Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis

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Abstract:

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

Methods Using health plan data from 2010 to 2014, patients with RA initiating tofacitinib or biologics with no history of HZ or HSV were identified, as were incident cases of HZ or HSV. 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 2526 patients initiating tofacitinib were compared with initiations of other biologics: anti-tumour necrosis factor (TNF) (n=42 850), abatacept (n=12 305), rituximab (n=5078) and tocilizumab (n=6967). Patients receiving tofacitinib were somewhat younger (mean age 55 years) versus those on other biologics, and somewhat less likely to use concomitant methotrexate (MTX) (39% vs 43%–56%, depending on drug). Crude incidence of HZ associated with tofacitinib was 3.87/100 patient-years (py). After multivariable adjustment, HZ risk was significantly elevated, HR 2.01 (95% CI 1.40 to 2.88) compared with abatacept. Rates and adjusted HRs for all other RA biologics were comparable with each other and abatacept. Older age, female sex, prednisone >7.5 mg/day, prior outpatient infection and greater number of hospitalisations were also associated with increased HZ risk. Incidence rates for the combined outcome were greatest for tofacitinib (7.61/100 py) and also significantly elevated after adjustment (HR=1.40, 95% CI 1.09 to 1.81).

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

Introduction

Tofacitinib is a novel small molecule approved in the USA in November 2012, for the treatment of rheumatoid arthritis (RA). While not a biologic, it has multiple immunomodulatory effects, primarily through inhibition of janus kinase (JAK) 1/3 kinases. In phase 1–3 trials,[1] ,[2] the incidence of most adverse events was generally comparable with that of biologics for RA. However, clinical trials and long-term extension studies within the RA development programme suggest that for tofacitinib, the incidence of herpes zoster (HZ) is elevated beyond that reported for biologics.[3] This is important because patients with RA already have an elevated HZ risk

compared with the general population.[4] ,[5] HZ complications can cause significant morbidity, for example chronic, debilitating pain syndromes. Because almost all data for tofacitinib are based upon placebo-controlled trials, the real-world safety profile of tofacitinib and its comparability with 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 have been found in blood and synovial fluid from patients with RA.[6] Because tofacitinib's mechanism of action potentially mitigates interferon signalling and is important to host antiviral 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 with biologics used for RA.

Methods

Data source and cohort eligibility

We used data from Medicare (2006–2013) and Marketscan (2010–2014) for this analysis. Medicare covers approximately 93% of patients over age 65 in the USA, and younger patients with certain disabling conditions (including RA) can qualify.[7] ,[8] Marketscan is a longitudinal US database of patient-level data for >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.[9] Patients eligible for this analysis were required to be of age ≥18 years and to have two or more physician billing diagnoses for RA (International Classification of Diseases (ICD)9 714.0, 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 (PPV) >85% when combined with disease-modifying antirheumatic drug (DMARD) or biologic use.[10] 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 HZ or HSU (ICD code 053.xx (HZ), 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 1 January 2010. This calendar time restriction was implemented to homogenise 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 PPV of an HZ diagnosis code for identifying clinical shingles events has been shown in validation studies to be 85% or greater.[11,12] A sensitivity analysis required both a HZ diagnosis code plus one of three antiviral 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 three antiviral drugs listed above. Given these drugs are highly specific to HZ or HSV, it is very likely that 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 characterise drug exposure cohorts and standardised mean differences (SMDs) estimated for each characteristic compared with 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.[13] 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 treatment episodes within patients.[14]Potential confounding or effect-modifying covariates were selected based upon clinical interest and based upon prior zoster analyses[15] and included age, sex and baseline factors: concomitant methotrexate use, glucocorticoid dose (none, or daily prednisone-equivalent dose above or below 7.5 mg/day calculated using the baseline 6 months period), prior outpatient infection, any hospitalisation and zoster vaccination.

After evaluating the proportional hazards assumption, we calculated the hazard rate using 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-tumour necrosis factor (TNF) drugs were combined into a single group since patients were relatively homogeneous (not shown). Compared with 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.

