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ORIGINAL RESEARCH

Herpes Zoster, Hepatitis C, and Tuberculosis Risk with Apremilast Compared to Biologics, DMARDs and Corticosteroids to Treat Psoriasis and Psoriatic Arthritis

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Purpose: Psoriasis and psoriatic arthritis (PsA) are associated with an increased infection risk. In this cohort study of patients with treated psoriasis or PsA, we used MarketScan (2014–2018) to estimate rates of herpes zoster, hepatitis C (HepC) and tuberculosis (TB) with apremilast compared to other systemic treatments.

Materials and Methods: Patients were exposed from first apremilast [APR], DMARD, TNF-inhibitor [TNF], IL-inhibitor [IL], or corticosteroids [CS] prescription after March 21, 2014. Study exposures were APR, DMARDs only, TNF-only, IL-only, CS-only, DMARDs +CS, TNF+DMARDs and/or CS, IL+DMARDs and/or CS. Cases had treated herpes zoster, HepC, or TB event. We calculated incidence rates (IRs) [95% confidence intervals] per 1000 patient-years.

Results: The study population included 131,604 patients. For herpes zoster (N=2271), IRs were highest for users of DMARDs+CS (12.5 [9.8–15.7]), CS-only (12.5 [10.4–14.1]), and TNF+DMARDs and/or CS (11.9 [10.6–13.4]), compared with DMARDs only (9.9 [8.7–11.2]). IRs were lowest for users of IL-only (6.7 [5.8–7.8]) and APR (7.0 [5.8–8.4]). IRs of HepC (N=150) and TB (N=81) were low and between-treatment differences were not significant.

Conclusion: Rates of herpes zoster varied by treatment: highest among those who received polytherapy, lowest in users of apremilast only. IRs for HepC and TB were low for all exposures.

Keywords: apremilast, psoriasis, psoriatic arthritis, herpes zoster, hepatitis C, tuberculosis

Introduction

Apremilast is a drug marketed in the United States as of March 2014 for the treatment of psoriasis and psoriatic arthritis (PsA). It is an oral medication that inhibits phosphodiesterase-4, a protein found in immune cells associated with inflammation. In randomized clinical trials of apremilast for the treatment of psoriasis or PsA, serious infections were rare and comparable across the various exposure groups.[1–6] No cases of active tuberculosis, herpes zoster, or reactivation of hepatitis C were reported in trials for apremilast, although active tuberculosis, history of tuberculosis, and/or positive hepatitis C antibodies at screening were the reason for exclusion from some of the studies.[1–6] While the safety profile for apremilast in the clinical trials is reassuring, drugs used to treat autoimmune

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disorders have been shown to increase the risk of serious infection, though there is no consensus on the magnitude of the risk.[7–26] Hepatitis C and tuberculosis are particularly rare and unlikely to occur in small selected clinical trial populations compared with larger epidemiological studies. Therefore, we conducted a post-marketing safety study to estimate rates of treated herpes zoster, hepatitis C, and tuberculosis in patients with psoriasis or PsA treated with apremilast compared with users of other systemic psoriasis and PsA treatments.

Methods

Study Population

We conducted a cohort study within the IBM MarketScan Commercial Claims and Encounters Database (CCE) with Medicare supplement, a large United States (US)-based claims database containing data on over 50 million patients from over 150 large employers distributed throughout the US that covers employees and their dependent family members. It has been reported that the age, sex, and geographic distribution of patients who participated in an employer-sponsored private insurance survey are similar to the US population.[27] The database contains basic demographics and information on pharmaceuticals (using National Drug Codes), diagnoses (using International Classification of Diseases (ICD)-9 and 10-CM), and procedures (using Current Procedural Terminology, Fourth Edition and the Healthcare Common Procedure Coding System).

The study population included all patients with a diagnosis of psoriasis and/or PsA who received ≥1 prescription for apremilast, a disease-modifying antirheumatic drug (DMARD), a tumor necrosis factor inhibitor (TNF-i) biologic, an interleukin-17 or −12/23 inhibitor (IL-i) biologic, or systemic corticosteroids between March 21, 2014 (when apremilast was marketed) and October 31, 2018 (end of study) (see Supplemental Table 1for a list of all study drugs). Because systemic corticosteroids are not indicated for treatment of psoriasis, patients with psoriasis only (ie, no PsA at any time) whose only study drug was a corticosteroid were not included in the study population. For patients with PsA, we required a PsA diagnosis on the same day as a corticosteroid injection or within 15 days before filling a prescription for oral corticosteroids because corticosteroids have multiple indications for use. Patients diagnosed with rheumatoid arthritis before psoriasis or PsA were excluded from the study population. Patients entered the study at the time of their first study drug prescription after March 21, 2014 (cohort entry date) and were followed through the censor date, defined as record end, date the patient became a case, or October 31, 2018 (end of the study period), whichever came first.

