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Herpes Zoster and Tofacitinib

Clinical Outcomes and the Risk of Concomitant Therapy

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Objective. **Patients with rheumatoid arthritis (RA) are at increased risk of herpes zoster (HZ), and the risk appears to be increased in patients treated with tofacitinib. The aim of this study was to evaluate whether concomitant treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or glucocorticoids (GCs) contributes to the increased risk of HZ in RA patients treated with tofacitinib.**

Methods. **HZ cases were identified from the databases of 2 phase I, 9 phase II, 6 phase III, and 2 long-term extension studies of tofacitinib in RA patients. Crude incidence rates (IRs) of all HZ events (serious and nonserious) per 100 patient-years (with 95% confidence intervals [95% CIs]) were calculated for unique patients. Within phase III studies, we described HZ rates according to concomitant csDMARD treatment and baseline GC use. A multivariable Cox proportional hazards regression model was used to evaluate HZ risk factors across studies.**

Results. **Across all studies (6,192 patients; 16,839 patient-years), HZ was reported in 636 tofacitinib-treated patients (IR 4.0, 95% CI 3.7–4.4). In most cases (93%), HZ was classified as nonserious, and the majority of patients (94%) had involvement of only 1 dermatome. HZ IRs varied across regions, from 2.4 (95% CI 2.0–2.9) in Eastern Europe to 8.0 (95% CI 6.6–9.6) in Japan and 8.4 (95% CI 6.4–10.9) in Korea. Within phase III studies, HZ IRs varied according to tofacitinib dose, background csDMARD treatment, and baseline use of GCs. The IRs were numerically lowest for monotherapy with tofacitinib 5 mg twice daily without GCs (IR 0.56 [95% CI 0.07–2.01]) and highest for tofacitinib 10 mg twice daily with csDMARDs and GCs (IR 5.44 [95% CI 3.72–7.68]). Age, GC use, tofacitinib dose, and enrollment within Asia were independent risk factors for HZ.**

Conclusion. **Patients receiving treatment with tofacitinib and GCs appear to have a greater risk of developing HZ compared with patients receiving tofacitinib monotherapy without GCs.**

Shingles, also known as herpes zoster (HZ), is caused by the reactivation of varicella zoster virus (VZV) and is a common and potentially debilitating illness (1,2).

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Approximately one-third of the general population will develop HZ within their lifetime (1), and ~10% of these patients develop postherpetic neuralgia, which can last for months to years and cause significant pain and morbidity (3). Rarely, but especially in immunosuppressed patients, reactivation can result in disseminated or visceral disease, such as encephalitis, or other complications (1). Patients with rheumatoid arthritis (RA) have a 1.5-fold to 2-fold higher risk of HZ compared with similarly aged individuals in the general population (4,5). This risk is related in part to the disease itself but can be further increased by RA treatments (4).

Glucocorticoids (GCs), including prednisone, are well-documented risk factors for HZ (6,7), and more recently, use of JAK inhibitors, including both tofacitinib and baricitinib, has been associated with a higher rate of HZ (8–10). In addition, although not all studies have documented an increased risk attributable to biologic therapies (11,12), a recent systematic review suggested an increased risk of HZ associated with tumor necrosis factor (TNF) antagonist treatment (13), and a theoretical risk is associated with various conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX) and chloroquine (14,15). Given the increased risk of HZ observed among patients with RA compared with the general population and the risk associated with RA therapies, it is possible that the risk of HZ may be further increased when such therapies are combined.

Tofacitinib is an oral JAK inhibitor for the treatment of RA. We recently reported an increased risk of HZ with tofacitinib therapy compared with placebo during the tofacitinib global clinical development program for RA (8). Although the risk of HZ was increased throughout the global program, this risk varied by geographic region, with significantly higher rates reported in Japan and Korea. Many of the patients in the phase III program also used concomitant csDMARDs as well as GCs (8). We undertook the current analysis to better characterize the clinical aspects of HZ events with longer periods of follow-up and exposure, and to evaluate whether the risk of HZ is greater in patients receiving tofacitinib and concomitant MTX and GCs.

