induction 1 and 2 [OCTAVE Sustain, NCT01458574]).[8] The long-term safety and efficacy of tofacitinib in patients with UC is being evaluated in an ongoing, open-label, long-term extension (OLE) study (OCTAVE Open, NCT01470612).[9] With the exception of a higher rate of herpes zoster (HZ) infection in tofacitinib-treated patients, compared with placebo-treated patients, integrated safety analyses of tofacitinib in the OCTAVE clinical trial program suggested a safety profile similar to that reported in clinical trials of biologic therapies used to treat UC, albeit not from head-to-head studies.[10]

Real-world data are important to aid in the interpretation of outcomes derived from the tofacitinib UC clinical trial program and to further characterize the safety profile of tofacitinib treatment. The IBM MarketScan® databases are a group of administrative databases, compiled and maintained by Truven Health Analytics, that contain inpatient and outpatient claims, outpatient prescription claims, clinical utilization records, and health expenditure data from patients in the United States.[11] This family of databases contains de-identified patient-level health data (medical, drug, and dental), productivity (workplace absence, short- and long-term disability and workers' compensation), laboratory results, health risk assessments, hospital discharges, and electronic medical records. Data are contributed by large employers, managed care organizations, hospitals, electronic medical record providers, Medicare, and Medicaid.[12]

In this population-based descriptive study, we utilized data from the IBM MarketScan® claims database to estimate the prevalence of comorbidities and background incidence rates for safety events of interest (serious infections, opportunistic infections [OIs; excluding HZ], HZ, malignancies [excluding nonmelanoma skin cancer (NMSC)], NMSC, major adverse cardiovascular events [MACE], pulmonary embolism [PE], deep vein thrombosis [DVT], and gastrointestinal [GI] perforations) in a cohort of adults with moderate to severe UC in a real-world setting. Data from the MarketScan® observational database were used to compare and contrast previously reported safety observations from the tofacitinib UC clinical trial program,[10] including contextualization of tofacitinib UC clinical trial safety data vs observational safety data for TNFi therapies.

METHODS

Study Design

This was a retrospective, descriptive study of US medical claims and pharmacy records data from patients diagnosed with UC from the IBM MarketScan® claims database for the period October 1, 2010, to September 30, 2015.

Patient Analysis

From the IBM MarketScan® claims database, a population-based cohort of patients with UC was identified using the following selection criteria: patients were 18 years or older with a diagnosis of UC, as defined by International Classification of Diseases, 9th Revision (ICD-9) code 556.X (but excluding ICD-9 code 556.4). Two separate diagnoses of UC were required at different points in time, with at least one made by a gastroenterologist. To identify patients with moderate to severe UC, eligible patients were restricted to those who were receiving or had received infliximab, adalimumab, golimumab, or vedolizumab; patients who were receiving or had received azathioprine, 6-mercaptopurine, methotrexate, tacrolimus, or cyclosporine; or patients who received more than 4000 mg of prednisone-equivalent oral systemic corticosteroids in the 6 months before the start of follow-up. Patients were also required to have at least 12 months of database enrollment before the index date (defined as the latest date that a patient satisfied all eligibility criteria), with no more than a 30-day gap in health care and pharmacy coverage. The follow-up period was defined from the index date to the earliest of either the date of death, date of lost medical or pharmacy coverage, or end of the study period.

From a population-based cohort of patients with UC selected from the MarketScan® claims database, a UC trial-like cohort was established using key trial-like selection criteria similar to those used in the phase 3 tofacitinib OCTAVE clinical trials.[8] The exclusion criteria applied were prior diagnosis of infection with HIV (ICD-9 codes 042, 0420-0422, 0429-0433, 0439-0440, and 0449), hepatitis B or C virus (ICD-9 codes 0702, 07020-07023, 0703, 07030-07033, 07041, 07044, 07051, 07054, and 07070-07071), diagnoses of cancer (excluding NMSC; detailed criteria for identification of malignancies are provided in the supplementary data),

Crohn's disease (gastroenterologist-diagnosed), prior surgery for UC, recent bowel surgery (within 6 months; identified based on ICD-9 and Current Procedural Terminology [CPT] codes), history of colectomy, solid organ transplantation, bone marrow transplantation, advanced kidney disease (ICD-9 codes 585.3, 585.4, 585.5, and 585.6), advanced liver disease (ICD-9 code 789.5), hepatic encephalopathy (ICD-9 code 572.2), or esophageal varices (ICD-9 codes 456.0, 456.1, and 456.2).

The index date was defined as the first date of prescription or administration of a new UC treatment in the pharmacy or procedure data after the population-based cohort index date, with no prior use of that therapy. The follow-up was defined from the index date to the earliest of the date of death, date of lost medical or pharmacy coverage, end of the study period, first outcome occurrence, or treatment switch or discontinuation. The baseline period was defined as the 12-month period before the index date.

New drug use exposure (ie, patients naïve to the drug or drug class before exposure) to the following categories of drugs was identified: immunomodulators/immunosuppressants (azathioprine, 6-mercaptopurine, oral or subcutaneous methotrexate, oral or intravenous [IV] tacrolimus, and oral or IV cyclosporine); biologics, including TNFi (adalimumab, infliximab, and golimumab); and vedolizumab. These analyses were performed before the approval of ustekinumab or tofacitinib for the treatment of UC.[13, 14] A patient could only be counted as a new user once per drug category; however, it was possible for a patient to be considered a new user for multiple drug categories (eg, a patient with new drug use exposure identified for azathioprine, 6-mercaptopurine, adalimumab, and vedolizumab would be included once in the immunomodulators/immunosuppressants category and once in the biologic category).

From the UC trial-like cohort, a subpopulation was selected in which patient follow-up was truncated to 12 months (post-index date) to mimic the study treatment duration from the tofacitinib maintenance study (OCTAVE Sustain).[8] Follow-up for the 12-month UC trial-like cohort was the same as for the UC trial-like cohort, but it included up to a maximum of 365 days after the index date instead of up to the end of the study period.

Tofacitinib Ulcerative Colitis Clinical Trial Overall Cohort

The tofacitinib UC clinical trial overall cohort included 1157 patients who received tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily in the tofacitinib UC clinical trial program (phase 2 and phase 3 induction studies, a phase 3 maintenance study, and an ongoing OLE study; data as of September 2018).[8, 10] The majority (n = 971) of the tofacitinib UC clinical trial overall cohort received tofacitinib 10 mg twice daily.[10] Incidence rates for safety events of interest in the tofacitinib UC clinical trial overall cohort were calculated based on the number of unique patients with ≥1 event per 100 patient-years (PY) of exposure.

Study Outcomes and Analyses

For the UC trial-like cohort, the following safety events of interest were reported (stratified by drug exposures of interest): serious infections (viral, bacterial, and fungal), OIs (excluding HZ), HZ, malignancies (excluding NMSC), NMSC, MACE (defined as myocardial infarction, stroke, or heart failure death in hospital), PE (defined as any inpatient diagnosis code of PE where the discharge disposition was that the patient had expired [died], or with subsequent administration or prescription of outpatient anticoagulant medication within 0–60 days of diagnosis code), DVT (defined as any inpatient hospitalization or outpatient diagnosis code of DVT, where [if hospitalized] the discharge disposition was that the patient had expired [died], or with subsequent outpatient administration or prescription of anticoagulant medication within 0–60 days of diagnosis code), and GI perforations. Serious infections were defined based on an inpatient primary discharge diagnosis of selected ICD-9 codes. Herpes zoster was defined as ICD-9 code 053 (inpatient discharge diagnosis code or outpatient physician evaluation and management encounter diagnosis code). Detailed criteria for identification of OIs, malignancies (excluding NMSC), NMSC, MACE, PE, DVT, and GI perforations are reported in the supplementary data. Gastrointestinal perforations were identified based on either (1) an inpatient diagnosis code that contained GI perforation or (2) an inpatient diagnosis code that suggested GI perforation without specific mention of GI perforation, when coupled with a GI surgery CPT code during the same hospitalization.