Table 1

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

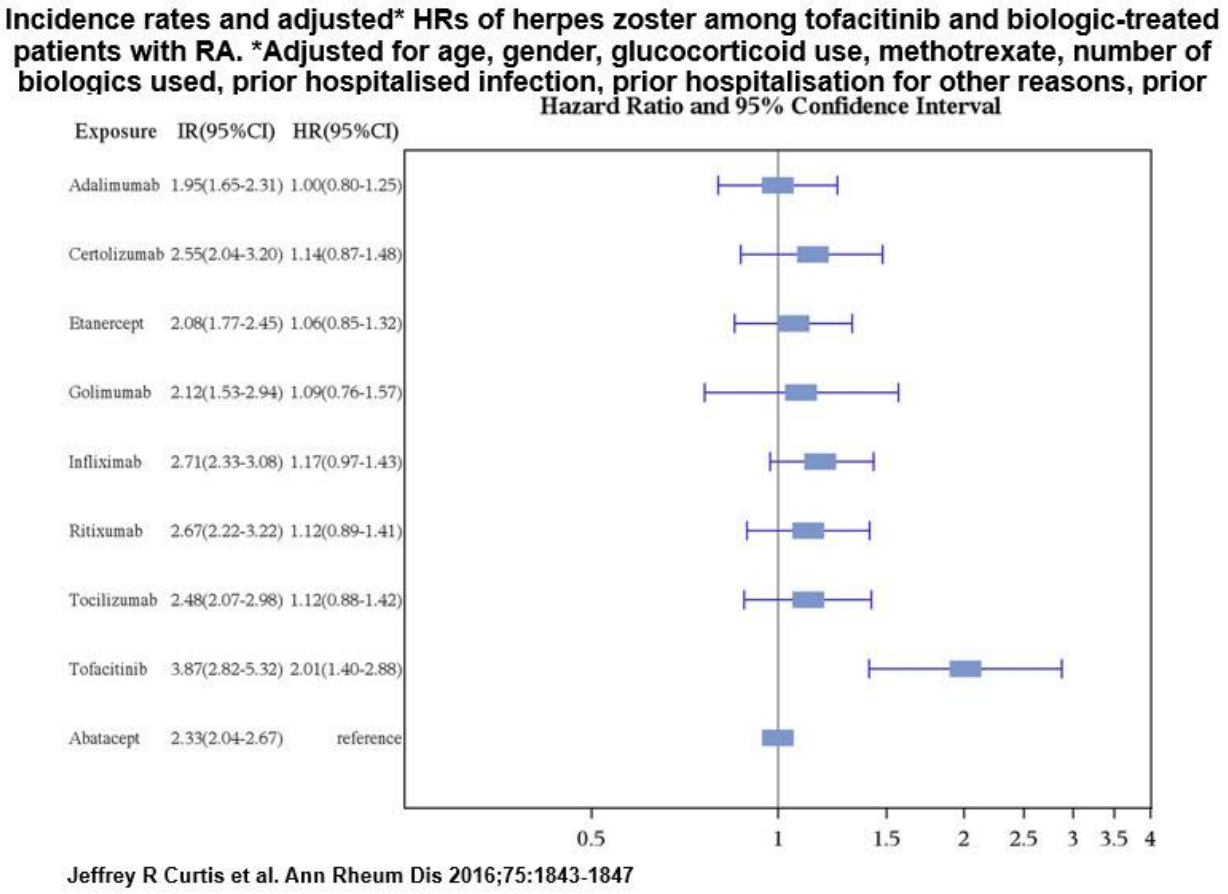
	Abatacept (N=12 305)	**Rituximab (N=5078)**	**TNF (N=42 850)**	**Tocilizumab (N=6967)**	**Tofacitinib (N=2526)**
Person-years of exposure	8960	4115	27122	4632	982
Age in Years, Mean (SD)	61.2 (13.4)	61.2 (13.0)	57.7 (13.5)*	60.1 (13.5)	55.4 (11.8)*
Women	83.2	80.8	79.6	82.2	83.2
Comorbidities					
Diabetes mellitus	21.0	21.5	19.6	21.0	16.7*
Chronic obstructive pulmonary disease	23.0	26.2	20.9	22.9	20.8
Heart failure	6.9	7.5	4.2*	5.8	4.2*
Renal disease	6.8	8.1	5.0	5.9	3.9
Any fracture	6.9	7.6	5.7	6.8	5.9
Hospitalized infections during baseline					
0	91.2	88.3	93.5	92.0	94.0*
1–2	8.3	10.5	6.0	7.4	5.4*
≥3	8.1	10.5	6.0	7.4	5.4
Outpatient infection	50.1	51.7	44.9	49.9	45.4
Medications					
Methotrexate†	46.7	44.1	55.5*	43.3	39.4*
Number of biologic agents previously used‡					
0	26.5	24.6	54.5*	8.9*	15.0*
1	46.3	36.4	32.1*	38.7*	29.5*
2	46.0	36.3	32.1*	38.6*	29.3*
3 or more	21.3	25.3	9.5	33.2	27.7