PATIENTS AND METHODS

The global tofacitinib RA development program consisted of 2 phase I, 9 phase II, 6 phase III, and 2 open-label long-term extension (LTE) studies and included a total of 6,192 tofacitinib-treated patients with 16,839 patient-years of tofacitinib exposure at the time of the datacut (April 2014). LTE study A3921024 data collection and analyses were still ongoing at the time of this analysis; because the study database had not yet been locked, some values may change in the final locked study database. Details of these trials with regard to tofacitinib dosing and study conduct have previously been published (16–33). Patients with a history of recurrent HZ (>1 episode), disseminated HZ (single episode), or disseminated herpes simplex (single episode) were excluded from these trials. Patients who had previously experienced an HZ event involving a single dermatome were eligible to participate.

All studies were conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the regulations of the relevant local countries. All enrolled patients provided written informed consent, and all participating institutions provided institutional review board or ethics committee approval prior to participation.

HZ reporting and adjudication. For each study, adverse event (AE) data were reported by site investigators and entered into the Pfizer clinical database. Standard Medical Dictionary for Regulatory Activities codes were used to categorize AEs, and infectious AEs, such as HZ, were graded as "serious" if they were associated with hospitalization or death, were medically important, or required treatment with parenteral therapy. All patients with serious HZ events discontinued tofacitinib treatment, according to the study protocols, but patients with nonserious HZ were permitted to continue in the trial. All cases of HZ reported to involve >1 dermatome were evaluated by an independent adjudication committee and designated as multidermatomal (nonadjacent or >2 adjacent dermatomes) or disseminated. Dermatome maps completed by investigators at the study sites were used during the adjudication process.

Incidence rate (IR) calculation. Across the global tofacitinib RA development program, HZ events in tofacitinib-treated patients were captured. We calculated crude IRs of the number of unique patients with HZ events per 100 patient-years (with 95% confidence intervals [95% CIs]), and stratified the data by race, age, baseline DMARD use, baseline GC use, and other factors. Patients were censored at the time of the first HZ event, death, or study withdrawal, whichever came first. Crude HZ IRs of the first HZ event over the entire phase I, phase II, phase III, and LTE study time period were calculated. Due to variability within this pooled data set with respect to concomitant DMARD treatment and tofacitinib dose, only phase III data (for which concomitant therapies and tofacitinib dose were held constant) were used to examine IRs stratified with regard to these factors.

Cox proportional hazards regression analysis of risk factors for HZ. To evaluate risk factors for HZ among tofacitinib-treated patients, we used pooled data from the phase I, phase II, phase III, and LTE studies. Univariate analysis using a Cox proportional hazards regression model was performed on known risk factors for HZ and those of potential interest based on clinical considerations (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40189/abstract). A pool of factors was then formed to select the final multivariable Cox proportional hazards regression model for the analysis of the time to HZ event from the first dose of tofacitinib, including age, sex, disease duration, baseline 4-variable Disease Activity Score in 28 joints (34) using the C-reactive protein level (DAS28-CRP), baseline absolute lymphocyte count, baseline diabetes mellitus, baseline Health Assessment Questionnaire

Table 1. Crude IRs of HZ in patients with RA treated with tofacitinib during phase I, phase II, phase III, and long-term extension studies, by region of enrollment*

	Unique patients with HZ events	Total patient-years of drug exposure	Crude IR (95% CI)†
Global RA program	636	16,839	4.0 (3.7–4.4)
By region			
US/Canada/Australia/New Zealand	159	3,910	4.3 (3.7–5.1)
Western Europe	43	1,395	3.3 (2.4–4.4)
Eastern Europe	105	4,509	2.4 (2.0–2.9)
Latin America	96	2,802	3.6 (3.0–4.5)
Asia	233	4,223	6.1 (5.4–7.0)
Japan	120	1,705	8.0 (6.6–9.6)
Korea	56	779	8.4 (6.4–10.9)
India	16	435	3.9 (2.2–6.3)
Thailand/Malaysia/Philippines	18	479	4.0 (2.4–6.3)
China/Taiwan	23	822	3.0 (1.9–4.5)