Statistical Analyses

Incidence rates (patients with events per 100 PY) for safety events of interest in the UC trial-like cohort were calculated based on the number of new events divided by the sum of the duration of patient exposures from the index date to censoring date during the risk period.

Associated 2-sided 95% confidence intervals (CIs) for incidence rates were calculated based on an assumed Poisson distribution.[15, 16] For malignancies (excluding NMSC) and NMSC, age-adjusted incidence rates in the UC trial-like cohort were calculated using the 2000 US Surveillance, Epidemiology, and End Results (SEER)[17] population by 10 years of age for the standardization.

Given the descriptive nature of this study, neither hypothesis testing nor multivariable modeling was performed. No imputation for missing data points was performed. Sensitivity analyses were conducted using alternative definitions for serious infections, NMSC, and GI perforation (see supplementary data online for alternative definitions).

All statistical analyses were performed using SAS version 9.4 (SAS Institute).

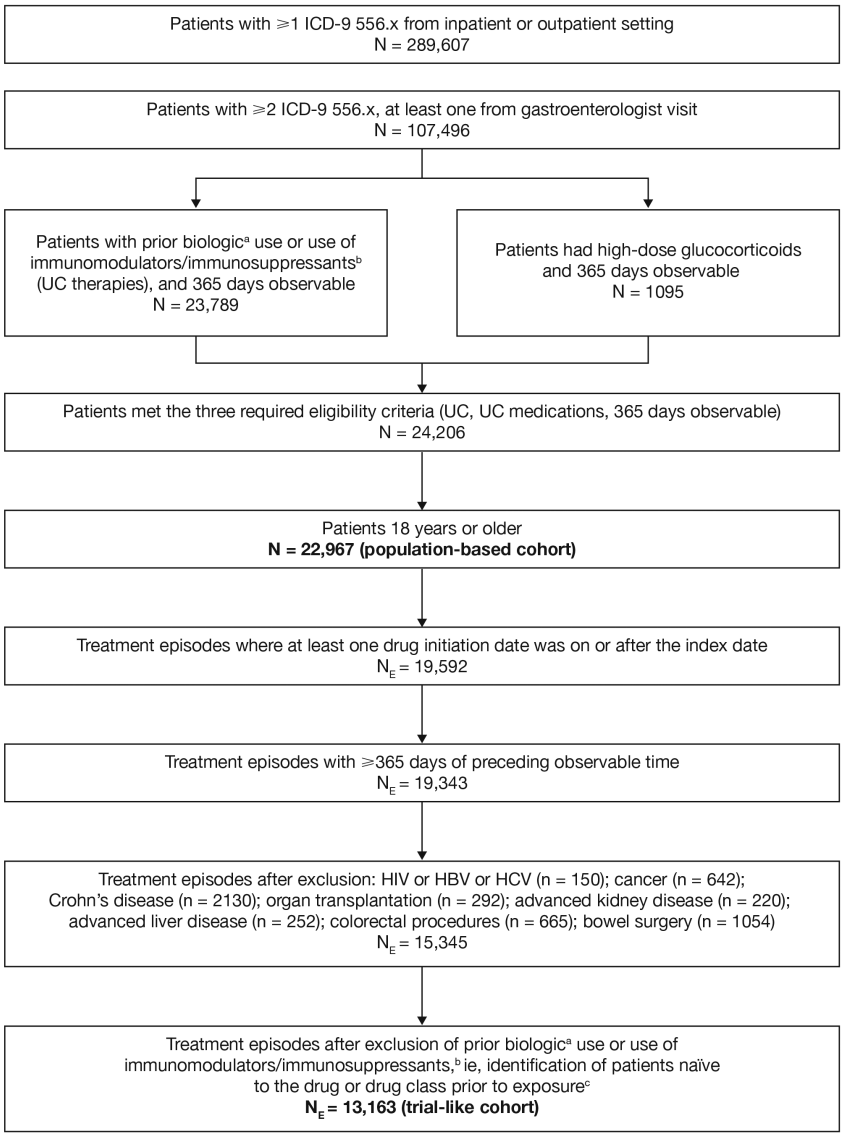

FIGURE 1. Selection of the UC trial-like cohort. [a]Adalimumab, infliximab, golimumab, and vedolizumab. [b]Azathioprine, 6-mercaptopurine, methotrexate, tacrolimus (oral or IV), and cyclosporine (oral or IV). [c]A patient could only be counted as a new user once per drug category; however, it was possible for a patient to be considered a new user for multiple drug categories. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; N, number of patients; N_E, number of treatment episodes.

Ethical Considerations

All patient data were in compliance with the Health Insurance Portability and Accountability Act confidentiality requirements. The study received Institutional Review Board approval from the University of Alabama at Birmingham, Birmingham, AB, USA.

RESULTS

Patients and Baseline Characteristics

Figure 1 shows the selection of patients for the UC trial-like cohort. A total of 22,967 patients with UC met the inclusion criteria for the overall population-based cohort. After application of the trial-like selection criteria, 13,163 treatment episodes were identified (ie, occurrences of patients newly initiating one or more UC therapies and meeting the selection criteria for inclusion in the trial-like cohort), and a total of 6366 unique patients contributed at least one treatment episode and were included in the UC trial-like cohort.

Baseline characteristics for the UC trial-like cohort are presented in Table 1. Baseline characteristics among patients were similar among patients initiating immunomodulators/immunosuppressants, biologics, and TNFi. Baseline characteristics for the overall MarketScan® UC population-based cohort are presented

TABLE 1. Baseline Characteristics of Patients in the UC Trial-like Cohort, Overall and by New User Treatment Group