Exposure Definition

The study exposures of interest were apremilast, TNF-i biologics, IL-i biologics, conventional DMARDs, and systemic corticosteroids. Current use of each study drug was calculated using the length of each prescription claim plus 30 days. For those who received the drug by injection or infusion, current use was defined as 60 days (or 120 days for ustekinumab). If a new prescription for the same drug was received before the end of the previous prescription duration, the number of days was truncated and days were accumulated from the date of the new prescription. A patient was considered exposed to multiple study drugs if the duration of different study drug prescriptions overlapped, except for TNF-i and IL-i biologics which were not allowed to overlap. We assigned exposure for each day of follow-up to one of the following mutually exclusive categories: apremilast only, apremilast with other study drugs, TNF-i biologics only, IL-i biologics only, DMARDs only, corticosteroids only, DMARDs + corticosteroids, TNF-i biologics with DMARDs and/or corticosteroids, IL-i biologics with DMARDs and/or corticosteroids, or unexposed (defined as any days after "current use" and before a new study drug prescription).

Case Definition

Cases were treated herpes zoster, treated hepatitis C, or treated tuberculosis, and included both newly diagnosed and reactivated infections. A patient was required to have both a diagnosis and treatment for the study infection within 15 days of each other to be a case, and the infection diagnosis and treatment had to first occur at least 7 days after cohort entry. We further required at least 60 days of treatment for cases of hepatitis C and tuberculosis. See Supplemental Table 2 for treatments for herpes zoster, hepatitis C, and tuberculosis included in the study. Patients with active, treated infections at cohort entry (prevalent cases) were not considered as cases; however, they did remain in the study population and were followed forward from their initial diagnosis date to determine if they later qualified to be a reactivated case. To be considered a case of reactivated infection, a 6-month treatment-free period after the initial infection was required before the next episode of

treated infection. Cases were censored at the first qualifying diagnosis code or treatment for that outcome, whichever came first. The electronic records of all hepatitis C cases, all tuberculosis cases, and a sample of herpes zoster cases were reviewed manually to confirm case status and index dates.

Covariates

We described the study population according to their exposure at cohort entry with respect to the presence of chronic infection risk factors (Table 1). We also described the presence of acute infection risk factors within the 60 days before the index date, including other immunosuppressant drugs (azathioprine, chloroquine, cyclophosphamide, hydroxychloroquine, leflunomide, minocycline, and sulfasalazine), fractures, major or minor surgical procedures, ventilator use, urinary catheter use, pressure ulcers, and diagnosis or treatment for malignant neoplasm. Duration of psoriasis or PsA was calculated using the date of the first diagnosis code in the patient record, categorized as <1 year, 1–2.9, 3–4.9, ≥5 years, and unknown (where the first psoriasis or PsA diagnosis was recorded less than 6 months after enrollment in MarketScan).

Statistical Analyses

We calculated incidence rates (IRs) with 95% confidence intervals (CIs) of treated herpes zoster, treated hepatitis C, and treated tuberculosis separately for each exposure. For herpes zoster, we calculated incidence rate ratios (IRRs) with 95% CIs and adjusted IRRs controlling for age, sex, calendar year and presence of rheumatoid arthritis for each exposure category compared to DMARDs only using Poisson regression, as well as stratified by indication for use (ie, PsA or psoriasis). There were too few exposed cases of hepatitis C and tuberculosis to calculate crude or adjusted IRRs. Studies using MarketScan are exempt from IRB review because the data is compliant with the Health Insurance Portability and Accountability Act (HIPAA) to protect patient privacy.

Results

The study population encompassed 131,604 patients with psoriasis or PsA (Table 1). At cohort entry, 10,074 (7.7%) patients were exposed to apremilast (alone or in combination with other study drugs), while 47,361 (36.0%) were exposed to TNF-i biologics only, 24,678 (18.8%) were exposed to DMARDs only, 12,438 (9.5%) were exposed to IL-i biologics only, 20,692 (15.7%) were exposed to CS only, and 16,361 (12.4%) were exposed to multiple study drugs (DMARDs+CS, or TNF-i with DMARDs and/or CS, or IL-i with DMARDs and/or CS). Half of the population (53.3%) were between 40 and 59 years old at cohort entry, and half (50.5%) were female. At cohort entry, proportionally more apremilast users had an indication of psoriasis rather than PsA compared to users of the other study drugs.