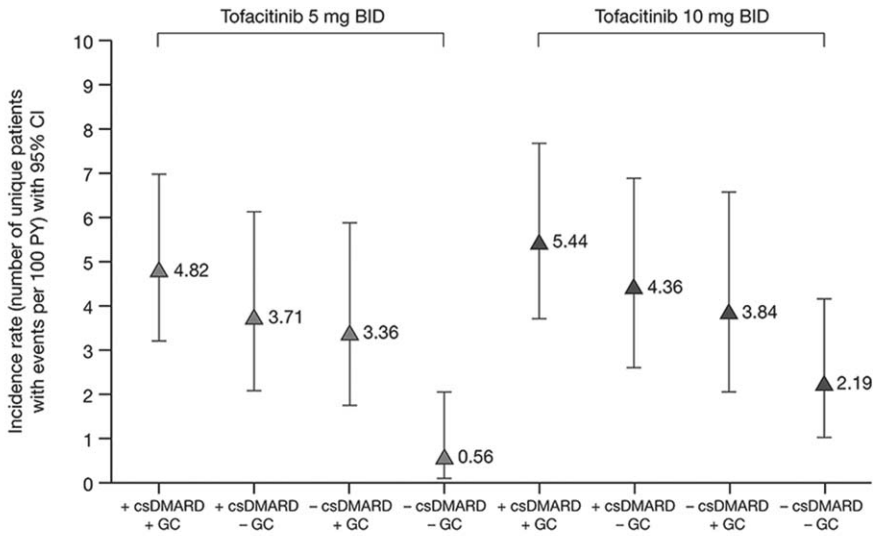
* HZ = herpes zoster; RA = rheumatoid arthritis; 95% CI = 95% confidence interval.
† Crude incidence rates (IRs) of an HZ event per 100 patient-years in unique patients (data as of April 2014, for all tofacitinib doses).

score (35), background therapy (any DMARD versus monotherapy), body mass index (BMI), baseline chronic obstructive pulmonary disease, smoking status (former or nonsmoker versus current smoker), baseline oral GC use, and geographic region. A backward selection process with the criterion to stay in the model fixed at 10% was used to screen and select the risk factors. The final Cox proportional hazards regression model included all of the risk factors that were selected using the backward procedure. The tofacitinib group was added in a time-varying format; any other risk factors that were not selected by the procedure but were considered as being clinically relevant would be forced back into the final model. Age, BMI, 4-variable DAS28-CRP, disease duration, and baseline absolute lymphocyte count were evaluated as continuous variables. All analyses were conducted using SAS software.

Table 2. Baseline characteristics of the patients with rheumatoid arthritis in phase III tofacitinib trials, by treatment group*