Baseline Characteristic	UC Trial-like Cohort[b] (N = 6366)	UC Trial-like Cohort New User Treatment Groups[a]					
		Immunomodulators/ Immunosuppressants[c] (N = 2982)	Biologics[d] (N = 4058)	TNFi (N = 3982)	Adalimumab (N = 2115)	Infliximab (N = 1939)	Golimumab (N = 367)
Age (years), mean (standard deviation)	42.8 (14.6)	43.5 (14.8)	42.1 (14.4)	42.1 (14.4)	42.6 (14.0)	41.4 (14.7)	43.4 (14.8)
Gender (female), %	48.5	48.7	48.4	48.5	47.4	49.0	47.7
US Region, n (%)							
North-East	1274 (20.0)	581 (19.5)	796 (19.6)	764 (19.2)	395 (18.7)	383 (19.8)	75 (20.4)
North-Central	1548 (24.3)	786 (26.4)	940 (23.2)	927 (23.3)	466 (22.0)	496 (25.6)	63 (17.2)
South	2465 (38.7)	1091 (36.6)	1634 (40.3)	1619 (40.7)	865 (40.9)	764 (39.4)	159 (43.3)
West	973 (15.3)	474 (15.9)	620 (15.3)	604 (15.2)	348 (16.5)	273 (14.1)	60 (16.3)
Unknown	106 (1.7)	50 (1.7)	68 (1.7)	68 (1.7)	41 (1.9)	23 (1.2)	10 (2.7)
Year of index date, n (%)							
2011	371 (5.8)	211 (7.1)	169 (4.2)	169 (4.2)	41 (1.9)	127 (6.5)	1 (0.3)
2012	1652 (26.0)	904 (30.3)	872 (21.5)	872 (21.9)	333 (15.7)	569 (29.3)	7 (1.9)
2013	1428 (22.4)	707 (23.7)	893 (22.0)	893 (22.4)	520 (24.6)	394 (20.3)	87 (23.7)
2014	1753 (27.5)	702 (23.5)	1264 (31.1)	1252 (31.4)	747 (35.3)	497 (25.6)	192 (52.3)
2015	1162 (18.3)	458 (15.4)	860 (21.2)	796 (20.0)	474 (22.4)	352 (18.2)	80 (21.8)
Current smoker, n (%)	216 (3.4)	93 (3.1)	150 (3.7)	149 (3.7)	66 (3.1)	90 (4.6)	11 (3.0)
Baseline glucocorticoid use, n (%)	3145 (49.4)	1699 (57.0)	1793 (44.2)	1767 (44.4)	907 (42.9)	895 (46.2)	159 (43.3)
Baseline immunomodulator/immuno-suppressant use, n (%)	1181 (18.6)	124 (4.2)	1708 (42.1)	1680 (42.2)	874 (41.3)	879 (45.3)	167 (45.5)
Azathioprine or 6-mercaptopurine	1068 (16.8)	116 (3.9)	1556 (38.3)	1530 (38.4)	772 (36.5)	829 (42.8)	145 (39.5)
Baseline biologic use, n (%)	494 (7.8)	0 (0.0)	498 (12.3)	463 (11.6)	454 (21.5)	252 (13.0)	180 (49.0)
Adalimumab	142 (2.2)	0 (0.0)	145 (3.6)	127 (3.2)	0 (0.0)	233 (12.0)	126 (34.3)
Infliximab	342 (5.4)	0 (0.0)	343 (8.5)	325 (8.2)	437 (20.7)	0 (0.0)	79 (21.5)
Golimumab	13 (0.2)	0 (0.0)	13 (0.3)	10 (0.3)	17 (0.8)	21 (1.1)	0 (0.0)
Vedolizumab	2 (<0.1)	0 (0.0)	2 (<0.1)	5 (0.1)	1 (<0.1)	3 (0.2)	1 (0.3)
Baseline TNFi use, n (%)	493 (7.7)	0 (0.0)	497 (12.2)	460 (11.6)	453 (21.4)	251 (12.9)	179 (48.8)
TNFi-experienced (any prior use), n (%)	566 (8.9)	0 (0.0)	570 (14.0)	526 (13.2)	506 (23.9)	264 (13.6)	194 (52.9)
Comorbidities, n (%)							
Metabolic syndrome	25 (0.4)	12 (0.4)	17 (0.4)	17 (0.4)	10 (0.5)	7 (0.4)	2 (0.5)
Diabetes	412 (6.5)	200 (6.7)	256 (6.3)	253 (6.4)	135 (6.4)	118 (6.1)	30 (8.2)
Nonalcoholic fatty liver disease	74 (1.2)	39 (1.3)	49 (1.2)	48 (1.2)	30 (1.4)	19 (1.0)	3 (0.8)
Hypertension	1178 (18.5)	569 (19.1)	726 (17.9)	712 (17.9)	401 (19.0)	336 (17.3)	61 (16.6)
Coronary heart disease	192 (3.0)	96 (3.2)	119 (2.9)	116 (2.9)	63 (3.0)	54 (2.8)	11 (3.0)
Concurrent NSAID use, n (%)							
Oral NSAID (non-COX)	932 (14.6)	440 (14.8)	581 (14.3)	574 (14.4)	324 (15.3)	259 (13.4)	45 (12.3)
Oral NSAID (COX)	133 (2.1)	51 (1.7)	102 (2.5)	102 (2.6)	54 (2.6)	46 (2.4)	10 (2.7)
Prior medical history defined by physician diagnosis during 1-year baseline, n (%)							
OIs (excluding HZ)	67 (1.1)	21 (0.7)	54 (1.3)	54 (1.4)	31 (1.5)	27 (1.4)	5 (1.4)

TABLE 1. Continued

Baseline Characteristic	UC Trial-like Cohort[b] (N = 6366)	UC Trial-like Cohort New User Treatment Groups[a]					
		Immunomodulators/ Immunosuppressants[c] (N = 2982)	Biologics[d] (N = 4058)	TNFi (N = 3982)	Adalimumab (N = 2115)	Infliximab (N = 1939)	Golimumab (N = 367)
HZ	80 (1.3)	28 (0.9)	62 (1.5)	60 (1.5)	31 (1.5)	31 (1.6)	7 (1.9)
Malignancies (excluding NMSC)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NMSC	28 (0.4)	13 (0.4)	17 (0.4)	17 (0.4)	10 (0.5)	7 (0.4)	5 (1.4)
MACE	51 (0.8)	32 (1.1)	25 (0.6)	25 (0.6)	14 (0.7)	14 (0.7)	2 (0.5)
GI perforations	225 (3.5)	101 (3.4)	150 (3.7)	146 (3.7)	60 (2.8)	84 (4.3)	12 (3.3)
HZ vaccination[e] (any prior use), n (%)	152 (2.4)	74 (2.5)	91 (2.2)	89 (2.2)	55 (2.6)	40 (2.1)	9 (2.5)

[a]New user drug exposures of interest (patients naïve to the drug or drug class before exposure) measured in the 12-month baseline and all preceding time (if available). Columns are not mutually exclusive: a patient could only be counted as a new user once per drug category; however, it was possible for a patient to be considered a new user for multiple drug categories. Each column reflects patient characteristics from baseline data at the start of the first of their drug-specific treatment episodes that contributed to the column-specific exposure analysis.
[b]Number of unique patients contributing at least one treatment episode.
[c]Azathioprine, 6- mercaptopurine, methotrexate (oral or subcutaneous), tacrolimus (oral or IV), and cyclosporine (oral or IV).
[d]Adalimumab, infliximab, golimumab, and vedolizumab.
[e]Vaccination with live virus vaccine.
Abbreviations: COX, cyclo-oxygenase; N, number of patients in the cohort or new user treatment group; n, number of patients in the specified category; NSAID, nonsteroidal anti-inflammatory drug.

in Supplementary Table 1. Baseline characteristics of patients who received tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily in OCTAVE Sustain and in the tofacitinib UC clinical trial overall cohort are presented in Supplementary Table 2.

Incidence Rates for Safety Events of Interest

Crude incidence rates (patients with events per 100 PY) for safety events of special interest in the population-based cohort are presented in Supplementary Figure 1.

Serious infections

In the UC trial-like cohort, there were 37 serious infection events (defined as inpatient hospitalization in the primary position) among 2830 patients receiving immunomodulators/immunosuppressants (incidence rate, 2.37; 95% CI, 1.67–3.27; Table 2). There were 107 serious infection events among 4420 patients receiving any TNFi, with an incidence rate of 3.33 (95% CI, 2.73–4.02; 3214.5 PY) in the UC trial-like cohort, compared with 1.75 (95% CI, 1.27–2.36; 2457.3 PY; 43 patients with serious infection events) in the tofacitinib UC clinical trial overall cohort (Table 3). In patients receiving any TNFi, the incidence rates for serious infection events were numerically higher among patients who had prior TNFi exposure, compared with TNFi-naïve patients (3.63 [95% CI, 2.30–5.45] vs 3.25 [95% CI, 2.60–4.03]). The incidence rate for patients receiving TNFi in combination with immunomodulators/immunosuppressants was 3.60 (95% CI, 2.41–5.17) vs 3.39 (95% CI, 2.59–4.36) for patients receiving TNFi alone. The incidence rate for patients receiving vedolizumab was 6.26 (95% CI, 1.29–18.28) based on 48.0 PY of exposure.

Opportunistic infections (excluding herpes zoster)

In the UC trial-like cohort, there were 17 OI events (excluding HZ) identified among 2830 patients receiving immunomodulators/immunosuppressants (incidence rate, 1.09; 95% CI, 0.63–1.74). There were 47 OI events among 4420 patients receiving any TNFi, with an incidence rate of 1.45 (95% CI, 1.06–1.93; 3243.4 PY) in the UC trial-like cohort, compared with 0.16 (95% CI, 0.04–0.42; 2464.2 PY; four patients with OI events) in the tofacitinib UC clinical trial overall cohort (Table 3). In patients receiving any TNFi, the incidence rate for OIs among TNFi-experienced patients was 2.03 (95% CI, 1.08–3.48) vs 1.31 (95% CI, 0.90–1.82) for TNFi-naïve patients. The incidence rate for patients receiving TNFi in combination with immunomodulators/immunosuppressants was 1.35 (95% CI, 0.68–2.42) vs 1.41 (95% CI, 0.91–2.07) for patients receiving TNFi alone. The incidence rate for patients receiving vedolizumab was 2.08 (95% CI, 0.05–11.60) based on 48.0 PY of exposure.

