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Real-World Comparative Risks of Herpes Virus Infections in Tofacitinib and Biologic-Treated Rheumatoid Arthritis Patients

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Abstract

Objective—To evaluate the risks of herpes zoster (HZ) and herpes simplex virus infection (HSV) associated with tofacitinib compared to biologic agents among patients with rheumatoid arthritis (RA).

Methods—Using health plan data from 2010–2014, RA patients initiating tofacitinib or biologics with no history of HZ or HSV were identified. Incident cases of HZ or HSV within this cohort were identified. Crude incidence rates were calculated by drug exposure. Cox proportional hazards models evaluated the adjusted association between tofacitinib and HZ, and a composite outcome of HZ or HSV.

Results—A total of 2,526 patients initiating tofacitinib were compared with initiations of other biologics: anti-TNF (n=42,850), abatacept (n=12,305), rituximab (n=5,078), and tocilizumab (n=6,967). Tofacitinib patients were somewhat younger (mean age 55 years) versus those on other biologics, and somewhat less likely to use concomitant MTX (39% vs. 43–56%, depending on drug).

Crude incidence of HZ associated with tofacitinib was 3.87/100py. After multivariable adjustment, HZ risk was significantly elevated, hazard ratio [HR] 2.01 (95%CI 1.40–2.88) compared to

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abatacept. Rates and adjusted HRs for all other RA biologics were comparable to each other and abatacept. Older age, female sex, prednisone >7.5mg/day, prior outpatient infection, and greater number of hospitalizations were also associated with increased HZ risk Incidence rates for the combined outcome were greatest for tofacitinib (7.61/100py) and significantly elevated after adjustment (HR=1.40, 95%CI 1.09–1.81).

Conclusion—The rate of zoster associated with tofacitinib was approximately double that observed in patients using biologics.

Keywords

Herpes zoster; herpes simplex; tofacitinib; rheumatoid arthritis; biologics; vaccination

Introduction

Tofacitinib is a novel small molecule approved in the U.S. in November, 2012, for the treatment of rheumatoid arthritis (RA). While not a biologic, it has multiple immunomodulatory effects, primarily through inhibition of JAK 1/3 kinases. In phase 1–3 trials [1, 2] the incidence of most adverse events is generally comparable to that of other biologics for RA.

However, clinical trials and long-term extension studies within the RA development program suggest that with tofacitinib, the incidence of herpes zoster (HZ) is elevated beyond that reported for biologics[3]. This is important because RA patients already have an elevated HZ risk compared to the general population [4]. HZ complications can cause significant morbidity, for example chronic, debilitating pain syndromes. Because almost all data for tofacitinib is based upon placebo-controlled trials, the real-world safety profile of tofacitinib and its comparability to biologics, especially as it relates to HZ or other types of viral infections such as herpes simplex virus (HSV), is unknown.

While varicella and HSV might largely be expected to be dormant except at the site of a local reactivation, both varicella and HSV 1 and 2 has been found in blood and synovial fluid from patients with RA [5]. Because tofacitinib's mechanism of action potentially mitigates interferon signaling and is important to host anti-viral responses, it is possible that HSV infections are also more common in this setting. We therefore examined the rates and comparative risks of HZ and a composite of HZ or HSV associated with tofacitinib compared to biologics used for RA.

Methods

Data Source & Cohort Eligibility

We used data from Medicare from (2006–2013) and Marketscan (2010–2014) for this analysis. Medicare covers approximately 93% of patients over age 65 in the U.S., and younger patients with certain disabling conditions (including RA) can qualify [6][7]. Marketscan is a longitudinal U.S. database of patient-level data for more than 143 million individuals and includes information regarding inpatient and outpatient encounters, lab and pharmaceutical use. Data are contributed by large employers, hospitals, and other healthcare

entities[8]. Patients eligible for this analysis were required to be age >= 18 years and to have 2 or more physician billing diagnoses for RA (ICD9 714.0, 714.2, 714.81), with at least one from a rheumatologist. The validity of this approach has been previously shown to be high, with positive predictive value > 85% when combined with DMARD or biologic use[9]. They also had to have at least 12 months of medical and pharmacy coverage prior to follow-up which began at first use of tofacitinib or RA biologics, as described below.