Characteristic	Tofacitinib 5 mg BID + csDMARDs (n = 973)	Tofacitinib 5 mg BID monotherapy (n = 616)	Tofacitinib 10 mg BID + csDMARDs (n = 969)	Tofacitinib 10 mg BID monotherapy (n = 642)
Age, mean ± SD years	53.4 ± 11.7	51.1 ± 12.0	52.6 ± 11.6	50.5 ± 12.4
Female	820 (84.3)	493 (80.0)	814 (84.0)	543 (84.6)
BMI, mean ± SD kg/m^2	27.0 ± 6.8	26.7 ± 5.9	27.0 ± 6.4	27.1 ± 6.3
Diabetes mellitus	83 (8.5)	47 (7.6)	81 (8.4)	46 (7.2)
COPD	78 (8.0)	47 (7.6)	83 (8.6)	51 (7.9)
RA disease duration, mean ± SD years	8.9 ± 8.0	4.9 ± 7.0	9.2 ± 8.2	5.4 ± 7.3
DAS28-ESR, mean ± SD	6.4 ± 1.0	6.7 ± 1.0	6.4 ± 1.0	6.6 ± 1.0
Baseline GC use	579 (59.5)	320 (51.9)	550 (56.8)	313 (48.8)
GC dose, mean (median) mg	6.3 (5.0)	7.3 (6.3)	6.3 (5.0)	7.4 (5.0)
Concomitant DMARDs				
Methotrexate	896 (92.1)	1 (0.2)	895 (92.4)	0 (0.0)
Leflunomide	90 (9.2)	0 (0.0)	84 (8.7)	0 (0.0)
Chloroquine	68 (7.0)	87 (14.1)	63 (6.5)	99 (15.4)
Race				
White	584 (60.0)	392 (63.6)	573 (59.1)	434 (67.6)
Black	33 (3.4)	25 (4.1)	25 (2.6)	22 (3.4)
Asian	286 (29.4)	109 (17.7)	282 (29.1)	95 (14.8)
Other	70 (7.2)	90 (14.6)	89 (9.2)	91 (14.2)
Smoking history				
Never smoker	644 (66.2)	410 (66.6)	647 (66.8)	444 (69.2)
Current smoker	136 (14.0)	97 (15.7)	168 (17.3)	114 (17.8)
Former smoker	193 (19.8)	109 (17.7)	154 (15.9)	84 (13.1)

* Except where indicated otherwise, values are the number (%). BID = twice daily; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; BMI = body mass index; COPD = chronic obstructive pulmonary disease; RA = rheumatoid arthritis; DAS28-ESR = 4-variable Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; GC = glucocorticoid.



	+ csDMARD + GC	+ csDMARD − GC	− csDMARD + GC	− csDMARD − GC	+ csDMARD + GC	+ csDMARD − GC	− csDMARD + GC	− csDMARD − GC
Total patients, N	579	394	320	296	550	419	313	329
Total tofacitinib exposure, PY	603	412	367	361	606	429	346	419
Unique patients with events, n	28	15	12	2	32	18	13	9
IR (95% CI)	4.82 (3.2, 7.0)	3.71 (2.1, 6.1)	3.36 (1.7, 5.9)	0.56 (0.07, 2.0)	5.44 (3.7, 7.7)	4.36 (2.6, 6.9)	3.84 (2.0, 6.6)	2.19 (1.0, 4.2)

Figure 1. Crude incidence rates (IRs) of first herpes zoster (HZ) events within pooled phase III studies of tofacitinib, with or without conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or baseline glucocorticoid (GC) use. Patients from all regions were included. HZ IRs (with 95% confidence intervals [95% CIs]) are expressed as the number of unique patients with an HZ event per 100 patient-years (PYs) of exposure. BID = twice daily.

RESULTS

Summary of HZ events during phase I, phase II, phase III, and LTE studies. Among 6,192 patients with 16,839 patient-years of tofacitinib exposure, we identified 636 patients (10%) who developed HZ over a median follow-up period of 3.0 years of tofacitinib exposure and in whom the median time to first HZ event was 1.6 years. The overall crude IR for the first HZ event in tofacitinib-treated patients was 4.0 (95% CI 3.7–4.4). Similar to a previous study by our group (8), the crude IRs varied widely across regions of enrollment and were numerically lowest in Eastern Europe (2.4 [95% CI 2.0–2.9]) and Western Europe (3.3 [95% CI 2.4–4.4]) and highest in Asia, particularly in Japan (8.0 [95% CI 6.6–9.6]) and Korea (8.4 [95% CI 6.4–10.9]) (Table 1).