We identified 2271 new or reactivated cases of treated herpes zoster (Table 2), yielding an IR in the entire study population and regardless of treatment of 8.9 (95% CI 8.5–9.3) per 1000 person-years (PY) (Table 3). IRs of treated herpes zoster were highest for current users of DMARDs+CS (12.5, 95% CI 9.8–15.7), CS only (12.5, 95% CI 10.4–14.1), TNF-i biologics with DMARDs and/or CS (11.9, 95% CI 10.6–13.4), and IL-i biologics with DMARDs and/or CS (10.3, 95% CI 7.6–13.7) (Table 3). IRs of treated herpes zoster were lowest for current users of IL-i biologics only (6.7, 95% CI 5.8–7.8) and apremilast alone or in combination (7.0, 95% CI 5.8–8.4). The crude and adjusted IRRs, with DMARDs only as the referent, were around 1.2 for current users of TNF-i biologics with DMARDs and/or CS, CS only, and DMARDs+CS, while the IRRs were close to or below 1.0 for all other exposure categories (Table 3). Compared to DMARDs only, the adjusted IRR for current use of apremilast only was 0.70 (95% CI 0.54–0.90) and 0.89 (95% CI 0.63–1.25) for current use of apremilast in combination with other study exposures. The results were similar when stratified by indication for use (ie, PsA or psoriasis) (Table 3).

We identified 150 new or reactivated cases of treated hepatitis C (Table 2), resulting in an IR for the entire study population, regardless of treatment, of 0.6 (95% CI 0.5–0.7) per 1000 PY (Table 4). IRs of treated hepatitis C were low for all exposure categories and there were only 12 cases with current exposure to apremilast. Finally, we identified 81 new or reactivated cases of treated tuberculosis (Table 2), yielding an IR in the entire study population, regardless of treatment, of 0.3 (95% CI 0.2–0.4) per 1000 person-years (PY) (Table 5). IRs of tuberculosis were low and there were only four cases were exposed to apremilast. The IRs were similar and not statistically different for all exposures. The crude IRRs were all below 1.0 (Table 5). There were too few exposed cases of hepatitis C and tuberculosis, especially in the reference group, to calculate stable IRRs and all estimates were based on small numbers.

