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Safety of Tofacitinib in the Treatment of Rheumatoid Arthritis in Latin America Compared With the Rest of the World Population

Oswaldo M. Castañeda, MD, Felix J. Romero, MD,† Ariel Salinas, MD,‡ Gustavo Citera, MD,§ Eduardo Mysler, MD,|| Oscar Rillo, MD,¶ Sebastiao C. Radominski, MD,# Mario H. Cardiel, MD, MSc,** Juan J. Jaller, MD,†† Carlos Alvarez-Moreno, MD,‡‡ Dario Ponce de Leon, MD,§§ Graciela Castelli, MD,|||| Erika G. García, MD,¶¶ Kenneth Kwok, MSc,## and Ricardo Rojo, MD****

Objective: Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by joint destruction. Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. This post hoc analysis assessed the safety of tofacitinib in Latin American (LA) patients with RA versus the Rest of World (RoW) population.

Methods: Data were pooled from 14 clinical studies of tofacitinib: six Phase 2, six Phase 3 and two long-term extension studies. Incidence rates (IRs; patients with events/100 patient-years of treatment exposure) were calculated for safety events of special interest combined across tofacitinib doses. 95% confidence intervals (CI) for IRs were calculated using the maximum likelihood method. Descriptive comparisons were made between LA and RoW (excluding LA) populations.

Results: This analysis included data from 984 LA patients and 4687 RoW patients. IRs for safety events of special interest were generally similar between LA and RoW populations, with overlapping 95% CIs. IRs for discontinuation due to adverse events, serious infections, tuberculosis, all herpes zoster (HZ), serious HZ, malignancies (excluding non-melanoma skin cancer) and major adverse cardiovascular events were numerically lower for LA versus RoW patients; IR for mortality was numerically higher. No lymphoma was reported in the LA population versus eight cases in the RoW population. Exposure (extent and length) was lower in the LA population (2148.33 patient-years [mean = 2.18 years]) versus RoW (10515.68 patient-years [mean = 2.24 years]).

Conclusion: This analysis of pooled data from clinical studies of tofacitinib in patients with RA demonstrates that tofacitinib has a consistent safety profile across LA and RoW patient populations.

Key Words: global, Janus kinase, Latin America, rheumatoid arthritis, safety, tofacitinib

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Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation and joint destruction, and affects approximately 0.5–1.0% of the adult population in industrialized countries.[1] In Latin American (LA) countries, the overall prevalence of RA is estimated to range from 0.4 to 1.6%,[2] with regional variation apparent throughout LA. LA patients with RA differ from patients from the Rest of the World (RoW) in terms of genetic and epidemiologic factors, and in prognosis.[2,3]

Common clinical practice for treatment of patients with RA in LA involves prescription of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) as first-line therapy, followed by biologic DMARDs (bDMARDs) in the case of inadequate response.[3] Despite the relative effectiveness of csDMARD treatment, not all patients with RA respond to treatment, and response may diminish over time.[4] Many patients experience an inadequate clinical response to methotrexate,[4] and although most patients treated aggressively with csDMARDs show rapid improvements, these effects are often not maintained following 1 year of treatment.[4] Several bDMARDs are approved for use in LA, including abatacept, rituximab, tocilizumab, and the tumor necrosis factor inhibitors (TNFi) adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab.[5,6] However, given that not all patients respond to or tolerate treatment with DMARDs,[4] and that the administration of injectable therapies represents a significant burden on

From the *Clínica Angloamericana, Lima, Peru; †Instituto Peruano del Hueso y la Articulación, Lima, Peru; ‡Hospital Nacional Alberto Sabogal, Bellavista, Callao, Peru; §Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina; ||Organización Médica de Investigación, Buenos Aires, Argentina; ¶Section of Rheumatology, Department of Medicine, Hospital Dr I Pirovano, Ciudad Autónoma de Buenos Aires, Argentina; #Universidade Federal do Paraná, Curitiba, Brazil; **Centro de Investigación Clínica de Morelia, Morelia, México; ††Centro de Reumatología y Ortopedia, Barranquilla, Colombia; ‡‡Facultad de Medicina, Universidad Nacional de Colombia, Bogotá, Colombia; §§Pfizer Inc., Lima, Peru; ||||Pfizer Inc., Buenos Aires, Argentina; ¶¶Pfizer Inc., Collegeville, PA, USA; ##Pfizer Inc., New York, NY, USA; and ***Pfizer Inc., Groton, CT, USA.