For the first HZ event, the majority of patients (597 [93.9%]) had single-dermatome involvement, 46 patients (7.2%) were classified as having a serious HZ event, and no case resulted in death. Most patients (570 [89.6%]) received antiviral therapy while being treated with tofacitinib. After the first HZ event, tofacitinib treatment was continued in 274 patients (43.1%), while 267 patients (42.0%) temporarily stopped receiving tofacitinib, 5 patients (0.8%) reduced the tofacitinib dose during the event, 51 patients (8.0%) permanently discontinued tofacitinib treatment, and treatment changes were not reported in 39 patients (6.1%). Of the first HZ events, 602 cases had resolved at the time of the current analysis, with a median time to resolution of 21 days (range 1–733). The clinical study investigators reported that 47 (7.4%) of the initial patients developed postherpetic neuralgia.

Similar outcomes were reported for subsequent HZ events. Forty-seven patients (0.8% of all patients; 7.4% of patients in whom HZ developed) reported having at least 1 additional HZ event later during the study. None of the patients with a second HZ event had multiple dermatomes or visceral dissemination; 2 patients (4.3%) were graded as having serious AEs, and these patients were withdrawn from the study. Among the patients with a second HZ event, 19 (40.4%) continued to receive therapy during the event, 22 (46.8%) stopped tofacitinib temporarily during the event, and 4 (8.5%) permanently discontinued tofacitinib. The median time to resolution of a second HZ event was 20 days (range 4–122). Eight patients reported a third HZ event, and 1 patient experienced a total of 6 separate HZ events.

Examination of the effect of concomitant DMARD or GC therapy in phase III studies. With the exception of mean disease duration (for combination therapy, range 8.9–9.2 years; for monotherapy, range

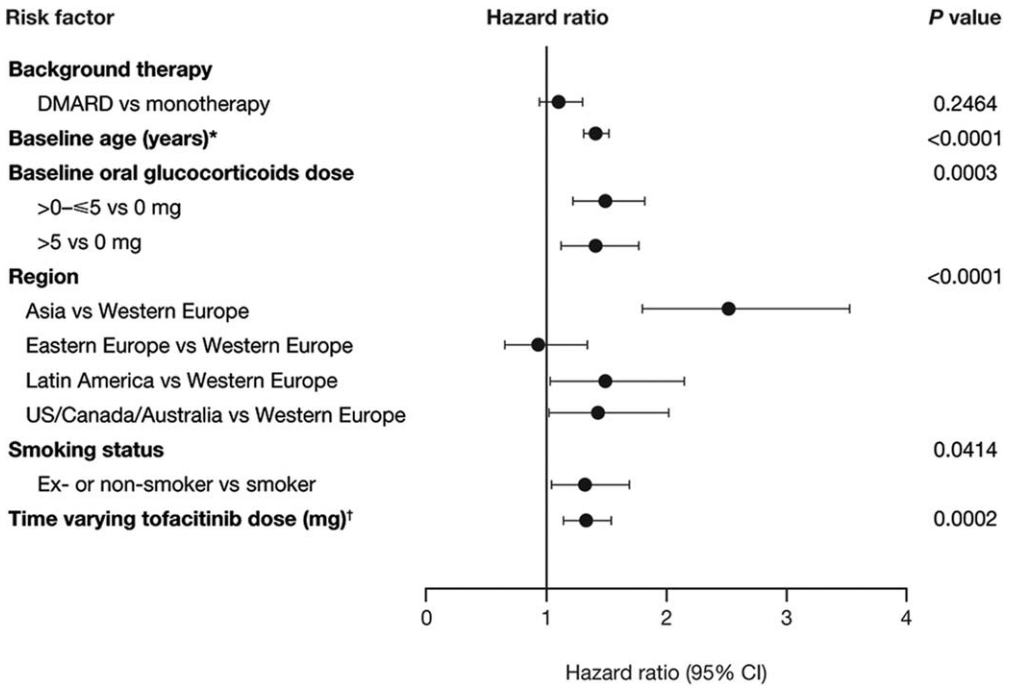


Figure 2. Cox proportional hazards regression model for the risk of herpes zoster with baseline factors among patients treated with tofacitinib in pooled phase I, II, III, and long-term extension studies. * = unit = 10 years. † = unit = 5 years. DMARD = disease-modifying antirheumatic drug; 95% CI = 95% confidence interval.