Herpes Zoster

In the UC trial-like cohort, a total of 15 HZ events were identified among 2830 patients receiving immunomodulators/

TABLE 2. Crude Incidence Rates (Patients With Events per 100 PY) for Serious Infections, OIs (Excluding HZ), HZ, Malignancies (Excluding NMSC), NMSC, MACE, PE, DVT, and GI Perforations in the UC Trial-like Cohort and UC 12-month Trial-like Cohort, by Treatment Exposure

	UC Trial-like Cohort				12-month UC Trial-like Cohort		
	n/N	PY	Incidence Rate per 100 PY (95% CI)	SEER Age-standardized Incidence Rate per 100 PY (95% CI)	n/N	PY	Incidence Rate per 100 PY (95% CI)
Serious Infection							
Any immunomodulator/immunosuppressant	37/2830	1558.77	2.37 (1.67–3.27)	N/A	35/2830	1212.12	2.89 (2.01–4.02)
Any TNFi	107/4420	3214.46	3.33 (2.73–4.02)	N/A	91/4420	2424.43	3.75 (3.02–4.61)
Any TNFi (TNFi-experienced)	23/964	633.08	3.63 (2.30–5.45)	N/A	20/964	499.31	4.01 (2.45–6.19)
Any TNFi (TNFi-naïve)	84/3456	2581.38	3.25 (2.60–4.03)	N/A	71/3456	1925.12	3.69 (2.88–4.65)
TNFi + immunomodulator/immunosuppressant	29/1635	806.31	3.60 (2.41–5.17)	N/A	27/1635	677.01	3.99 (2.63–5.80)
TNFi alone	60/2785	1770.03	3.39 (2.59–4.36)	N/A	52/2785	1380.26	3.77 (2.81–4.94)
Adalimumab	40/2115	1439.01	2.78 (1.99–3.79)	N/A	30/2115	1120.63	2.68 (1.81–3.82)
Infliximab	64/1939	1564.52	4.09 (3.15–5.22)	N/A	58/1939	1125.11	5.16 (3.91–6.66)
Golimumab	3/367	210.98	1.42 (0.29–4.16)	N/A	3/367	178.75	1.68 (0.35–4.90)
Vedolizumab	3/163	47.95	6.26 (1.29–18.28)	N/A	3/163	47.65	6.30 (1.30–18.40)
OIs (Excluding HZ)							
Any immunomodulator/immunosuppressant	17/2830	1562.9	1.09 (0.63–1.74)	N/A	16/2830	1216.57	1.32 (0.75–2.14)
Any TNFi	47/4420	3243.43	1.45 (1.06–1.93)	N/A	39/4420	2441.96	1.60 (1.14–2.18)
Any TNFi (TNFi-experienced)	13/964	639.05	2.03 (1.08–3.48)	N/A	11/964	503.06	2.19 (1.09–3.91)
Any TNFi (TNFi-naïve)	34/3456	2604.38	1.31 (0.90–1.82)	N/A	28/3456	1938.9	1.44 (0.96–2.09)
TNFi + immunomodulator/immunosuppressant	11/1635	811.86	1.35 (0.68–2.42)	N/A	10/1635	681.21	1.47 (0.70–2.70)
TNFi alone	25/2785	1778.67	1.41 (0.91–2.07)	N/A	19/2785	1387.63	1.37 (0.82–2.14)
Adalimumab	16/2115	1449.15	1.10 (0.63–1.79)	N/A	14/2115	1126.13	1.24 (0.68–2.09)
Infliximab	31/1939	1581.75	1.96 (1.33–2.78)	N/A	25/1939	1136.58	2.20 (1.42–3.25)
Golimumab	0/367	212.58	0.00 (0.00–1.74)	N/A	0/367	179.31	0.00 (0.00–2.06)
Vedolizumab	1/163	48.03	2.08 (0.05–11.60)	N/A	1/163	47.73	2.10 (0.05–11.67)
HZ							
Any immunomodulator/immunosuppressant	15/2830	1564.26	0.96 (0.54–1.58)	N/A	10/2830	1218.09	0.82 (0.39–1.51)
Any TNFi	57/4420	3226.62	1.77 (1.34–2.29)	N/A	46/4420	2436.91	1.89 (1.38–2.52)
Any TNFi (TNFi-experienced)	14/964	635.3	2.20 (1.20–3.7)	N/A	13/964	499.46	2.60 (1.39–4.45)
Any TNFi (TNFi-naïve)	43/3456	2591.32	1.66 (1.20–2.24)	N/A	33/3456	1937.45	1.70 (1.17–2.39)
TNFi + immunomodulator/immunosuppressant	20/1635	802.52	2.49 (1.52–3.85)	N/A	17/1635	677.09	2.51 (1.46–4.02)
TNFi alone	27/2785	1775.98	1.52 (1.00–2.21)	N/A	26/2785	1385.36	1.88 (1.23–2.75)
Adalimumab	21/2115	1447.09	1.45 (0.90–2.22)	N/A	19/2115	1123.74	1.69 (1.02–2.64)
Infliximab	35/1939	1568.1	2.23 (1.55–3.10)	N/A	26/1939	1134.74	2.29 (1.50–3.36)
Golimumab	1/367	211.49	0.47 (0.01–2.63)	N/A	1/367	178.48	0.56 (0.01–3.12)
Vedolizumab	0/163	48.29	0.00 (0.00–7.64)	N/A	0/163	47.99	0.00 (0.00–7.69)
Malignancies (Excluding NMSC)							
Any immunomodulator/immunosuppressant	18/2830	3068.22	0.59 (0.35–0.93)	0.48 (0.21–0.96)	9/2830	1829.82	0.49 (0.22–0.93)
Any TNFi	31/4420	4894.56	0.63 (0.43–0.90)	0.59 (0.33–0.98)	22/4420	3074.35	0.72 (0.45–1.08)
Any TNFi (TNFi-experienced)	6/964	982.91	0.61 (0.22–1.33)	0.56 (0.13–1.57)	5/964	648.46	0.77 (0.25–1.80)
Any TNFi (TNFi-naïve)	25/3456	3911.65	0.64 (0.41–0.94)	0.59 (0.30–1.03)	17/3456	2425.89	0.70 (0.41–1.12)
TNFi + immunomodulator/immunosuppressant	11/1635	988.01	1.11 (0.56–1.99)	0.81 (0.28–1.85)	10/1635	780.84	1.28 (0.61–2.36)