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Correspondence: Dario Ponce de Leon, MD, Jr Gonzalo Martin de Trujillo, 250 Dpt: 301 Lima, 33 Santiago de Surco, Peru.
E-mail: Dario.PoncedeLeon@pfizer.com.

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LA health systems,[2] new therapies that demonstrate clinical effectiveness and acceptable safety over time are required for the treatment of RA in LA. Additionally, for patients with RA, the route of drug administration may influence their everyday lives. In certain regions, patients may have to travel long distances to access medical centers, which may preclude treatment compliance. In this sense, the majority of patients with RA would prefer oral treatment rather than an injection or intravenous infusion.[7]

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. The efficacy and safety of tofacitinib in the treatment of RA, as monotherapy or in combination with csDMARDs, has been demonstrated in several Phase 2,[8–13] Phase 3[14–19] and long-term extension (LTE) studies.[20,21] In LA, based on these results, tofacitinib has been included as second- or third-line treatment for RA in clinical practice guidelines from Argentina,[22] Chile,[23] Colombia,[24] Mexico[5] and Brazil.[25] American College of Rheumatology (ACR) 2015 guidelines for RA treatment recommend tofacitinib therapy for patients with inadequate response to, or failed treatment with, traditional DMARD therapy.[26]

The management of RA in LA faces a number of challenges that can influence treatment response, including delays in specialist referral, limited resources, limited access to affordable medication, lack of informed decision making regarding public policies, and lack of education surrounding RA.[2,3,27] Moreover, tuberculosis, visceral leishmaniasis, paracoccidioidomycosis, histoplasmosis, Chagas disease and malaria, among other infectious diseases, are endemic in some LA countries and also need to be taken into account when considering treatments for patients with RA due to an increased risk of infections with immunosuppressive therapies.[28]

In this post hoc analysis of pooled data from Phase 2, Phase 3 and LTE studies of tofacitinib, the safety of tofacitinib in LA patients with RA was assessed in comparison with the RoW population.

MATERIALS AND METHODS

Patients and Study Treatments

Data from 14 studies of tofacitinib in patients with RA (six Phase 2, six Phase 3 and two LTE studies) were pooled for this analysis (Table 1). Eligible patients were ≥18 years of age with active RA. Active RA was defined as ≥6 tender or painful joints (68-joint count) and ≥6 swollen joints (66-joint count) and by an erythrocyte sedimentation rate of >28 mm/hr or C-reactive protein level of >7 mg/l.

Phase 2 Studies

In two studies (NCT00413660[10]; NCT00603512[12]), patients were required to have a previous inadequate response to methotrexate; in three studies (NCT00147498[9]; NCT00550446[8]; NCT00687193[13]), patients had previous inadequate response to csDMARDs or bDMARDs; one study had no criteria for prior DMARD exposure (NCT01059864[11]). Patients received tofacitinib 1–30 mg twice daily (BID) or placebo (tofacitinib 20 mg once-daily dose was included in one study [NCT00413660][10]) as monotherapy (NCT00147498; NCT00550446; NCT00687193; NCT01059864) or in combination with background csDMARDs (mainly methotrexate; NCT00413660; NCT00603512). One study (NCT00550446[8]) included an active control arm of adalimumab 40 mg administered subcutaneously once every 2 weeks.

Phase 3 Studies

Patients had a previous inadequate response to methotrexate (ORAL Scan[18] and ORAL Standard[16]), DMARDs (ORAL Solo[14] and ORAL Sync[19]), or TNFi (ORAL Step[17]). ORAL Start[15] enrolled patients who were methotrexate-naïve or had received ≤3 doses of methotrexate. At the time of this analysis, ORAL Start was an ongoing study; therefore, the study database had not yet been locked; some values may change for the final, locked study database; data presented here include up to Month 12 of the study. Patients were randomized to receive tofacitinib 5 mg BID, tofacitinib 10 mg BID, methotrexate (ORAL Start only[15]), adalimumab (ORAL Standard only[16]) or placebo as monotherapy (ORAL Start and ORAL Solo) or in combination with csDMARDs (ORAL Sync, ORAL Standard, ORAL Scan and ORAL Step). In ORAL Solo[14] and ORAL Step[17] patients randomized to receive placebo were automatically advanced to receive tofacitinib 5 mg BID or tofacitinib 10 mg BID in a blinded manner after 3 months. In ORAL Standard,[16] ORAL Scan[18] and ORAL Sync,[19] patients receiving placebo and not achieving ≥20% reduction from baseline in swollen and tender joint counts were advanced to receive tofacitinib 5 mg BID or tofacitinib 10 mg BID in a blinded manner after 3 months; all patients continuing to receive placebo were advanced in a blinded manner to tofacitinib after 6 months. In ORAL Start,[15] patients randomized to receive methotrexate initiated treatment at a dose of 10 mg per week, with increments of 5 mg per week every 4 weeks to 20 mg per week by Week 8.