Table 1 Characteristics of Study Population at Cohort Entry Date by Exposure

	Total, N=131,604 (%)	Exposure on Cohort Entry Date								
		DMARDs Only, N=24,678 (%)	Apremilast Only, N=9422 (%)	Apremilast + Other, N=652 (%)	TNF-I Biologics Only, N=47,361 (%)	IL-i Biologics Only, N=12,438 (%)	CS Only, N=20,692 (%)	DMARDs + CS, N=6318 (%)	TNF-i with DMARDs and/or CS, N=9029 (%)	IL-i with DMARDs and/or CS, N=1014 (%)
Age at cohort entry										
Less than 40 years	32,024 (24.3)	5305 (21.5)	2286 (24.3)	112 (17.2)	13,067 (27.6)	3928 (31.6)	4336 (21.0)	1107 (17.5)	1694 (18.8)	189 (18.6)
40–49 years	30,748 (23.4)	5142 (20.8)	2103 (22.3)	155 (23.8)	11,933 (25.2)	3194 (25.7)	4569 (22.1)	1345 (21.3)	2051 (22.7)	256 (25.3)
50–59 years	39,376 (29.9)	7484 (30.3)	2896 (30.7)	208 (31.9)	13,601 (28.7)	3381 (27.2)	6410 (31.0)	2034 (32.2)	2995 (33.2)	367 (36.2)
60–69 years	23,308 (17.7)	5115 (20.7)	1712 (18.2)	134 (20.6)	7334 (15.5)	1644 (13.2)	3989 (19.3)	1317 (20.9)	1896 (21.0)	167 (16.5)
≥70 years	6148 (4.7)	1632 (6.6)	425 (4.5)	43 (6.6)	1426 (3.0)	291 (2.3)	1388 (6.7)	515 (8.2)	393 (4.4)	35 (3.5)
Median (years)	50	52	51	53	48	47	52	53	52	51
Sex										
Female	66,474 (50.5)	13,422 (54.4)	4941 (52.4)	400 (61.4)	20,874 (44.1)	5667 (45.6)	11,790 (57.0)	3828 (60.6)	5018 (55.6)	534 (52.7)
Male	65,130 (49.5)	11,256 (45.6)	4481 (47.6)	252 (38.7)	26,487 (55.9)	6771 (54.4)	8902 (43.0)	2490 (39.4)	4011 (44.4)	480 (47.3)
Indication for use										
PsA (with or without psoriasis)	56,549 (43.0)	10,471 (42.4)	1997 (21.2)	197 (30.2)	19,364 (40.9)	2159 (17.4)	12,894 (62.3)	2977 (47.1)	6132 (67.9)	359 (35.4)
Psoriasis only	75,055 (57.0)	14,207 (57.6)	7425 (78.8)	455 (69.8)	27,998 (59.1)	10,279 (82.6)	7798 (37.7)	3341 (52.9)	2897 (32.1)	655 (65.6)
Duration of psoriasis/PsA before cohort entry										
<1 year	33,027 (25.1)	7870 (31.9)	2672 (28.4)	226 (34.7)	7904 (16.7)	1361 (10.9)	8312 (40.2)	2920 (46.2)	1607 (17.8)	155 (15.3)
1–<3 years	16,723 (12.7)	3131 (12.7)	1203 (12.8)	78 (12.0)	6146 (13.0)	1295 (10.4)	2545 (12.3)	820 (13.0)	1376 (15.2)	129 (0.8)
3–<5 years	3433 (2.6)	618 (2.5)	691 (7.3)	35 (5.4)	738 (1.6)	240 (1.9)	819 (4.0)	202 (3.2)	76 (0.8)	14 (0.4)
≥5 years	2634 (2.0)	413 (1.7)	693 (7.4)	33 (5.1)	500 (1.1)	302 (2.4)	515 (2.5)	119 (1.9)	48 (0.5)	11 (0.4)
Unknown	75,787 (57.6)	12,646 (51.2)	4163 (44.2)	280 (42.9)	32,073 (67.7)	9240 (74.3)	8501 (41.1)	2257 (35.7)	5922 (65.6)	705 (69.5)
Median (years) (excluding unknown)	0.6	0.3	1.0	0.4	0.9	1.4	0.1	0.1	0.9	1.0
Chronic infection risk Factors before cohort entry										
Diabetes	19,824 (15.1)	3818 (15.5)	1454 (15.4)	137 (21.0)	6217 (13.1)	1654 (13.3)	3581 (17.3)	1123 (17.8)	1641 (18.2)	199 (19.6)
Chronic obstructive pulmonary disease and other lung diseases*	15,686 (11.9)	2966 (12.0)	1148 (12.2)	124 (19.0)	4011 (8.5)	990 (8.0)	3698 (17.9)	1232 (19.5)	1359 (15.1)	158 (15.6)

Heart failure	2771 (2.1)	565 (2.3)	247 (2.6)	22 (3.4)	604 (1.3)	193 (1.6)	657 (3.2)	234 (3.7)	224 (2.5)	25 (2.5)
Angina	2303 (1.8)	414 (1.7)	179 (1.9)	24 (3.7)	565 (1.2)	154 (1.2)	574 (2.8)	171 (2.7)	206 (2.3)	16 (1.6)
Gastrointestinal ulcer	1539 (1.2)	267 (1.1)	99 (1.1)	10 (1.5)	420 (0.9)	101 (0.8)	353 (1.7)	125 (2.0)	155 (1.7)	9 (0.9)
Dementia	224 (0.2)	54 (0.2)	19 (0.2)	0 (0.0)	48 (0.1)	15 (0.1)	59 (0.3)	16 (0.3)	12 (0.1)	1 (0.1)
Crohn's disease	3555 (2.7)	206 (0.8)	40 (0.4)	8 (1.2)	2046 (4.3)	114 (0.9)	249 (1.2)	95 (1.5)	779 (8.6)	18 (1.8)
Ulcerative colitis	2388 (1.8)	173 (0.7)	61 (0.7)	9 (1.4)	1155 (2.4)	79 (0.6)	296 (1.4)	86 (1.4)	522 (5.8)	7 (0.7)
Diffuse diseases of connective tissue*	4028 (3.1)	938 (3.8)	191 (2.0)	23 (3.5)	792 (1.7)	90 (0.7)	1020 (4.9)	556 (8.8)	388 (4.3)	30 (3.0)
Multiple sclerosis	458 (0.4)	119 (0.5)	46 (0.5)	2 (0.3)	56 (0.1)	42 (0.3)	119 (0.6)	45 (0.7)	23 (0.3)	6 (0.6)
Rheumatoid arthritis	12,532 (9.5)	2384 (9.7)	289 (3.1)	33 (5.1)	3994 (8.4)	268 (2.2)	2079 (10.1)	1017 (16.1)	2370 (26.3)	98 (9.7)
Peripheral vascular disease	2667 (2.0)	525 (2.1)	237 (2.5)	24 (3.7)	607 (1.2)	143 (1.2)	672 (3.3)	238 (3.8)	206 (2.3)	15 (1.5)