Using all available previous data (minimum of 12 months), and to increase certainty that all HZ cases were incident cases, patients were excluded if they had any prior diagnosis of ICD code 053.xx (herpes zoster), 054.xx (herpes simplex), any diagnostic code for mucocutaneous ulcers (ICD9 528.xx, Diseases of the oral soft tissues excluding lesions specific for gingiva and tongue), or any prior use of acyclovir, valacyclovir, or famciclovir. Because HZ rates vary across rheumatic diseases [Yun et. al., ACR 2014], patients were excluded if they had any diagnosis for ankylosing spondylitis, psoriasis, psoriatic arthritis, or inflammatory bowel disease. Given potential HZ risks with chemotherapy, patients were excluded if they had any cancer diagnosis, other than non-melanoma skin cancer.

Exposure

Our main exposures were tofacitinib and approved biologics for RA initiated on or after January 1st, 2010. This calendar time restriction was implemented to homogenize temporal trends that might affect treatment or vaccination patterns for RA or HZ. Patients were considered currently exposed based upon the quantity dispensed of each filled prescription or the typical RA infusion intervals (56 days for infliximab, 30 days for tocilizumab and abatacept, and 183 days for rituximab). Patients must have been new users, defined as no prior use of each specific drug using all prior data.

Outcome

The primary outcome of interest was first HZ event, as defined by either an inpatient or outpatient ICD9 physician diagnosis code 053.xx. The positive predictive value (PPV) of an HZ diagnosis code for identifying clinical shingles events has been shown in validation studies to be 85% or greater [10, 11]. A sensitivity analysis required both a HZ diagnosis code plus one of three anti-viral drugs (acyclovir, valacyclovir, or famciclovir) within 7 days of the diagnosis code. A secondary outcome was a composite of first event of either HZ or HSV, defined by a HZ diagnosis code (ICD9 053.XX), a herpes simplex diagnosis code (ICD9 054.XX), or use of any of the 3 anti-viral drugs listed above. Given these drugs are highly specific to HZ or HSV, it is very likely their new use (after at least 12 months of no use) signified treatment for acute HZ or HSV.

Statistical analysis

Descriptive statistics were used to characterize drug exposure cohorts and standardized mean differences (SMDs) estimated for each characteristic compared to the abatacept cohort. SMDs >0.10 were considered imbalanced. Follow-up began at the time of drug initiation of biologics or tofacitinib and ended at the first occurrence of the outcome of interest, loss of medical+pharmacy coverage, death, the end of the data, or end of drug exposure plus a 30 day extension [12]. First-time switches from tofacitinib to a RA biologic and vice-versa

were included in the analyses. Standard errors were adjusted to reflect the clustering of these treatment episodes within patients[13]. Potentially confounding or effect modifying covariates were selected based upon clinical interest and based upon prior zoster analyses [14] and included age, sex, and baseline factors: concomitant methotrexate use, glucocorticoid dose (none, or daily prednisone-equivalent dose above or below 7.5mg/day calculated using the baseline 6 months period), prior outpatient infection, any hospitalization, and zoster vaccination.

After evaluating proportional hazards assumption, we calculated the hazard rate (HR) of the outcomes Cox proportional hazards models, stratified by data source. Abatacept was made the referent category given its common use as a second or subsequent-line therapy in RA. All analyses were done in SAS 9.4. The university institutional review board approved the study protocol.

Results

Patient characteristics stratified by medication exposure are presented in Table 1; anti-TNF drugs were combined into a single group since patients were relatively homogeneous (not shown). Compared to other RA therapies and based on SMDs > 0.10, patients receiving tofacitinib were younger, had a slightly lower prevalence of some comorbidities, and used less methotrexate. Otherwise, characteristics were broadly similar.

The forest plot (Figure 1) describes crude rates and adjusted hazard ratios of HZ according to drug exposure. HZ rates ranged from a low of 1.95 (95% CI:1.65–2.31) per 100 patient years for adalimumab to a high of 3.87 (2.82–5.32) for tofacitinib. After multivariable adjustment for a variety of potentially confounding factors, the risk for HZ associated with tofacitinib was 2.01 (95% CI 1.40–2.88) compared to abatacept. No biologics were significantly different compared to this same referent, and all of them were numerically close to 1.00 (no excess risk versus abatacept). The reasons patients ended follow-up were shown in Supplemental Table 1. There were no major differences except that given the more recent approval date of tofacitinib compared to other therapies, patients were more likely to be censored because they reached the end of the study period.