LTE Studies

Patients participating in qualifying Phase 1, Phase 2 or Phase 3 index studies were eligible for inclusion in one of two open-label LTE studies (ORAL Sequel[20] and NCT00661661[29]; studies were ongoing at the time of analysis; therefore, the study databases had not yet been locked; some values may change for the final, locked study databases; data cut-off date: April 2013).

Patients from qualifying index studies initiated treatment in the LTE studies with tofacitinib 5 or 10 mg BID as monotherapy or in combination with background csDMARDs. For patients enrolling in the LTE within 14 days of participation in the index study, baseline values were those of the index study; for all other patients baseline was the start of the LTE study. Adjustments to tofacitinib dose and concomitant RA medications were permitted at the discretion of the investigator.

All studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines established by the International Conference on Harmonization, and local country regulations. The studies were approved by a central or local institutional review board or an independent ethics committee. All patients provided written informed consent.

Safety Analyses

Safety data were pooled across all patients who received at least one dose of tofacitinib in any study included in the analysis. Data from patients in the placebo, adalimumab and methotrexate comparator treatment groups were not included due to small sample size in the LA population. LA countries that enrolled patients were Argentina, Brazil, Chile, Colombia, Costa Rica, the Dominican Republic, Mexico, Peru and Venezuela. The RoW population included all patients from the global population in the tofacitinib RA clinical program (all studies outlined in Table 1), excluding those patients from LA countries.

Safety data were calculated as incidence rates (IR; patients with events per 100 patient-years of treatment exposure) for safety events of special interest combined across tofacitinib doses. Safety events of special interest included in this analysis were discontinuations due to adverse events (AEs), serious infection events (SIEs), tuberculosis, opportunistic infections (excluding tuberculosis), all herpes zoster (HZ), serious HZ, malignancies (excluding non-melanoma skin cancer [NMSC]), lymphoma, major adverse

TABLE 1. Summary of the Tofacitinib Clinical Studies Included in this Analysis

Study	Phase	Main Inclusion Criteria	Duration	Background DMARD Therapy	Primary Endpoint
A3921019[9]	Phase 2a[a]	Active RA DMARD-IR or unacceptable toxicity (therapy discontinued)	6 weeks	None	ACR20 response rates at week 6
A3921025[10]	Phase 2b[a]	Active RA MTX-IR	24 weeks	MTX	ACR20 response rates at week 12
A3921035[b8]	Phase 2b[a]	Active RA DMARD-IR or unacceptable toxicity (therapy discontinued)	24 weeks	None	ACR20 response rates at week 12
A3921039[12]	Phase 2[a]	Active RA MTX-IR	12 weeks	MTX	ACR20 response rates at week 12
A3921040[13]	Phase 2[ad]	Active RA DMARD-IR	12 weeks	None	ACR20 response rates at week 12
A3921109[11]	Phase 2[e]	Active RA	12 weeks	None	Change from baseline (week 6) in low density lipoprotein-cholesterol level at week 12
ORAL Solo[14] A3921045	Phase 3[a]	Active RA DMARD-IR	6 months	None	ACR20 response rates, HAQ-DI change from baseline and DAS28-4(ESR) < 2.6 at month 3
ORAL Start[15c] A3921069	Phase 3[a]	Active RA MTX-naïve	24 months (month 12 data-cut presented in this analysis)	None	vdH mTSS change from baseline and ACR70 response rates at month 6
ORAL Sync[19] A3921046	Phase 3[a]	Active RA DMARD-IR	12 months	csDMARDs	ACR20 response rates and DAS28-4(ESR) < 2.6 at month 6; HAQ-DI change from baseline at month 3
ORAL Standard[16] A3921064	Phase 3[a]	Active RA MTX-IR	12 months	MTX	ACR20 response rates and DAS28-4(ESR) < 2.6 at month 6; HAQ-DI change from baseline at month 3
ORAL Scan[18] A3921044	Phase 3[a]	Active RA ≥3 distinct joint erosions MTX-IR	24 months	MTX	ACR20 response rates, vdH mTSS change from baseline and DAS28-4(ESR) < 2.6 at month 6; HAQ-DI change from baseline at month 3
ORAL Step[17] A3921032	Phase 3[a]	TNFi-IR	6 months	MTX	ACR20 response rates, HAQ-DI change from baseline and DAS28-4(ESR) < 2.6 at month 3
ORAL Sequel[20] A3921024	LTE[f]	Participation in a qualifying Phase 1, 2 or 3 study	Long-term	Concomitant therapy with csDMARDs was permitted	Laboratory safety data (chemistry, hematology, etc.) and adverse event reports
A3921041[29]	LTE[fd]	Participation in a qualifying Phase 1, 2 or 3 study	Long-term	Concomitant therapy with csDMARDs was permitted	Adverse event reports, laboratory safety data and vital signs