Notes: *Chronic obstructive pulmonary disease and other lung diseases included asthma, bronchitis, emphysema, bronchiectasis and pneumoconiosis. Diffuse diseases of connective tissue included systemic lupus erythematosus, dermatopolymyositis, systemic sclerosis and other systemic disorders of connective tissue.

Discussion

In this large study of patients with psoriasis and PsA, there was no suggestion that patients treated with apremilast were at higher risk of new or recurrent infections of treated herpes zoster, hepatitis C, or tuberculosis compared to patients with psoriasis or PsA treated with DMARDs only. The IRs and IRRs of herpes zoster among apremilast users were slightly lower compared with those of users of other treatments for psoriasis or PsA evaluated in this study, whereas the IRs of hepatitis C and tuberculosis were similar to those of patients treated with DMARDs and/or biologics. The results of this study provide reassurance that apremilast is not likely to be associated with a high risk of herpes zoster, hepatitis C, or tuberculosis in patients with psoriasis or PsA.

The incidence of herpes zoster for users of DMARDs and biologics in our study was similar to those reported in several other studies and systematic reviews.[8–17] This provides confidence in the quality of the data and the ability to detect associations between these exposures and outcomes. This further provides reassurance that the incidence of herpes zoster among patients exposed to apremilast, which was slightly lower than users of DMARDS only, is not elevated compared with users of other psoriasis and PsA treatments.

The available literature describing hepatitis C among patients treated for rheumatoid arthritis, psoriasis or PsA is limited and consists primarily of case reports of hepatitis C reactivation or liver function changes among these patients.[7,19–22,28] There was one retrospective cohort study that found that biologic treatment in patients with psoriasis increased the risk of reactivation of hepatitis C infection; however, there was no data on apremilast users in particular.[23] Overall, we identified 150 cases of treated hepatitis C in our entire cohort, only 12 of which were exposed to apremilast (alone or in combination with other study drugs), indicating that hepatitis C is rare in patients with psoriasis or PsA and does not occur more often in apremilast users compared with users of other treatments.

Few studies have been conducted since the implementation of tuberculosis screening to assess the incidence of tuberculosis among patients with rheumatoid arthritis, psoriasis or PsA.[24–26,29] We found a few cases of patients with treated tuberculosis in our cohort, four of whom were exposed to apremilast. The IRs for treated tuberculosis among users of DMARDs and