Older age, female sex, prednisone > 7.5mg/day, prior outpatient infection, and greater number of hospitalizations were associated with increased HZ risk (Supplemental Table 2), whereas vaccination was associated with a lower risk (HR=0.66 95% CI 0.48–0.91). In the Medicare analysis where race information was available, Asian race was not significantly associated with the HZ outcome (HR 1.36, 95% CI 0.81–2.28), although risk was lower in African Americans (HR 0.69, 95% CI 0.53–0.92). However, race was not a significant confounder and had minimal effect on the main effect estimates so was not included in the final adjusted model. The sensitivity analysis that required anti-viral drug use in order to meet the HZ case definition resulted in approximately 20% lower crude rates of HZ for each exposure. For example, the incidence rate of HZ associated with tofacitinib was 3.25 (95% CI 2.30–4.59). As in the main multivariable analysis, only tofacitinib was associated with a significantly elevated HZ risk (HR = 1.98, 95% CI 1.34–2.94).

Rates of the composite outcome of HZ and HSV infections are shown in Table 2. Rates were highest for tofacitinib (7.61/100py), which was significantly higher than for other biologics, which were generally in the 5–6/100py range. After multivariable adjustment, the risk associated with tofacitnib was the only medication that was significantly elevated compared to abatacept (HR=1.40, 95% CI 1.09–1.81). There was no violation of the proportional hazards assumption in either of the two multivariable-adjusted results.

Discussion

In this analysis of real-world U.S. data, we found that the risk for HZ in tofacitinib treated RA patients was approximately double compared to RA patients using biologics. The association was significant even after controlling for potentially confounding factors including age, glucocorticoid use, and comorbidities. In comparison to our estimated HZ incidence (3.87/100py) that seen in the tofacitinib clinical trial program was 3.3/100py, 95% CI 2.4–4.5[3].

HZ is an emerging complication of JAK inhibition; incidence within the global tofacitnib development program are elevated several fold higher than that previously reported for biologics such as TNF inhibitors. Our analysis is the first real world evaluation of HZ risk involving tofacitinib and biologic therapies simultaneously, while controlling for other HZ risk factors. Our observations are consistent with the conclusions from the tofacitinib clinical trial experience and provide real-world comparative evidence.

How tofacinitib causes HZ is unclear. Cell mediated immunity is clearly important in controlling varicella virus, and patients with waning VZV-specific CD4 T- cell function are at high risk for HZ [15]. In-vitro, tofactinib diminishes CD4 T-cell proliferation and subsequent interferon-gamma production providing a potential explanation for this effect [16]. Further, innate anti-viral defenses in humans rely upon interferon signaling via the JAK1 receptor that is inhibited by tofacitinib [17]. Interestingly, published data do not suggest that disseminated or invasive forms of HZ are more common with tofacitinib. While data from other JAK inhibitor programs is largely unpublished, ruxolitinib used in myelofibrosis which inhibits JAK1 and JAK2 primarily also increases HZ risk [18].

Strengths of our study include an early look at the real-world safety profile of tofacitinib using sufficient sample size to provide meaningful information about HZ incidence. However, despite using validated methods to identify cases of HZ [10], we did not have access to medical records to confirm events, nor do we know of the existence of a validation study for incident HSV. While we were unable to adjust for RA disease activity and severity, we made abatacept our referent exposure group given that it is often used as a second or later line agent in patients that may be more comparable to tofacitinib treated patients. Finally, we recognize the potential for surveillance bias if patients initiating tofacitinib were counseled about zoster risk and thus might be more likely to present for evaluation of suspected HZ to a physician. Results from our sensitivity analysis where the outcome event was only included if the patient received prescription anti-viral therapy suggests that events were real given that they were treated. Moreover, HZ events are typically painful and would be

commonly come to medical attention. We therefore think it is unlikely that a large number of HZ events in the non- tofacitinib groups were missed.