TABLE 2. Continued

	UC Trial-like Cohort				12-month UC Trial-like Cohort		
	n/N	PY	Incidence Rate per 100 PY (95% CI)	SEER Age-standardized Incidence Rate per 100 PY (95% CI)	n/N	PY	Incidence Rate per 100 PY (95% CI)
TNFi alone	12/2785	2603.39	0.46 (0.24–0.81)	0.44 (0.16–0.96)	10/2785	1726.82	0.58 (0.28–1.06)
Adalimumab	9/2115	2210.16	0.41 (0.19–0.77)	0.42 (0.11–1.07)	6/2115	1446.89	0.41 (0.15–0.90)
Infliximab	20/1939	2363.51	0.85 (0.52–1.31)	0.76 (0.36–1.41)	14/1939	1385.59	1.01 (0.55–1.70)
Golimumab	2/367	320.95	0.62 (0.08–2.25)	0.71 (0.02–3.72)	2/367	241.92	0.83 (0.10–2.99)
Vedolizumab	1/163	73.7	1.36 (0.03–7.56)	1.13 (0.00–9.71)	1/163	72.53	1.38 (0.03–7.68)
NMSC[a]							
Any immunomodulator/immunosuppressant	50/2830	3035.73	1.65 (1.22–2.17)	1.52 (0.96–2.29)	32/2830	1817.1	1.76 (1.20–2.49)
Any TNFi	82/4420	4841.87	1.69 (1.35–2.10)	1.53 (1.08–2.11)	57/4420	3053.04	1.87 (1.41–2.42)
Any TNFi (TNFi-experienced)	21/964	969.83	2.17 (1.34–3.31)	2.22 (0.86–4.66)	14/964	642.25	2.18 (1.19–3.66)
Any TNFi (TNFi-naïve)	61/3456	3872.04	1.58 (1.21–2.02)	1.42 (0.95–2.03)	43/3456	2410.79	1.78 (1.29–2.40)
TNFi + immunomodulator/immunosuppressant	26/1635	974.19	2.67 (1.74–3.91)	2.68 (1.28–4.93)	21/1635	775.6	2.71 (1.68–4.14)
TNFi alone	37/2785	2580.22	1.43 (1.01–1.98)	1.35 (0.79–2.16)	27/2785	1715.63	1.57 (1.04–2.29)
Adalimumab	39/2115	2193.85	1.78 (1.26–2.43)	1.76 (0.99–2.88)	28/2115	1437.13	1.95 (1.29–2.82)
Infliximab	33/1939	2337.71	1.41 (0.97–1.98)	1.24 (0.72–2.01)	20/1939	1378.16	1.45 (0.89–2.24)
Golimumab	11/367	312.05	3.53 (1.76–6.31)	2.78 (0.99–6.18)	9/367	237.8	3.78 (1.73–7.18)
Vedolizumab	0/163	73.88	0.00 (0.00–4.99)	0.00 (0.00–4.99)	0/163	72.54	0.00 (0.00–5.09)
MACE[b]							
Any immunomodulator/immunosuppressant	18/2830	2075.78	0.87 (0.51–1.37)	N/A	11/2830	1505.38	0.73 (0.36–1.31)
Any TNFi	20/4420	3903.27	0.51 (0.31–0.79)	N/A	18/4420	2794.76	0.64 (0.38–1.02)
Any TNFi (TNFi-experienced)	2/964	786.54	0.25 (0.03–0.92)	N/A	2/964	589.49	0.34 (0.04–1.23)
Any TNFi (TNFi-naïve)	18/3456	3116.73	0.58 (0.34–0.91)	N/A	16/3456	2205.27	0.73 (0.41–1.18)
TNFi + immunomodulator/immunosuppressant	8/1635	913.44	0.88 (0.38–1.73)	N/A	8/1635	748.78	1.07 (0.46–2.11)
TNFi alone	12/2785	2124.44	0.56 (0.29–0.99)	N/A	10/2785	1581.27	0.63 (0.30–1.16)
Adalimumab	9/2115	1768.33	0.51 (0.23–0.97)	N/A	7/2115	1306.27	0.54 (0.22–1.10)
Infliximab	8/1939	1870.07	0.43 (0.18–0.84)	N/A	8/1939	1271	0.63 (0.27–1.24)
Golimumab	3/367	264.93	1.13 (0.23–3.31)	N/A	3/367	217.55	1.38 (0.28–4.03)
Vedolizumab	0/163	65.84	0.00 (0.00–5.60)	N/A	0/163	65.43	0.00 (0.00–5.64)
PE[c]							
Any immunomodulator/immunosuppressant	7/2771	2040.45	0.34 (0.14–0.71)	N/A	3/2771	1474.44	0.20 (0.04–0.59)
Any TNFi	15/3125	2785.25	0.54 (0.30–0.89)	N/A	14/3125	1963.82	0.71 (0.39–1.20)
Any TNFi (TNFi-experienced)	1/428	388.54	0.26 (0.01–1.43)	N/A	1/428	269.11	0.37 (0.01–2.07)
Any TNFi (TNFi-naïve)	14/2697	2396.71	0.58 (0.32–0.98)	N/A	13/2697	1694.71	0.77 (0.41–1.31)
TNFi + immunomodulator/immunosuppressant	1/790	474.29	0.21 (0.01–1.17)	N/A	1/790	378.08	0.26 (0.01–1.47)
TNFi alone	12/2335	1795.47	0.67 (0.35–1.17)	N/A	11/2335	1319.05	0.83 (0.42–1.49)
Adalimumab	4/1548	1288.98	0.31 (0.08–0.79)	N/A	3/1548	946.25	0.32 (0.07–0.93)
Infliximab	10/1366	1351.67	0.74 (0.35–1.36)	N/A	10/1366	898.78	1.11 (0.53–2.05)
Golimumab	1/211	144.60	0.69 (0.02–3.85)	N/A	1/211	118.79	0.84 (0.02–4.69)
Vedolizumab	0/64	24.51	0.00 (0.00–15.05)	N/A	0/64	24.40	0.00 (0.00–15.12)
DVT[d]							
Any immunomodulator/immunosuppressant	15/2771	2036.32	0.74 (0.41–1.21)	N/A	11/2771	1470.21	0.75 (0.37–1.34)
Any TNFi	39/3125	2769.13	1.41 (1.00–1.93)	N/A	33/3125	1955.43	1.69 (1.16–2.37)

TABLE 2. Continued

	UC Trial-like Cohort				12-month UC Trial-like Cohort		
	n/N	PY	Incidence Rate per 100 PY (95% CI)	SEER Age-standardized Incidence Rate per 100 PY (95% CI)	n/N	PY	Incidence Rate per 100 PY (95% CI)
Any TNFi (TNFi-experienced)	2/428	388.26	0.52 (0.06–1.86)	N/A	2/428	269.5	0.74 (0.09–2.68)
Any TNFi (TNFi-naïve)	37/2697	2380.87	1.55 (1.09–2.14)	N/A	31/2697	1685.93	1.84 (1.25–2.61)
TNFi + immunomodulator/immunosuppressant	12/790	466.89	2.57 (1.33–4.49)	N/A	12/790	373.36	3.21 (1.66–5.61)
TNFi alone	22/2335	1786.67	1.23 (0.77–1.86)	N/A	18/2335	1315.4	1.37 (0.81–2.16)
Adalimumab	15/1548	1280.52	1.17 (0.66–1.93)	N/A	12/1548	941.76	1.27 (0.66–2.23)
Infliximab	21/1366	1344.56	1.56 (0.97–2.39)	N/A	18/1366	895.16	2.01 (1.19–3.18)
Golimumab	3/211	144.05	2.08 (0.43–6.09)	N/A	3/211	118.51	2.53 (0.52–7.40)
Vedolizumab	0/64	24.51	0.00 (0.00–15.05)	N/A	0/64	24.4	0.00 (0.00–15.12)
GI Perforation[e]							
Any immunomodulator/immunosuppressant	4/2830	2092.76	0.19 (0.05–0.49)	N/A	4/2830	1509.24	0.27 (0.07–0.68)
Any TNFi	12/4420	3915.1	0.31 (0.16–0.54)	N/A	11/4420	2798.46	0.39 (0.20–0.70)
Any TNFi (TNFi-experienced)	1/964	787.5	0.13 (0.00–0.71)	N/A	1/964	589.8	0.17 (0.00–0.94)
Any TNFi (TNFi-naïve)	11/3456	3127.6	0.35 (0.18–0.63)	N/A	10/3456	2208.66	0.45 (0.22–0.83)
TNFi + immunomodulator/immunosuppressant	4/1635	915.83	0.44 (0.12–1.12)	N/A	4/1635	749.14	0.53 (0.15–1.37)
TNFi alone	6/2785	2132.55	0.28 (0.10–0.61)	N/A	6/2785	1583.13	0.38 (0.14–0.82)
Adalimumab	5/2115	1776.07	0.28 (0.09–0.66)	N/A	4/2115	1308.94	0.31 (0.08–0.78)
Infliximab	7/1939	1873.94	0.37 (0.15–0.77)	N/A	7/1939	1271.79	0.55 (0.22–1.13)
Golimumab	0/367	265.16	0.00 (0.00–1.39)	N/A	0/367	217.78	0.00 (0.00–1.69)
Vedolizumab	0/163	65.84	0.00 (0.00–5.60)	N/A	0/163	65.43	0.00 (0.00–5.64)