[a]Randomized, double-blind, placebo-controlled, parallel-group studies; [b]active comparator = 40 mg QOW adalimumab; [c]active comparator = MTX 10–20 mg/week; [d]study in Japanese patients; [e]all patients received open-label tofacitinib weeks 1 to 12, and randomized to receive atorvastatin or matching placebo weeks 6 to 12; [f]non-randomized, open-label, parallel-group study.

ACR indicates American College of Rheumatology; DAS28-4(ESR), disease activity score in 28 joints using the erythrocyte sedimentation rate; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD-IR, inadequate response to disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire—Disability Index; MTX, methotrexate; MTX-IR, inadequate response to MTX; QOW, every other week; TNFi-IR, inadequate response to tumor necrosis factor inhibitors; vdH mTSS, van der Heijde modified total Sharp score.

cardiovascular events (MACE), and all-cause mortality. 95% confidence intervals (CI) for IRs were calculated using the maximum likelihood method. Descriptive comparisons were made between the LA and RoW populations of patients with RA; statistical comparisons were not performed.

RESULTS

Patients

Data from patients recruited in LA countries (n = 984) and the RoW (n = 4687) in the 14 Phase 2, Phase 3 and LTE tofacitinib clinical studies were included in the analysis. Baseline demographic characteristics were generally similar between LA and the RoW patient populations (Table 2). Total tofacitinib exposure was 2148.33 patient-years in the LA population and 10515.68 patient-years in the RoW population; mean exposure was 2.18 years and 2.24 years, respectively.

Safety

The IRs for safety events of special interest in patients receiving tofacitinib were generally similar between the LA and RoW populations, with 95% CIs that were generally overlapping (Table 3). IRs for opportunistic infections were similar for LA patients and RoW patients. Opportunistic infections that occurred in LA patients were esophageal candidiasis (n = 4; one patient had 2 separate events), sepsis (n = 1), pneumonia (n = 1), and separate events of HZ (n = 1) and cytomegalovirus hepatitis (n = 1) in the same patient.

IRs for discontinuation due to AEs, SIEs, tuberculosis, all HZ, serious HZ, malignancies (excluding NMSC) and MACE were numerically lower for LA patients compared with RoW patients. No cases of lymphoma were reported in the LA population; the IR for the RoW population was 0.08 (95% CI: 0.04–0.15; Table 3).

In the LA cohort, 10 patients died during the studies (IR for all-cause mortality 0.47 [95% CI: 0.25–0.87]), accounting for 30 days after the last dose of tofacitinib, compared with 25 patients (IR 0.24 [95% CI: 0.16–0.35]) from the RoW population (Table 3). Cause of death in LA patients was determined by the investigator to be related to tofacitinib treatment in 5 of the 10 cases—three cases of pneumonia, one case of appendicitis, and one case of cardio-respiratory arrest (investigator assessment). Causes of death for patients in the LA and RoW cohorts are listed in Table 4.

TABLE 2. Demographics and Baseline Disease Characteristics for Patients from LA and Patients from RoW

	Latin America (N = 984)	Rest of World (N = 4687)
Age (years), mean (range)	48.7 (18.0–77.0)	53.0 (18.0–86.0)
Gender, n (%)		
Male	86 (8.7)	873 (18.6)
Female	898 (91.3)	3814 (81.4)
RA duration (years), mean (range)	8.1 (0.0–43.6)	8.6 (0.0–65.0)
HAQ-DI, mean (SD)	1.7 (0.7)	1.5 (0.7)
DAS28-4(ESR), mean (SD)	6.5 (1.1)	6.4 (0.9)
CRP (mg/L), mean (SD)	20.2 (25.3)	17.9 (22.8)
Prior MTX, n (%)	184 (18.7)	813 (17.3)
Concomitant corticosteroid at baseline, n (%)	159 (64.6)	607 (58.6)

CRP indicates C-reactive protein; DAS28-4(ESR), disease activity score in 28 joints using the erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire—Disability Index; MTX, methotrexate; RA, rheumatoid arthritis; SD, standard deviation.