Table 2 Characteristics of Cases at the Index Date

Characteristic	Herpes Zoster Cases, N=2271 (%)	Hepatitis C Cases, N=150 (%)	Tuberculosis Cases, N=81 (%)
Age at index date			
Less than 40 years	283 (12.5)	7 (4.7)	16 (19.8)
40–49 years	421 (18.5)	13 (8.7)	18 (22.2)
50–59 years	785 (34.6)	63 (42.0)	22 (27.2)
60–69 years	580 (25.5)	62 (41.3)	15 (18.5)
≥70 years	202 (8.9)	5 (3.3)	10 (12.4)
Median (years)	56	58	53
Sex			
Female	1386 (61.0)	43 (28.7)	39 (48.2)
Male	885 (39.0)	107 (71.3)	42 (51.9)
Index year			
2014	357 (15.7)	35 (23.3)	14 (17.3)
2015	472 (20.8)	52 (34.7)	21 (25.9)
2016	535 (23.6)	34 (22.7)	19 (23.5)
2017	528 (23.2)	20 (13.3)	19 (23.5)
2018	379 (16.7)	9 (6.0)	8 (9.9)
Indication at index date			
PsA (with or without psoriasis)	1268 (55.8)	73 (48.7)	43 (53.1)
Psoriasis	1003 (44.2)	77 (51.3)	38 (46.9)
Psoriasis/PsA disease duration before index date			
<1 year	148 (6.5)	11 (7.3)	9 (11.1)
1–<3 years	336 (14.8)	12 (8.0)	6 (7.4)
3–<5 years	266 (11.7)	12 (8.0)	6 (7.4)
≥5 years	423 (18.6)	18 (12.0)	15 (18.5)
Unknown	1098 (48.4)	97 (64.7)	45 (55.6)
Median (years), excluding unknown	3.1	2.6	7.3
Infection risk factors before index date			
Diabetes	532 (23.4)	30 (20.0)	22 (27.2)
Chronic obstructive pulmonary disease and other lung diseases*	522 (23.0)	25 (16.7)	17 (21.0)
Heart failure	116 (5.1)	9 (6.0)	5 (6.2)
Angina	82 (3.6)	5 (3.3)	0 (0.0)
Gastrointestinal ulcer	59 (2.6)	4 (2.7)	2 (2.5)
Dementia	5 (0.2)	0 (0.0)	0 (0.0)
Crohn's disease	127 (5.6)	8 (5.3)	8 (9.9)
Ulcerative colitis	96 (4.2)	4 (2.7)	3 (3.7)
Diffuse diseases of connective tissue*	157 (6.9)	5 (3.3)	1 (1.2)
Multiple sclerosis	19 (0.8)	0 (0.0)	0 (0.0)
Rheumatoid arthritis	484 (21.3)	16 (10.7)	15 (18.5)
Peripheral vascular disease	108 (4.8)	2 (1.3)	2 (2.5)
Infection risk factors within 60 days before index date			
Other immunosuppressant use	127 (5.6)	3 (2.0)	3 (3.7)
Any fracture	21 (0.9)	2 (1.3)	2 (2.5)
Surgical procedures (major or minor) **	526 (23.2)	51 (34.0)	32 (29.5)
Ventilator use	0 (0.0)	0 (0.0)	0 (0.0)
Urinary catheter use	0 (0.0)	0 (0.0)	0 (0.0)
Pressure ulcer	4 (0.2)	1 (0.7)	0 (0.0)
Diagnosis or treatment for malignant neoplasm	75 (3.3)	7 (4.7)	0 (0.0)

Notes: *Chronic obstructive pulmonary disease and other lung diseases included asthma, bronchitis, emphysema, bronchiectasis and pneumoconiosis. Diffuse diseases of connective tissue included systemic lupus erythematosus, dermatopolymyositis, systemic sclerosis and other systemic disorders of connective tissue. **Includes all major and minor surgical procedures CPT codes 100021–69990, excluding venous and capillary blood specimen collection CPT codes 36415 and 36416.

biologics in our study fall within the range previously reported.[23–26] Our results provide reassurance that apremilast is not likely to be associated with a high risk of reactivation of latent tuberculosis in patients with psoriasis or PsA.

Our study evaluated a large cohort of more than 10,000 apremilast exposed patients with psoriasis and PsA. We required all cases of herpes zoster, hepatitis C, and tuberculosis to have received treatment for the infection to minimize case misclassification. We were also able to classify all study exposures according to whether or not they were prescribed in combination with other treatments. There were small numbers of cases in some exposure categories, particularly for hepatitis C and tuberculosis, resulting in wide confidence intervals. While due to small numbers we were unable to include all infection risk factors in our adjusted models, there were enough cases of herpes zoster to evaluate the impact of important covariates (sex, age, calendar year, and rheumatoid arthritis) on the association of treatment and infection. Due to the nature of ICD coding in claims data, differentiating between screening, infection, and routine follow-up visits for patients with a history of hepatitis C or tuberculosis is challenging. To minimize case misclassification, we reviewed the records of every case and required each to have received at least 60 days of treatment; however, it remains possible that some of these infection

Table 3 Incidence Rates (IR) and Incidence Rate Ratios (IRR) for Treated Herpes Zoster by Exposure in Patients with Psoriasis or PsA