	Abatacept (N=12 305)	Rituximab (N=5078)	TNF (N=42 850)	Tocilizumab (N=6967)	Tofacitinib (N=2526)
Prednisone, mean mg/day§					
None	36.1	30.5*	38.4	33.8	34.8
≤7.5	44.4	41.6	44.2	43.8	45.5
>7.5	44.5	41.6*	44.2	43.8	45.5
Health behaviors and health services utilization					
Lookback period in Days, median (IQR)	1149 (692, 1738)	1221 (699, 1788)	981* (605, 1576)	1217 (686, 1831)	1316* (911, 1709)
Zoster vaccine‡	5.0	4.1	4.5	3.8	4.9
PSA screening test (men only)	41.4	39.6	37.4	41.2	32.2
Mammography (women only)	39.7	38.6	37.6	38.3	37.2
All-cause hospitalizations during baseline					
0–1	93.7	90.6*	95.1	94.1	95.6
2	4.4	5.4	3.2	4.0	2.8
≥3	4.2	5.4*	3.2	4.0	2.8

- Note: all covariates assessed in baseline 12 months prior to the start of follow-up, unless otherwise noted.
- Data are shown as % unless otherwise specified.
- *Standardised mean difference >0.10 compared with abatacept.
- †Assessed using 4-month baseline data.
- ‡Assessed using all available data prior to index date.
- §Assessed using 6-month average daily dose.
- PSA, prostate specific antigen; TNF, tumour necrosis factor.

The forest plot (figure 1) describes crude rates and adjusted HRs of HZ according to drug exposure. HZ rates ranged from a low of 1.95 (95% CI 1.65 to 2.31) per 100 patient-years (py) for adalimumab to a high of 3.87 (2.82 to 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 to 2.88) compared with abatacept. No biologics were significantly different compared with this same referent, and all of them were numerically close to 1.00 (no excess risk

vs abatacept). The reasons patients ended follow-up were shown in online supplementary table S1. There were no major differences except that given the more recent approval date of tofacitinib compared with other therapies, patients were more likely to be censored because they reached the end of the study period.



Older age, female sex, prednisone >7.5 mg/day, prior outpatient infection and greater number of hospitalisations were associated with increased HZ risk (see online supplementary table S2), whereas vaccination was associated with a lower risk (HR=0.66 95% CI 0.48 to 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 to 2.28), although risk was lower in African Americans (HR 0.69, 95% CI 0.53 to 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 antiviral 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 to 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 to 2.94).

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

Table 2

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

	Event	Person-years	Incidence rate	Adjusted† HR (95% CI)
Abatacept	483	8790.2	5.49 (5.03–6.01)	1.0 (referent)
Adalimumab	330	6832.8	4.83 (4.34–5.38)	0.89 (0.77–1.03)
Certolizumab	161	2940.7	5.47 (4.69–6.39)	1.00 (0.83–1.19)
Etanercept	335	6995.8	4.79 (4.30–5.33)	0.86 (0.74–1.00)
Golimumab	89	1670.8	5.33 (4.33–6.56)	1.01 (0.80–1.27)
Infliximab	492	8201.4	6.00 (5.49–6.55)	1.06 (0.93–1.21)
Rituximab	220	4044.2	5.44 (4.77–6.21)	0.98 (0.83–1.15)
Tocilizumab	278	4538.3	6.13 (5.45–6.89)	1.15 (0.99–1.34)
Tofacitinib	74	972.9	7.61 (6.06–9.55)	1.40 (1.09–1.81)

- *Per 100 person-years.
- †Adjusted for age, sex, baseline glucocorticoid use, methotrexate, number of biologics used, hospitalisation, hospitalised infection, outpatient infection and zoster vaccination.

Discussion

In this analysis of real-world US data, we found that the risk for HZ in tofacitinib-treated patients with RA was approximately double compared with patients with RA 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 (3.87/100 py) the rate seen in the tofacitinib clinical trial programme was 3.3/100 py, 95% CI 2.4 to 4.5.[3]

HZ is an emerging complication of JAK inhibition; incidence within the global tofacitinib development programme is 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 tofacitinib 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.[16] In vitro, tofacitinib diminishes CD4 T-cell proliferation and subsequent interferon-γ production providing a potential explanation for this effect.[17] Furthermore, innate antiviral defences in humans rely upon interferon signalling via the JAK1 receptor that is inhibited by tofacitinib.[18] Interestingly, published data do not suggest that disseminated or invasive forms of HZ are more common with tofacitinib. While data from other JAK inhibitor programmes are largely unpublished, ruxolitinib used in myelofibrosis which inhibits JAK1 and JAK2 primarily also increases HZ risk.[19]

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,[11] 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 with tofacitinib-treated patients.[20] Finally, we recognise the potential for surveillance bias if patients initiating tofacitinib were counselled 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 antiviral therapy suggest that events were real given that they were treated. Moreover, HZ events are typically painful and would 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 two per 100 py 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 HZ risk for all patients with RA through more aggressive vaccination efforts remains key.

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