In conclusion, the absolute rate differences for HZ were approximately 2 per 100 patient-years higher than other biologics. The clinical importance of this finding must be judged in light of the overall risk profile of each therapy. Importantly, the potential to mitigate herpes zoster risk for all RA patients through more aggressive vaccination efforts remains key.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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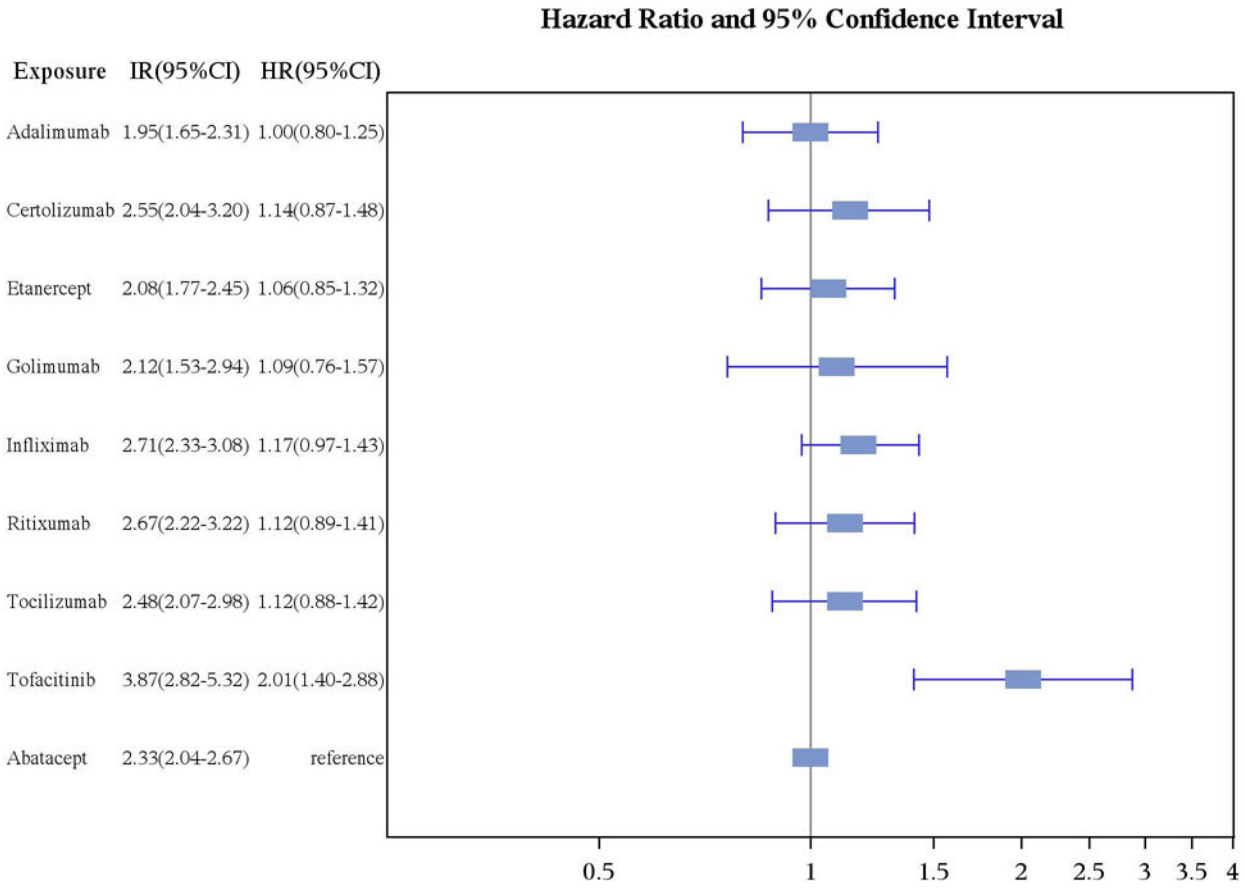

Figure 1. Incidence Rates and Adjusted* Hazard Ratios of Herpes Zoster among Tofacitinib and Biologic-Treated RA Patients

*adjusted for age, gender, glucocorticoid use, methotrexate, number of biologics used, prior hospitalized infection, prior hospitalization for other reasons, prior outpatient infection (other than varicella), and zoster vaccination