TABLE 3. Incidence Rates for Safety Events of Special Interest for Patients from LA and Patients from RoW

Patients With Event (n) IR (95% CI), Patients With Events/100 Patient-Years	Latin America (N = 984)	Rest of World (N = 4687)
Total exposure, patient-years	2148.33	10,515.68
Mean exposure, patient-years	2.18	2.24
Discontinuation due to AEs	111	815
	5.22 (4.33–6.29)	7.84 (7.32–8.40)
Serious infection events	50	318
	2.35 (1.78–3.11)	3.05 (2.73–3.40)
Tuberculosis	1	25
	0.05 (0.01–0.33)	0.24 (0.16–0.35)
Opportunistic infections[a]	6	26
	0.28 (0.13–0.62)	0.25 (0.17–0.36)
All herpes zoster	69	435
	3.39 (2.68–4.29)	4.39 (4.00–4.83)
Serious herpes zoster	2	33
	0.09 (0.02–0.37)	0.31 (0.22–0.44)
Malignancies (excluding NMSC)	9	98
	0.42 (0.22–0.81)	0.93 (0.77–1.14)
Lymphoma	0	8[b]
	N/A	0.08 (0.04–0.15)
MACE[c]	1	37
	0.08 (0.01–0.56)	0.53 (0.39–0.73)
All-cause mortality[d]	10	25
	0.47 (0.25–0.87)	0.24 (0.16–0.35)

[a]Excluding tuberculosis; [b]an additional 2 cases of lymphoma have been reported from the ongoing blinded Phase 3 study (A3921069); [c]exposure for MACE is lower than for other safety events as MACE adjudication only applied to data after February 25, 2009; exposure in LA population = 1274.39 patient-years; exposure in RoW population = 7001.95 patient-years; [d]within 30 days of last study drug.

AE indicates adverse event; CI, confidence interval; IR, incidence rate; N/A, not applicable; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer.

DISCUSSION

The safety profile of tofacitinib across the global clinical trial program in patients with RA has been well characterized and previously reported.[20,30–32] This pooled, post hoc analysis of tofacitinib was conducted to compare the safety of tofacitinib in LA versus RoW, and includes one of the largest cohorts of DMARD-treated patients with RA from LA countries to be evaluated.

Our findings suggest that the safety profile of tofacitinib in patients with RA is generally similar between patients from LA and patients from RoW. The IRs for discontinuation due to AEs, SIEs, tuberculosis, malignancies (excluding NMSC) and MACE reported for patients receiving tofacitinib in the LA and RoW populations are generally consistent with those reported for biologic DMARDs in the global population of patients with RA.[32–35] The rate of opportunistic infections in LA tofacitinib-treated patients was similar compared with the RoW population and consistent with the global analysis of tofacitinib-treated patients.[36]

TABLE 4. Causes of Death in Patients from LA and Patients from RoW

	No. Patients	
Cause of Death[a]	**Latin America**	**RoW**
Acute myocardial infarction		1
Acute respiratory distress syndrome		1
Appendicitis	1	
Arrhythmia		1
Arteriosclerosis		1
Aspiration		1
Bronchopneumonia		1
Cardiac arrest	1	1
Cardiac failure acute		1
Cardiopulmonary failure		1
Cardio-respiratory arrest	1	1
Cerebrovascular accident	1	
Completed suicide		2
Death[b]	1	
Dyspnea	1	
Encephalitis		1
Gallbladder cancer	1	
Hemorrhage intracranial		1
Lung cancer metastatic		3
Pancreatitis acute		1
Pneumonia	3	2
Pulmonary embolism		1
Renal failure acute		1
Respiratory failure		1
Road traffic accident		1
Sepsis		1
Total deaths	10	25

[a]The preferred term adverse event leading to death is listed for deaths occurring within 30 days of last study drug; [b]70-year-old patient died suddenly, cause unknown.