Immunomodulators/immunosuppressants included: azathioprine, 6-mercaptopurine, methotrexate, tacrolimus (oral or IV), and cyclosporine (oral or IV).
[a]Specific definition (basal cell carcinoma or squamous cell carcinoma).
[b]Myocardial infarction, stroke, or heart failure associated death in hospital.
[c]Any inpatient diagnosis code of PE with administration or prescription of anticoagulant medication within 0–60 days of diagnosis code—one episode per patient.
[d]Any inpatient or outpatient diagnosis code of DVT with administration or prescription of anticoagulant medication within 0–60 days of diagnosis code—one episode per patient.
[e]Sensitive definition—GI diagnosis for inpatient discharge diagnosis code with no mention of perforation, when coupled with a GI surgery CPT code during the same hospitalization.
Abbreviations: n, number of events; N, number of treatment episodes.

immunosuppressants (incidence rate, 0.9; 95% CI, 0.54–1.58). A total of 57 HZ events occurred among 4420 patients receiving any TNFi, with an incidence rate of 1.77 (95% CI, 1.34–2.29; 3226.6 PY) in the UC trial-like cohort, compared with 3.57 (95% CI, 2.84–4.43; 2325.1 PY; 83 patients with HZ events) in the tofacitinib UC clinical trial overall cohort (Table 3). In patients receiving any TNFi, the incidence rate for HZ was numerically higher among TNFi-experienced patients (2.20; 95% CI, 1.20–3.70) vs TNFi-naïve patients (1.66; 95% CI, 1.20–2.24). The incidence rate for patients receiving TNFi in combination with immunomodulators/immunosuppressants was 2.49 (95% CI, 1.52–3.85) vs 1.52 (95% CI, 1.00–2.21) for patients receiving TNFi alone. The incidence rate for patients receiving vedolizumab was 0.00 (95% CI, 0.00–7.64) based on 48.3 PY of exposure.

Malignancies (excluding nonmelanoma skin cancer)

In the UC trial-like cohort, 18 malignancies (excluding NMSC) were recorded among 2830 patients receiving immunomodulators/immunosuppressants (incidence rate, 0.59; 95% CI, 0.35–0.93). There were 31 malignancies (excluding NMSC) recorded among patients receiving any TNFi, with an incidence rate of 0.63 (95% CI, 0.43–0.90; 4894.6 PY) in the UC trial-like cohort, compared with 0.69 (95% CI, 0.40–1.11; 2461.2 PY; 17 patients with malignancies [excluding NMSC]) in the tofacitinib UC clinical trial overall cohort (Table 3). In patients receiving any TNFi, the incidence rates for malignancies (excluding NMSC) were similar for TNFi-experienced (0.61; 95% CI, 0.22–1.33) and TNFi-naïve (0.64; 95% CI, 0.41–0.94) patients. The incidence rate for patients receiving TNFi in combination with immunomodulators/immunosuppressants was 1.11 (95% CI, 0.56–1.99) vs 0.46 (95% CI, 0.24–0.81) for patients receiving TNFi alone. The incidence rate for patients receiving vedolizumab was 1.36 (95% CI, 0.03–7.56) based on 73.7 PY of exposure. Corresponding age-standardized rates of malignancies (excluding NMSC) in the trial-like cohort were numerically similar to the crude incidence rates.

Nonmelanoma skin cancer

In the UC trial-like cohort, there were 50 NMSC events identified among 2830 patients receiving immunomodulators/immunosuppressants (incidence rate, 1.65; 95% CI, 1.22–2.17). There were 82 NMSC events among patients receiving any TNFi, with an incidence rate of 1.69 (95% CI, 1.35–2.10; 4841.9 PY) in the UC trial-like cohort, compared with 0.78 (95% CI, 0.47–1.22; 2427.3 PY; 19 patients with NMSC events) in the tofacitinib UC clinical trial overall cohort (Table 3). In patients receiving any TNFi, the incidence rates for NMSC were numerically higher among patients who had prior TNFi exposure, compared with TNFi-naïve patients (2.17 [95% CI, 1.34–3.31] vs 1.58 [95% CI, 1.21–2.02]). The incidence rate for patients receiving TNFi in combination with immunomodulators/

TABLE 3. Incidence Rates (Patients With Events per 100 PY) for Serious Infections, OIs (Excluding HZ), HZ, Malignancies (Excluding NMSC), NMSC, MACE, PE, DVT, and GI Perforations in the Tofacitinib UC Clinical Trial Overall Cohort and in the UC Trial-like Cohort of the MarketScan® Analysis for Patients Receiving any TNFi, TNFi as Monotherapy, and TNFi plus Immunomodulators/Immunosuppressants

	Tofacitinib UC Clinical Trial Overall Cohort			UC Trial-like Cohort		
	Incidence Rate per 100 PY (95% CI)			Incidence Rate per 100 PY (95% CI)		
Adverse Event of Special Interest	All	Prior TNFi—Yes	Prior TNFi—No	Any TNFi	TNFi Monotherapy	TNFi + Immunomodulators/Immunosuppressants
Serious Infections	1.75 (1.27–2.36)	1.77 (1.11–2.69)	1.57 (0.95–2.45)	3.33 (2.73–4.02)	3.39 (2.59–4.36)	3.6 (2.41–5.17)
OIs (Excluding HZ)	0.16 (0.04–0.42)	0.16 (0.02–0.58)	0.16 (0.02–0.59)	1.45 (1.06–1.93)	1.41 (0.91–2.07)	1.35 (0.68–2.42)
HZ	3.57 (2.84–4.43)	4.69 (3.52–6.11)	2.40 (1.60–3.47)	1.77 (1.34–2.29)	1.52 (1.00–2.21)	2.49 (1.52–3.85)
Malignancies (Excluding NMSC)	0.69 (0.4–1.11)	0.96 (0.50–1.68)	0.41 (0.13–0.96)	0.63 (0.43–0.90)	0.46 (0.24–0.81)	1.11 (0.56–1.99)
NMSC	0.78 (0.47–1.22)	1.23 (0.69–2.04)	0.33 (0.09–0.84)	1.69 (1.35–2.10)	1.43 (1.01–1.98)	2.67 (1.74–3.91)
MACE	0.28 (0.11–0.59)	0.24 (0.05–0.70)	0.33 (0.09–0.84)	0.51 (0.31–0.79)	0.56 (0.29–0.99)	0.88 (0.38–1.73)
PE	0.16 (0.04–0.41)	—	—	0.54 (0.30–0.89)	0.67 (0.35–1.17)	0.21 (0.01–1.17)
DVT	0.04 (0.00–0.23)	—	—	1.41 (1.00–1.93)	1.23 (0.77–1.86)	2.57 (1.33–4.49)
GI Perforations	0.12 (0.03–0.36)	0.16 (0.02–0.58)	0.08 (0.00–0.46)	0.31 (0.16–0.54)	0.28 (0.10–0.61)	0.44 (0.12–1.12)

In the tofacitinib UC clinical trial overall cohort, most patients (83.9%; n = 971) received tofacitinib 10 mg twice daily.[10]
Incidence rates for individual TNFi therapies and for vedolizumab are reported in Supplementary Figure 2.

immunosuppressants was 2.67 (95% CI, 1.74–3.91) vs 1.43 (95% CI, 1.01–1.98) for patients receiving TNFi alone. The incidence rate for patients receiving vedolizumab was 0.00 (95% CI, 0.00–4.99) based on 73.9 PY of exposure. Corresponding age-standardized rates of NMSC in the UC trial-like cohort were numerically similar to the crude incidence rates.

Major adverse cardiovascular events

In the UC trial-like cohort, there were 18 MACE events identified among 2830 patients receiving immunomodulators/immunosuppressants (incidence rate, 0.87; 95% CI, 0.51–1.37). There were 20 MACE events among patients receiving any TNFi, with an incidence rate of 0.51 (95% CI, 0.31–0.79; 3903.3 PY) in the UC trial-like cohort, compared with 0.28 (95% CI, 0.11–0.59; 2459.3 PY; seven patients with MACE events) in the tofacitinib UC clinical trial overall cohort (Table 3). Among patients receiving any TNFi, the incidence rate for MACE in patients with prior TNFi exposure was 0.25 (95% CI, 0.03–0.92) vs 0.58 (95% CI, 0.34–0.91) for TNFi-naïve patients. The incidence rate for patients receiving TNFi in combination with immunomodulators/immunosuppressants was 0.88 (95% CI, 0.38–1.73) vs 0.56 (95% CI, 0.29–0.99) for patients receiving TNFi alone. The incidence rate for patients receiving vedolizumab was 0.00 (95% CI, 0.00–5.60) based on 65.8 PY of exposure.