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Table 1

Characteristics of patients treated with abatacept, rituximab, anti-TNF, tocilizumab, and tofacitinib

	Abatacept (N=11,434)	Rituximab (N=4,785)	TNF (N=38,871)	Tocilizumab (N=6,266)	Tofacitinib (N=1,746)
Person-years of exposure, n	8,960	4,115	27,122	4,632	982
Age in Years, Mean (SD)	62.0 (13.3)	61.8 (13.0)	58.5 (13.5) †	61.2 (13.4)	57.1 (12.5) †
Women	83.3	80.9	79.7	82.3	83.7
Comorbidities					
Diabetes mellitus	21.6	22.0	20.4	21.9	18.9†
Chronic obstructive pulmonary disease	23.6	26.6	21.7	23.7	22.9
Heart failure	7.3	7.9	4.5†	6.3	5.5†
Renal disease	7.0	8.4	5.4	6.4	4.8†
Any fracture	7.1	7.7	6.0	7.1	6.9
Hospitalized infections during baseline					
0	90.8	88.0	93.2	91.5	93.2†
1–2	8.5	10.9	6.4	7.9	6.3†
≥3	0.7	1.1	0.5	0.6	0.5
Medications					
Methotrexate *	46.9	44.2	55.6†	43.6	39.1†
Number of biologic agents previously used **		†			
0	27.2	24.8	55.0†	9.3†	15.0†
1	46.5	36.8†	31.9†	38.3†	28.4†
2	20.5	25.3	9.4†	33.2†	26.9†
3 or more	6.0	13.2†	3.6†	19.3†	29.8†
Prednisone, mean mg/day ***					
None	35.9	30.3†	38.3	33.6	34.6
≤7.5	44.2	41.8	43.8	43.5	44.1
>7.5	19.9	27.9†	17.8	22.9	21.3

	Abatacept (N=11,434)	Rituximab (N=4,785)	TNF (N=38,871)	Tocilizumab (N=6,266)	Tofacitinib (N=1,746)
Health behaviors and health services utilization					
Lookback period in Days, median (IQR)	1120 (684, 1773)	4498 (691, 1814)	945† (594, 1558)	1184 (674, 1903)	1275† (886, 2040)
Zoster vaccine**	5.1	4.1	4.5	3.9	5.0
PSA screening test (men only)	41.8	39.8	38.4	42.2	32.6
Mammography (women only)	39.6	38.8	37.5	38.4	35.1
All-cause hospitalizations during baseline					
0–1	93.4	90.4†	94.8	93.7	95.0
2	4.4	5.5	3.4	4.2	3.2
≥3	2.2	4.2†	1.8	2.1	1.8
Outpatient infection	50.3	51.7	45.4	50.4	46.3

Note: all covariates assessed in baseline 12 months prior to the start of follow-up, unless otherwise noted

* assessed using 4 month baseline data

** assessed using all available data prior to index date

*** assessed using 6 month average daily dose

† standardized mean difference > 0.10 compared to abatacept

Table 2

Incidence rate* of herpes zoster and herpes simplex associated with each biologic and tofacitinib

	Event	Person Years	Incidence Rate	Adjusted** Hazard Ratio (95% CI)
abatacept	450	8191.3	5.49 (5.01–6.03)	1.0 (referent)
adalimumab	295	5933.3	4.97 (4.44–5.57)	0.91 (0.78–1.06)
certolizumab	153	2748.9	5.57 (4.75–6.52)	1.01 (0.84–1.22)
etanercept	302	6087.5	4.96 (4.43–5.55)	0.89 (0.76–1.03)
golimumab	79	1452.9	5.44 (4.36–6.78)	1.02 (0.80–1.30)
infliximab	477	7760.5	6.15 (5.62–6.72)	1.10 (0.96–1.25)
rituximab	204	3739.6	5.46 (4.76–6.26)	0.97 (0.82–1.15)
tocilizumab	255	4068.2	6.27 (5.54–7.09)	1.16 (0.99–1.36)
tofacitinib	49	525.2	9.33 (7.05–12.3)	1.65 (1.21–2.23)

*per 100 person years

**adjusted for age, sex, baseline glucocorticoid use, methotrexate, number of biologics used, hospitalization, hospitalized infection, outpatient infection, and zoster vaccination