4.9–5.4 years), baseline characteristics in phase III studies were similar between patients receiving concomitant DMARDs and those receiving tofacitinib monotherapy (Table 2). For patients receiving concomitant DMARDs, most (92.2%) were receiving MTX. GC use was similar (~50%) between patients receiving either dose of tofacitinib with or without concomitant csDMARDs.

Although 681 patients received placebo in the phase III studies, the exposure time was very limited (202.7 patient-years), and only 3 patients were reported as having HZ during their exposure to placebo, with a crude IR of 1.5 (95% CI 0.3–4.3). As such, placebo data were not included in this stratified analysis. Details of these events in placebo-treated patients have previously been reported (8). All placebo-treated patients who reported HZ received concomitant csDMARDs, and 1 patient also received background GCs.

Crude IRs varied according to tofacitinib dose as well as treatment with background GCs and csDMARDs. Overall, the crude HZ IR among patients receiving tofacitinib 10 mg was numerically higher than that among those receiving 5 mg twice daily (4.1 [95% CI 3.3–5.2] versus 3.3 [95% CI 2.6–4.3]). Trends were seen for both the 5 mg twice daily and 10 mg twice daily dosage groups, in which the HZ IR was numerically lower in the absence of either background csDMARD or GC treatment (Figure 1). Numerically, the highest crude IR was observed in patients receiving tofacitinib 10 mg twice daily and both background DMARDs and GCs (5.4 [95% CI 3.7–7.7], based on 32 unique patients with events from among 550 patients with 606 patient-years of exposure) and the lowest crude IR was observed among patients receiving tofacitinib 5 mg twice daily as monotherapy without GCs (0.56 [95% CI 0.07–2.0], based on 2 unique patients with events among 296 patients with 361 patient-years of exposure).

Univariate and multivariable Cox proportional hazards regression analysis of HZ risk factors among patients treated with tofacitinib in pooled phase I, phase II, phase III, and LTE studies. In the Cox univariate analysis, a number of factors showed an association with an increased risk of HZ (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40189/abstract). Using the pool of risk factors identified by the univariate analysis and based on clinical consideration, after applying the backward selection procedure, 4 factors were selected for the final Cox proportional hazards regression model (Figure 2). These factors included baseline age (hazard ratio [HR] 1.41, 95% CI 1.31–1.52; unit = 10 years), baseline GC use (for >0 to ≤5 mg/day versus 0 mg/day, HR 1.49, 95% CI 1.22–

1.82; for >5 mg/day versus 0 mg/day, HR 1.41, 95% CI 1.12–1.77); region (for Asia versus Western Europe, HR 2.52, 95% CI 1.80–3.53; for Latin America versus Western Europe, HR 1.49, 95% CI 1.03–2.15; for US/Canada/Australia versus Western Europe, HR 1.43, 95% CI 1.02–2.02), and smoking status (former smoker or nonsmoker versus smoker, HR 1.32, 95% CI 1.04–1.69). The time-varying tofacitinib dose, which was added to the final model, also appeared to be a risk factor for HZ (HR 1.33, 95% CI 1.14–1.54; unit = 5 mg, e.g., an increase from 5 mg to 10 mg). Background csDMARD treatment was considered to be clinically relevant and was forced back into the final model, although it was not selected using the backward selection procedure. This factor did not appear to show an association with an increased risk of HZ (background DMARDs versus monotherapy, HR 1.10 [95% CI 0.94–1.30]).