Pulmonary embolism

In the UC trial-like cohort, there were seven PE events identified among 2771 patients receiving immunomodulators/immunosuppressants (incidence rate, 0.34; 95% CI, 0.14–0.71). There were 15 PE events among patients receiving any TNFi, with an incidence rate of 0.54 (95% CI, 0.30–0.89; 2785.3 PY) in the UC trial-like cohort, compared with 0.16 (95% CI, 0.04–0.41; 2468.6 PY; four patients with PE events) in the tofacitinib UC clinical trial overall cohort (Table 3). Among patients receiving any TNFi, the incidence rate for PE in patients with prior TNFi exposure was 0.26 (95% CI, 0.01–1.43; based on one PE event) vs 0.58 (95% CI, 0.32–0.98) for TNFi-naïve patients. The incidence rate for patients receiving TNFi in combination with immunomodulators/immunosuppressants was 0.21 (95% CI, 0.01–1.17) vs 0.67 (95% CI, 0.35–1.17) for patients receiving TNFi alone. The incidence rate for patients receiving vedolizumab was 0.00 (95% CI, 0.00–15.05) based on 24.5 PY of exposure.

Deep vein thrombosis

In the UC trial-like cohort, there were 15 DVT events identified among 2771 patients receiving immunomodulators/immunosuppressants (incidence rate, 0.74; 95% CI, 0.41–1.21). There were 39 DVT events among patients receiving any TNFi, with an incidence rate of 1.41 (95% CI, 1.00–1.93; 2769.1 PY) in the UC trial-like cohort, compared with 0.04 (95% CI, 0.00–0.23; 2472.6 PY; one patient with DVT event) in the tofacitinib UC clinical trial overall cohort (Table 3). Among patients receiving any TNFi, the incidence rate for DVT in patients with prior TNFi exposure was 0.52 (95% CI, 0.06–1.86) vs 1.55 (1.09–2.14) for TNFi-naïve patients. The incidence rate for patients receiving TNFi in combination with immunomodulators/immunosuppressants was 2.57 (95% CI, 1.33–4.49) vs 1.23 (95% CI, 0.77–1.86) for patients receiving TNFi alone. The incidence rate for patients receiving vedolizumab was 0.00 (95% CI, 0.00–15.05) based on 24.5 PY of exposure.

Gastrointestinal perforations

In the UC trial-like cohort, there were four GI perforations identified among 2830 patients receiving immunomodulators/immunosuppressants (incidence rate, 0.19; 95% CI, 0.05–0.49). There were 12 GI perforations among 4420 patients receiving any TNFi, with an incidence rate of 0.31 (95% CI, 0.16–0.54; 3915.1 PY) in the UC trial-like cohort, compared with 0.12 (95% CI, 0.03–0.36; 2465.0 PY; three patients with GI perforations) in the tofacitinib UC clinical trial overall cohort (Table 3). Among patients receiving TNFi, the incidence rate for GI perforations in patients with prior TNFi exposure was 0.13 (95% CI, 0.00–0.71) vs 0.35 (95% CI, 0.18–0.63) for TNFi-naïve patients. The incidence rate for patients receiving TNFi in combination with immunomodulators/immunosuppressants was 0.44 (95% CI, 0.12–1.12) and 0.28 (95% CI, 0.10–0.61) for patients receiving TNFi alone. The incidence rate for patients receiving vedolizumab was 0.00 (95% CI, 0.00–5.60) based on 65.8 PY of exposure.

Impact of Duration of Exposure on Outcomes

For most outcomes and categories of prior treatment exposure, incidence rates were numerically slightly higher when limiting the follow-up time to 1 year (ie, in the 12-month UC trial-like cohort), compared with using all of the follow-up time (ie, in the UC trial-like cohort; Table 2). However, 95% CIs typically overlapped when comparing the UC trial-like cohort and the 12-month UC trial-like cohort. Figure 2 shows incidence rates for safety events of special interest in patients receiving any TNFi in the MarketScan® 12-month UC trial-like cohort alongside incidence rates in the 12-month tofacitinib maintenance study (OCTAVE Sustain). In general, the same pattern was observed for the comparison of the uncensored UC trial-like cohort vs the tofacitinib UC clinical trial overall cohort, with a numerically higher rate of serious infections and OIs (excluding HZ) in the 12-month UC trial-like cohort, a numerically higher rate of HZ in the tofacitinib maintenance cohort, and similar rates for malignancies (excluding NMSC), NMSC, MACE, PE, DVT, and GI perforations.

DISCUSSION

This large retrospective cohort study of adult patients from the IBM MarketScan® database generated important contextualizing information regarding the epidemiological

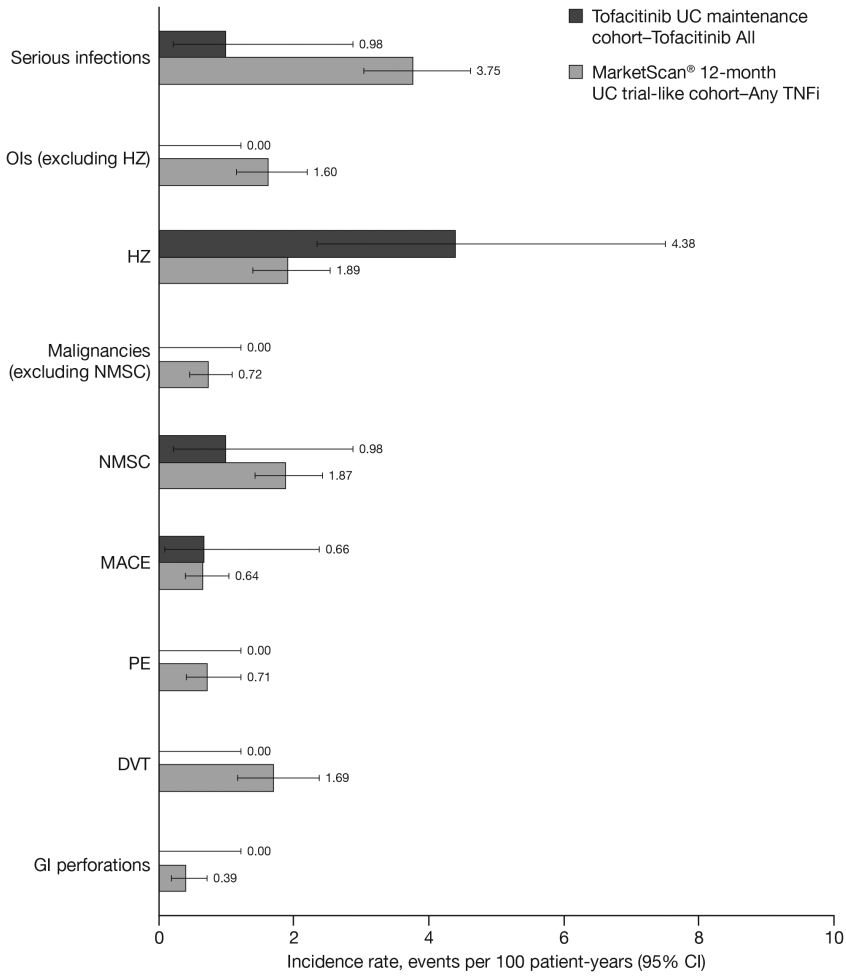

FIGURE 2. Incidence rates (patients with events per 100 PY) for serious infections, OIs (excluding HZ), HZ, malignancies (excluding NMSC), NMSC, MACE, PE, DVT, and GI perforations in the tofacitinib UC maintenance cohort (ie, data from the 52-week OCTAVE Sustain study) and the 12-month UC trial-like cohort of the MarketScan® analysis for patients receiving any TNFi.

safety profile of therapies for the treatment of moderate to severe UC, including immunomodulators/immunosuppressants and biologic therapies. The large cohort size provided sufficient statistical power to generate robust incidence rates for a number of safety outcomes relevant to advanced treatments of moderate to severe UC, allowing for qualitative comparability with the tofacitinib UC clinical trial program. Consideration of these findings alongside available data for tofacitinib and biologic therapies used to treat UC (ie, infliximab, adalimumab, golimumab, and vedolizumab) revealed similarities in terms of the overall incidence rates for malignancies.[18–21] The incidence rate for serious infections in the tofacitinib UC clinical trial program was numerically lower than that observed in the observational cohorts for patients with UC studied in this analysis. Conversely, the rate of HZ in the tofacitinib UC clinical trial program was approximately twice as high as that observed in the observational cohort.