Exposure at Index Date	Cases	Person-Years	IR per 1000 PY (95% CI)	Crude IRR (95% CI)	Adjusted IRR (95% CI) *
All Patients	**N=2271**	**Total=255,451**	**8.9 (8.5–9.3)**	–	–
DMARDs only	256	25,865	9.9 (8.7–11.2)	Reference	Reference
Apremilast	120	17,180	7.0 (5.8–8.4)	0.71 (0.57–0.88)	0.75 (0.60–0.94)
Apremilast only	82	12,842	6.4 (5.1–7.9)	0.65 (0.50–0.83)	0.70 (0.54–0.90)
Apremilast + other	38	4338	8.8 (6.2–12.0)	0.89 (0.63–1.24)	0.89 (0.63–1.25)
TNF-i biologics only	712	75,547	9.4 (8.7–10.1)	0.95 (0.83–1.10)	1.11 (0.96–1.28)
IL-i biologics only	173	25,654	6.7 (5.8–7.8)	0.68 (0.56–0.83)	0.82 (0.68–1.00)
CS only	169	13,943	12.5 (10.4–14.1)	1.22 (1.01–1.49)	1.22 (1.01–1.49)
DMARDs + CS	75	5990	12.5 (9.8–15.7)	1.27 (0.98–1.64)	1.19 (0.92–1.54)
TNF-i with DMARDs and/or CS	284	23,806	11.9 (10.6–13.4)	1.21 (1.02–1.43)	1.23 (1.04–1.46)
IL-i with DMARDs and/or CS	49	4742	10.3 (7.6–13.7)	1.04 (0.77–1.42)	1.12 (0.82–1.52)
Unexposed	433	62,723	6.9 (6.3–7.6)	0.70 (0.60–0.81)	0.77 (0.66–0.90)
All patients with PsA	**N=1268**	**Total=132,721**	**9.6 (9.0–10.1)**	–	–
DMARDs only	141	14,154	10.0 (8.4–11.7)	Reference	Reference
Apremilast	67	7,367	9.1 (7.0–11.5)	0.91 (0.68–1.22)	0.95 (0.71–1.28)
Apremilast only	37	4515	8.2 (5.8–11.3)	0.82 (0.57–1.18)	0.87 (0.61–1.25)
Apremilast + other	30	2852	10.5 (7.1–15.0)	1.06 (0.71–1.20)	1.08 (0.73–1.60)
TNF-i biologics only	392	39,734	9.9 (8.9–10.9)	0.99 (0.82–1.20)	1.13 (0.93–1.38)
IL-i biologics only	59	8068	7.3 (5.6–9.4)	0.73 (0.54–0.99)	0.86 (0.63–1.16)
CS only	102	8349	12.2 (10.0–14.8)	1.23 (0.95–1.58)	1.22 (0.94–1.57)
DMARDs + CS	44	3668	12.0 (8.7–16.1)	1.20 (0.86–1.69)	1.15 (0.82–1.62)
TNF-i with DMARDs and/or CS	220	18,477	11.9 (10.4–13.6)	1.20 (0.97–1.48)	1.24 (1.00–1.53)
IL-i with DMARDs and/or CS	32	2793	11.5 (7.8–16.2)	1.15 (0.78–1.69)	1.23 (0.84–1.82)
Unexposed	211	30,111	7.0 (6.1–8.0)	0.70 (0.57–0.87)	0.75 (0.60–0.93)
All patients with psoriasis only	**N=1003**	**Total=122,730**	**8.2 (7.7–8.7)**	–	–
DMARDs only	115	11,711	9.8 (8.1–11.8)	Reference	Reference
Apremilast	53	9813	5.4 (4.0–7.1)	0.55 (0.40–0.76)	0.59 (0.42–0.82)
Apremilast only	45	8327	5.4 (3.9–7.2)	0.55 (0.40–0.78)	0.59 (0.42–0.84)
Apremilast + other	8	1486	5.4 (2.3–10.6)	0.55 (0.27–1.12)	0.56 (0.27–1.15)
TNF-i biologics only	320	35,813	8.9 (8.0–10.0)	0.91 (0.74–1.13)	1.09 (0.88–1.36)
IL-i biologics only	114	17,587	6.5 (5.3–7.8)	0.66 (0.51–0.86)	0.80 (0.61–1.68)
CS only	67	5594	12.0 (9.3–15.2)	1.22 (0.90–1.65)	1.24 (0.84–1.85)
DMARDs + CS	31	2322	13.4 (9.1–19.0)	1.36 (0.91–2.02)	1.24 (0.84–1.85)
TNF-i with DMARDs and/or CS	64	5330	12.0 (9.2–15.3)	1.22 (0.90–1.66)	1.30 (0.96–1.77)
IL-i with DMARDs and/or CS	17	1950	8.7 (5.1–14.0)	0.89 (0.53–1.48)	0.97 (0.58–1.61)
Unexposed	222	32,612	6.8 (5.9–7.8)	0.69 (0.55–0.87)	0.78 (0.62–0.98)

Note: *Adjusted for sex, age, calendar year, and rheumatoid arthritis.