DISCUSSION

We evaluated the long-term risk of HZ within the tofacitinib clinical development program for RA, with specific attention to the contribution of concomitant csDMARD therapy and GCs to the development of HZ. This analysis was performed following our preliminary evaluation of this question, in which we noted high rates of HZ among tofacitinib-treated patients compared with the expected rates in other studies in RA patients receiving TNF inhibitor (TNFi) therapy (8). Our current analysis includes a greater number of patients and longer exposure to tofacitinib than in the preliminary study. Analysis of this RA cohort, with almost 17,000 patient-years of tofacitinib exposure, suggests that use of concomitant GCs and age contribute to the risk of HZ, and that patients receiving tofacitinib at a dosage of 10 mg twice daily may be at higher risk than those using 5 mg twice daily. Data from phase III studies also indicated a trend toward higher rates of HZ in patients receiving background csDMARDs, particularly when combined with GCs. Our findings suggest that the use of the Food and Drug Administration–approved 5 mg twice daily dosage, and elimination of concomitant therapies, may represent potential risk-reduction strategies for physicians and patients, provided disease activity remains controlled. Overall, the HZ events seemed to be clinically manageable and resolved in the majority of cases. Regardless of concomitant therapy or tofacitinib dose, patients from Japan and Korea have the highest risk of HZ compared with that in other regions. It has also previously been reported that the HZ incidence is consistent over time in tofacitinib-treated patients, suggesting no increased risk for HZ with longer exposure to tofacitinib (10).

In our analysis of phase III studies, we observed that patients receiving tofacitinib at a dosage of 5 mg twice daily as monotherapy without GCs had a numerically 10-fold lower incidence of HZ compared with the patients receiving tofacitinib at a dosage of 10 mg twice daily with concomitant csDMARDs and GCs (exposure time was lower in the former group, which may increase variance). The incidence of HZ in patients receiving tofacitinib 5 mg twice daily as monotherapy without GCs (crude IR 0.56 [95% CI 0.07–2.01]) was similar to the incidence reported in those receiving biologic therapies, including patients who were and those who were not receiving concomitant MTX and GCs (6,12). GCs are a well-described dose-dependent risk factor for HZ worldwide (6,7).

Several studies have also shown an increased risk of HZ in association with biologic therapies, with similar risk factors for HZ identified, including the use of GCs (6,11–13). There are limited data, however, showing that MTX itself increases the risk of HZ in patients with RA (4). A prior meta-analysis of observational studies in RA failed to identify an association (14), and a subsequent population-based study in Minnesota also demonstrated no increased risk with MTX (36). A study in patients with psoriasis showed no increased risk of HZ in patients treated with MTX but did document an increased risk when MTX was combined with TNF blockers (37), and an analysis of psoriatic arthritis had similar findings, in that MTX was a risk only when it was administered in combination with biologic agents (38). We could not evaluate whether MTX alone causes HZ, and although concomitant csDMARD treatment appeared to increase the incidence of HZ in phase III studies, csDMARD treatment was not identified as an independent risk factor for HZ based on the Cox proportional hazards regression model used to evaluate HZ risk factors across all phases of the tofacitinib program.

The mechanism by which tofacitinib increases the risk of HZ is not well understood but may be related to inhibition of interferon (IFN) signaling. Antiviral defenses rely on type I and II IFN signaling via the JAK/STAT pathway (39), which is inhibited by tofacitinib (40,41). This hypothesis is supported by results from studies of sifalimumab, an anti-IFNα monoclonal antibody, which showed a substantial dose-dependent increase in the incidence of HZ following antibody treatment in patients with systemic lupus erythematosus (SLE) (42). An increase in the incidence of HZ was also observed in patients with SLE in a phase II

study of the anti-IFN inhibitor anifrolumab (43) and in a phase I study of rontalizumab (44). The association between MTX treatment, GC treatment, and an increased risk of HZ may also be explained by changes in IFN signaling, because concomitant GC and/or MTX treatment has been shown to suppress IFN signaling in patients with RA (45,46). Other mechanisms, including T cell alterations and cytokine inhibition, may also be involved.

Similar to the observations in our prior analysis (8), these data showed the risk of HZ to be substantially higher in certain areas of Asia. The IRs were shown to be highest in Japan and Korea, whereas rates elsewhere in Asia were comparable to those seen in Western Europe or North America. This raises the possibility that a genetic predisposition toward HZ under the condition of JAK inhibition might exist in some of these populations. However, regional differences in HZ reporting due to different access to health care professionals may also contribute. Bing et al reported 2 polymorphisms that were suggested to be associated with a higher risk of HZ in tofacitinib-treated patients, although these polymorphisms were relatively rare and explained only a fraction of the increased risk observed in the Japanese patients (47). It is possible that other genetic factors could explain this. However, it is unlikely that this is attributable to a difference in background varicella rates, because the seroprevalence of varicella in these Asian regions is similar to that in North America (48).