Although the LA region is associated with increased risk of tuberculosis,[37] and the risk of tuberculosis when using immunomodulatory therapies is proportional to the background rate of tuberculosis,[38] the rate of tuberculosis observed in LA tofacitinib-treated patients in this analysis was low, and similar to that observed for RoW patients (which included patients from countries in Asia and Eastern Europe that also have high rates of tuberculosis and other opportunistic infections). Given the increased risk of tuberculosis in LA countries, it may be possible that physicians in LA are inherently more aware of the relevant risks of immunosuppressant therapy for patients with RA. This may contribute to the similar observed rate of tuberculosis compared to the RoW population, despite the high background tuberculosis prevalence in LA. It should also be noted that patients who had tuberculosis at the screening visit were excluded from Phase 2 tofacitinib studies; however, in tofacitinib Phase 3 studies, patients with tuberculosis at screening were permitted entry after they received preventative isoniazid therapy. No patients in this group developed tuberculosis. These observations also support the recent ACR recommendation that patients with RA initiating tofacitinib therapy should undergo screening for tuberculosis (and treatment, if necessary) as is recommended for patients undergoing therapy with bDMARDs.[26]

The all-cause mortality rate for patients with RA from LA countries was numerically higher than that for patients with RA in the RoW population. This observed difference may be a consequence of differences between the two populations in terms of comorbidities or socioeconomic factors including increased mortality rates due to infection which are observed in many LA countries.[39] The IR for all-cause mortality (death within 30 days post-last dose) for tofacitinib in the LA population was similar to rates reported with TNFi and other bDMARDs.[32–34,40]

It is known that patients with RA have an increased risk of HZ compared with the general population, and that certain RA therapies can exacerbate this risk.[30,41] In this analysis, the IRs of all HZ events with tofacitinib in both the LA and RoW populations were higher than those reported for bDMARDs.[42] Rates of HZ reported in this analysis are consistent with crude incidence rates for HZ reported with baricitinib in patients with RA,[43] suggesting that the increased rate of HZ may be a class effect of JAK inhibitors and not specific to tofacitinib. The IRs for all HZ events and serious HZ events were numerically lower in the LA population versus RoW population. Data presented here are also consistent with a pooled analysis of tofacitinib Phase 2 and Phase 3 studies comparing US versus RoW populations,[44] where the IRs for all HZ and serious HZ were numerically lower in the US population versus the RoW (non-US) population. In the tofacitinib RA development program, the overall risk of HZ was increased and particularly in patients from Japan and Korea.[30] Additionally, genetic analysis of ~5300 tofacitinib-treated patients identified that interleukin-17RB polymorphism associated with increased risk of HZ was more prevalent in East Asian patients.[45] In patients with RA initiating therapy with tofacitinib, zoster vaccination has been shown to be effective in boosting immunity against varicella zoster virus.[46]

A pooled analysis of data from tofacitinib Phase 1, 2, 3, and LTE studies (cut-off date was April 2014 and included up to 72 months of follow-up) identified geographic region (Asia—specifically Japan/Korea), baseline glucocorticoid use, higher doses of tofacitinib, age, and background DMARD use as risk factors for HZ in tofacitinib-treated patients (after adjusting for other covariates). This analysis suggested that patients using tofacitinib monotherapy without glucocorticoids have a lower risk of developing HZ.[42] Additionally, a post hoc analysis showed that the following baseline risk factors were associated with the development of HZ in tofacitinib-treated LA patients: increased age; age category (≥50 vs. <50 years) and baseline corticosteroid use.[41] Therefore, physicians should consider these risk factors when deciding treatment regimens for patients with RA.

A number of limitations of the current analysis should be considered. This was a retrospective, post hoc analysis of clinical studies that were not designed for the purpose of comparing LA and RoW data. Data were pooled across Phase 2, Phase 3, and LTE studies; therefore, safety data in LA patients included in this analysis are subject to different patient populations, including differences in previous treatment and failed treatments, different concomitant therapies and different study durations. The LA patient population in this analysis was substantially smaller than the RoW population and had less extent and duration of exposure. These factors should be considered when interpreting the findings; in particular, any comparison of long-latency AEs should be made with caution. Safety data for the LA subpopulation receiving tofacitinib were not compared with data from the placebo, adalimumab and methotrexate arms included in the original studies due to the small sample sizes. Furthermore, no formal statistical comparisons of safety data in LA patients versus RoW patients were conducted due to the relatively low number of patients in the LA patient population compared with the RoW population.

This analysis represents one of the largest datasets comparing the safety of DMARD therapy for RA in the LA population versus the RoW population. Data such as these are important in assessing the long-term safety and tolerability of novel therapies, including tofacitinib, for the treatment of patients with RA in LA. In summary, these data provide evidence that tofacitinib has a consistent safety profile across LA and RoW patient populations.

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