Abbreviations: CI, confidence interval; CS, corticosteroids; DMARDs, disease-modifying antirheumatic drugs; IL-I, interleukin-17, −23 or −12/23 inhibitor biologics; IR, incidence rate; IRR, incidence rate ratio; PY, person-years; TNF-I, tumor necrosis factor inhibitor biologics.

cases may have received chemoprophylaxis and the event was not a true latent infection reactivation. Because the total number of hepatitis C (N=150) and tuberculosis (N=83) cases identified in this study were small, we only presented rates of these infections and did not calculate IRRs between exposure categories; thus, the presented results are not biased by differential case misclassification. Finally, at cohort entry proportionally more users of apremilast had an indication of psoriasis compared with the other study exposures, and due to small numbers, we were unable to adjust our estimates by indication for use. Thus, disease severity should be taken into consideration and the results of this study should be interpreted with caution.

Conclusion

These data suggest that rates of hepatitis C and tuberculosis were low among commercially insured US patients for all types of psoriasis and PsA treatment. Rates of herpes zoster varied by treatment and were lowest in users of apremilast only. The results of this study provide

Table 4 Incidence Rates (IR) for Treated Hepatitis C by Exposure in Patients with Psoriasis or PsA

Exposure at Index Date	Cases	Person-Years	IR per 1000 PY (95% CI)
All Patients	**N=150**	**Total=255,451**	**0.6 (0.5–0.7)**
DMARDs only	13	25,865	0.5 (0.3–0.9)
Apremilast	12	17,180	0.7 (0.4–1.2)
Apremilast only	8	12,842	0.6 (0.3–1.2)
Apremilast + other	4	4338	0.9 (0.2–2.4)
TNF-i biologics only	44	75,547	0.6 (0.4–0.8)
IL-i biologics only	14	25,654	0.5 (0.3–0.9)
CS only	17	13,943	1.2 (0.7–2.0)
DMARDs + CS	0	5990	0.0 (0.0–0.6)
TNF-i with DMARDs and/or CS	14	23,806	0.6 (0.3–1.0)
IL-i with DMARDs and/or CS	2	4742	0.4 (0.0–1.5)
Unexposed	34	62,723	0.5 (0.4–0.8)

Note: Number of cases were too small to calculate stable IRR estimates.
Abbreviations: CI, confidence interval; CS, corticosteroids; DMARDs, disease-modifying antirheumatic drugs; IL-i, interleukin-17, −23 or −12/23 inhibitor biologics; IR, incidence rate; PY, person-years; TNF-i, tumor necrosis factor inhibitor biologics.

Table 5 Incidence Rates (IR) for Treated Tuberculosis by Exposure in Patients with Psoriasis or PsA

Exposure at Index Date	Cases	Person-Years	IR per 1000 PY (95% CI)
All Patients	**N=81**	**Total=255,451**	**0.3 (0.2–0.4)**
DMARDs only	3	25,865	0.1 (0.0–0.3)
Apremilast	4	17,180	0.2 (0.1–0.6)
Apremilast only	2	12,842	0.2 (0.0–0.6)
Apremilast + other	2	4338	0.5 (0.1–1.7)
TNF-i biologics only	27	75,547	0.4 (0.2–0.5)
IL-i biologics only	6	25,654	0.2 (0.1–0.5)
CS only	7	13,943	0.5 (0.2–1.0)
DMARDs + CS	5	5990	0.8 (0.3–1.9)
TNF-i with DMARDs and/or CS	8	23,806	0.3 (0.1–0.7)
IL-i with DMARDs and/or CS	1	4742	0.2 (0.0–1.2)
Unexposed	20	62,723	0.3 (0.2–0.5)

Note: Number of cases were too small to calculate stable IRR estimates.
Abbreviations: CI, confidence interval; CS, corticosteroids; DMARDs, disease-modifying antirheumatic drugs; IL-i, interleukin-17, −23 or −12/23 inhibitor biologics; IR, incidence rate; PY, person-years; TNF-i, tumor necrosis factor inhibitor biologics.

reassurance that apremilast is not likely to be associated with a high risk of reactivation of herpes zoster, hepatitis C, or latent tuberculosis in patients with psoriasis or PsA. However, the outcomes evaluated in this study are relatively rare events and some exposure groups had limited numbers of cases; thus, these results should be interpreted with caution.

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