Data from the MarketScan® UC trial-like observational cohort allowed for contextualization of safety data from the tofacitinib UC clinical trial program vs TNFi therapies or immunomodulators/immunosuppressants used to treat UC. The incidence rate for HZ among patients receiving any TNFi in the UC trial-like cohort was lower than the corresponding incidence rate in the tofacitinib UC clinical trial program. Conversely, incidence rates for serious infections, OIs (excluding HZ), NMSC, and DVT were numerically higher among patients receiving any TNFi in the UC trial-like cohort vs patients receiving tofacitinib in the UC clinical trial program. These findings are generally consistent with comparisons of clinical trial data for tofacitinib and TNFi therapies, in which safety with tofacitinib seemed similar to that observed with TNFi therapies, with the exception of increased HZ incidence rate.[10, 22–25] Similar to TNFi therapies, the incidence rate for HZ was numerically lower, and the incidence rates for other safety outcomes were numerically higher, among patients receiving immunomodulators/

immunosuppressants in the UC trial-like cohort vs patients receiving tofacitinib in the UC clinical trial program.

Tofacitinib has been associated with increased risk of HZ; however, most HZ cases are noncomplicated, mild to moderate in severity, and manageable with standard antiviral therapy.[26] Furthermore, most patients with HZ during the tofacitinib clinical trials were able to continue tofacitinib treatment.[26, 27]

Safety events of interest and corresponding incidence rates varied according to patients' prior medication exposure. Patients previously exposed to TNFi therapies generally had higher incidence rates for most outcomes, compared with TNFi-naïve patients. Incidence rates for safety events of special interest were numerically slightly higher in the 12-month UC trial-like cohort—where follow-up time was limited to 12 months to mimic clinical trial conditions—than in the UC trial-like cohort. This may indicate a time-dependent risk for these events or may be due to physicians choosing not to continue therapy in patients who experience an event while using a particular treatment. It is also possible that greater systemic inflammation, which may coincide with new treatment initiation, was associated with higher incidence rates for some events. Similarly, concomitant therapies, including corticosteroids, may be used more frequently and at higher doses around the time of starting a new therapy. Sensitivity analyses showed that the specific definitions used for serious infections, NMSC, and GI perforations had an impact on the number of events identified and corresponding incidence rates, with the variability most noticeable for alternative definitions of serious infections.

Venous thromboembolism (DVT and PE) has been identified to be an important potential risk of treatment with tofacitinib. In the MarketScan® UC trial-like cohort, the incidence rate for DVT and PE in patients receiving any TNFi was numerically higher than that observed in the tofacitinib UC clinical trial overall cohort. In the tofacitinib UC clinical trial overall cohort, one patient had DVT and four had PE. All patients had received a predominant dose of tofacitinib 10 mg twice daily (average daily dose ≥15 mg) and had risk factors for venous thromboembolism alongside UC.[28]

A strength of this analysis is the large number of patients included in the UC trial-like cohort that provided sufficient statistical power to generate robust incidence rate estimates for the various outcomes assessed. A key limitation of this analysis is that the algorithm for identifying UC was not validated by review of medical records, and thus misclassification of the disease was possible. However, the selection criteria for the UC trial-like cohort required patients to have received biologic or immunosuppressant UC therapies or high-dose corticosteroids, decreasing the likelihood of misclassification.

Patients' lifetime medical history before enrollment was not available, which may also have led to misclassification of baseline covariates. Safety outcomes in this analysis were classified based on diagnosis codes and not the gold standard of medical record review, which may have resulted in possible misclassification. However, evidence on the agreement of diagnosis codes with medical records has demonstrated generally high agreement, with positive predictive values of 75%–95%.[29–31] Although validation of diagnosis codes with medical records has not to our knowledge been performed in patients with inflammatory bowel disease, multiple retrospective studies have utilized the IBM MarketScan® claims database to identify cohorts of patients with inflammatory bowel disease.[32–34]

A limitation of the analyses of MACE, malignancies (excluding NMSC), NMSC, OIs, and GI perforations was that the definitions of these events used in the MarketScan® analysis were based on diagnosis codes, whereas in the tofacitinib UC clinical trial program, they were adjudicated by a blinded review committee. Thus, differences in rates of these events between the cohorts should be interpreted cautiously. A limitation relating to the identification of MACE was that the definition employed did not capture deaths that occurred outside of a hospital setting. In addition, as only in-hospital deaths were captured in the MarketScan® database, we did not evaluate mortality as a safety outcome of interest, as it would likely have been underestimated.

A further limitation is that claims data lack detail regarding disease severity and rely on filled prescriptions as evidence of drug consumption. Patients electing to participate in a clinical trial may have somewhat more active disease, which is why we created the UC trial-like cohort of new UC therapy initiators to reflect this circumstance for comparability. The potential for a healthy volunteer bias is also a concern for the generalizability of trial results, in that patients who elected to participate in the trial may have fewer comorbidities than real-world patients, for example. This concern is borne out by comparing the prevalence of hypertension and diabetes, which were more prevalent in the population-based cohort, compared with the UC trial-like cohort.

Furthermore, health plan data do not capture medications acquired over the counter or as free samples. These data also reflect only one insured patient population, in this case commercially insured patients. For the analyses performed based on new drug use exposure, though we evaluated incidence rates among patients taking any TNFi alone and with concomitant immunomodulators/immunosuppressants, we did not evaluate concomitant steroid use.

There were also limited data available for patients using vedolizumab, representing few PY of exposure, compared with other therapies, and this analysis predated the approval of ustekinumab or tofacitinib for the treatment of UC. When comparing data from the MarketScan® UC trial-like cohort with data from the tofacitinib UC clinical trial program, it should be acknowledged that the tofacitinib UC clinical trial program was a multinational trial, and there may be variations in the background regional incidence and fidelity of case ascertainment for certain conditions (eg, NMSC, outpatient DVT). Finally, these analyses were descriptive, and no hypothesis testing or multivariable modeling was performed. Accordingly,

further studies are required to test hypotheses generated by these analyses.

A limitation of the venous thromboembolic event data is that outpatient DVT events in a clinical trial program are probably underascertained, and this can potentially lead to an underestimation of the DVT rate in comparison to MarketScan®, a population-based cohort, or most other data sources where outpatient events are probably more completely captured. This will make DVT rates lower than in MarketScan®.

In conclusion, despite the aforementioned limitations, the characterization of safety in the IBM MarketScan® claims database demonstrated that observed incidence rates for safety events of interest in the observational cohorts varied depending on the specific definition used to identify them. Follow-up time also had an effect on observed incidence rates, with higher rates observed for safety events of interest when limiting follow-up time to 12 months (ie, to mimic follow-up time typical in the UC maintenance clinical trials). These population-based data were used as the basis for safety characterization and comparison of current and investigational therapeutic agents for the treatment of moderate to severe UC. Rates of HZ observed among TNFi-treated patients in the population-based cohort of patients with UC were lower than in the tofacitinib UC clinical trial cohort; rates of serious infections, OIs (excluding HZ), NMSC, and DVT were numerically higher in the population-based cohort. Rates of malignancies (excluding NMSC), MACE, PE, and GI perforations were numerically similar among TNFi-treated patients in the population-based cohort and the tofacitinib UC clinical trial cohort.

SUPPLEMENTARY DATA

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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DATA SHARING STATEMENT

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (i) for indications that have been approved in the US and/or EU or (ii) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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