Although we are uncertain how many of the patients enrolled in this program in North America or elsewhere received shingles vaccination, because we did not collect a vaccination history prior to study entry, it is likely that very few or no patients received the vaccination prior to entering these studies. Population-based studies suggested that vaccine uptake during the period in which these studies were conducted was very poor among patients with RA in the US (49), and the vaccine was not available for use in some countries where enrollment took place (e.g., Japan). Furthermore, the vaccine is currently contraindicated for use during tofacitinib or biologic therapy, so it is unlikely that any patients were vaccinated during the LTE studies. However, studies are ongoing to evaluate the safety and immunogenicity of this vaccine when it is given before starting tofacitinib treatment (50).

Tofacitinib appears to be associated with an increased risk of HZ compared with TNFi therapy, and other JAK inhibitors, such as baricitinib, have also been associated with higher rates of HZ (9,51). However, direct comparisons with baricitinib are limited by the considerably shorter follow-up period and number of patient-years of exposure to baricitinib compared with tofacitinib. A large proportion of patients continued or only temporarily discontinued tofacitinib treatment during their HZ event, although almost all patients received antiviral therapy while receiving tofacitinib, which could potentially have protected against dissemination. According to the tofacitinib product label, treatment should be temporarily withdrawn during any serious infection, including HZ, until the infection is resolving, and patients should be closely monitored during any infection (52).

A recent analysis showed that postherpetic neuralgia occurred in 9.1% of patients with RA in whom HZ developed, with the incidence of postherpetic neuralgia increasing with age (53). In the tofacitinib development program, 7.4% of patients developed postherpetic neuralgia following their first HZ event. However, because reports of postherpetic neuralgia were not systematically requested, our findings may represent an underestimation of this complication. Interestingly, our study showed that current smoking was protective against HZ. There is some evidence that smoking can influence IFN signaling in mice (54). However, to our knowledge, our study is the first to demonstrate that smoking is protective against HZ. This finding is in contrast to at least 1 study of zoster ophthalmicus, in which smokers had a much earlier onset of HZ compared with nonsmokers (55).

In this analysis, our ability to evaluate the influence of GC dosage on the risk of HZ was limited. The exact dose of GCs and the total duration of GC use was not reported for many patients. In addition, we were unable to evaluate the influence of MTX dosage on the risk of HZ. Another limitation of this analysis was the substantially smaller number of patient-years of tofacitinib exposure in the monotherapy group compared with the combination therapy groups, leading to less robust incidence estimates for the monotherapy group.

In summary, we have described the long-term risk of HZ among patients treated with tofacitinib. Importantly, we found that the risk of HZ is likely to be greater in patients receiving tofacitinib in combination with GCs compared with those receiving monotherapy without GCs. Given that similar efficacy has been observed with tofacitinib in phase III clinical studies regardless of whether it is administered as monotherapy or in combination with csDMARDs and/or GCs (56), the use of tofacitinib monotherapy without GCs could represent a risk-reduction strategy for physicians and patients with regard to HZ and provide an effective

treatment strategy for reduction of the signs and symptoms of RA, provided the patient's RA remains controlled. It is also notable that HZ events were mostly nonserious and resolved with standard antiviral treatment. Furthermore, physicians should continue to consider shingles vaccination prior to starting tofacitinib or biologic therapy. Further research is necessary to understand why Japanese and Korean patients are at increased risk, as well as to understand the mechanism by which JAK inhibition combined with GCs leads to higher rates of VZV reactivation.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Winthrop had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Winthrop, Curtis, Fan, Chen, Bananis.

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