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ORIGINAL RESEARCH

Adverse events of special interest in clinical trials of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and psoriasis with 37 066 patient-years of tofacitinib exposure

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ABSTRACT

Objectives To analyse adverse events (AEs) of special interest across tofacitinib clinical programmes in rheumatoid arthritis (RA), psoriatic arthritis (PsA), ulcerative colitis (UC) and psoriasis (PsO), and to determine whether the incidence rates (IRs; unique patients with events per 100 patient-years) of these events are consistent across diseases.

Methods The analysis included data from patients exposed to ≥1 dose of tofacitinib in phase 1, 2, 3 or 3b/4 clinical trials and long-term extension (LTE) studies (38 trials) in RA (23 trials), PsA (3 trials), UC (5 trials) and PsO (7 trials). All studies were completed by or before July 2019, except for one ongoing UC LTE study (data cut-off May 2019). IRs were obtained for AEs of special interest.

Results 13 567 patients were included in the analysis (RA: n=7964; PsA: n=783; UC: n=1157; PsO: n=3663), representing 37 066 patient-years of exposure. Maximum duration of exposure was 10.5 years (RA). AEs within the 'infections and infestations' System Organ Class were the most common in all diseases. Among AEs of special interest, IRs were highest for herpes zoster (non-serious and serious; 3.6, 1.8, 3.5 and 2.4 for RA, PsA, UC and PsO, respectively) and serious infections (2.5, 1.2, 1.7 and 1.3 for RA, PsA, UC and PsO, respectively). Age-adjusted and sex-adjusted mortality ratios (weighted for country) were ≤0.2 across cohorts.

Conclusions The tofacitinib safety profile in this analysis was generally consistent across diseases and with longer term follow-up compared with previous analyses.

Key messages

What is already known about this subject?

- Long-term extension studies and integrated analyses of data from the tofacitinib clinical programmes for rheumatoid arthritis (RA), psoriatic arthritis (PsA), ulcerative colitis (UC) and psoriasis (PsO) have demonstrated that the safety profile of tofacitinib is stable over time and is consistent across the studies for each of these indications.

What does this study add?

- This study compares and contrasts adverse events (AEs) of special interest for tofacitinib across the RA, PsA, UC and PsO clinical programmes using data from randomised controlled clinical trials and long-term extension studies.

How might this impact on clinical practice or future developments?

- The data from this analysis of the RA, PsA, UC and PsO clinical programmes demonstrate a consistent safety profile across indications.
- The findings reinforce the recommendations on screening, testing and monitoring given in the tofacitinib prescribing information.
- Continued surveillance is required to monitor the incidence of AEs of special interest with longer term use of tofacitinib in clinical practice and registries.

INTRODUCTION

Janus kinase (JAK) inhibitors join a growing number of advanced targeted therapies that are indicated for multiple immune-mediated inflammatory diseases.[1] Evaluation of the safety risks associated with long-term exposure across diseases is important because the patient populations under treatment differ in many respects (eg, age, use of concomitant immunosuppressive agents, degree of inflammation and the prevalence of other factors such as smoking, alcohol use and obesity). These factors may be responsible for potential differences in a drug's risk–benefit profile across disease populations, which might affect patient management.

Tofacitinib is an oral JAK inhibitor. Tofacitinib is approved for use in adults with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ulcerative colitis (UC) and in children with polyarticular course juvenile idiopathic arthritis,[2] but not for psoriasis (PsO), with the exception of Russia where it is approved for use in moderate to severe plaque PsO.[3]

Long-term extension (LTE) studies of tofacitinib included patients with RA, PsA, UC and PsO, with exposures up to 9.5, 3, 5.9 and 5.5 years, respectively, and demonstrated a consistent safety profile over time.[4–7] The objectives of this analysis were to provide a comparison of adverse events (AEs) of special interest from integrated pooled studies of the tofacitinib clinical programmes in RA, PsA, UC and PsO[8–11]; to determine whether the incidence rates (IRs; unique patients with events per 100 patient-years) of these events remain consistent across diseases after longer term exposure to tofacitinib; and to understand what factors might contribute to any differences.

METHODS

Patients and studies

This exploratory analysis includes pooled data for patients who received ≥1 dose of tofacitinib in clinical trials and open-label LTE studies across each disease. Full details of the individual studies have been published previously (online supplemental table S1).

All cohorts included patients aged ≥18 years who received tofacitinib as monotherapy (RA, UC and PsO) or with background conventional synthetic disease-modifying antirheumatic drugs (csDMARDs; RA, PsA). All studies had been completed by July 2019, with the exception of one ongoing LTE study in the UC cohort (data cut-off 27 May 2019). Final data for the RA and PsA cohorts are from 18 April 2019 and 31 July 2019, respectively. Final data for the PsO cohort are from 18 August 2016, as the programme was terminated when the objectives of characterising long-term safety and tolerability were met.

All patients provided written, informed consent.

Dosing

Patients received tofacitinib 0.5, 1, 2, 3, 5, 10, 15 or 30 mg two times per day or 20 mg once a day in phase 1/2 studies, and tofacitinib 5 or 10 mg two times per day or 11 mg extended-release once a day in phase 3 and phase 3b/4 studies (online supplemental table S1). In LTE studies, the tofacitinib dose could be switched for efficacy or safety reasons. Data are reported for the following treatment groups: tofacitinib 5 mg two times per day (average total daily dose <15 mg); tofacitinib 10 mg two times per day (average total daily dose ≥15 mg); and all tofacitinib doses (ie, average tofacitinib 5 mg two times per day and average tofacitinib 10 mg two times per day populations pooled).

Analysis of AEs

The analyses for each disease have been described previously.[8–11] Data on AEs and serious AEs (SAEs) were collected and coded using Medical Dictionary for Regulatory Activities (MedDRA) V.22.0 (RA, PsA and UC) or V.20.0 (PsO). AEs, SAEs and deaths occurring on treatment or within 28 days after discontinuation of tofacitinib were reported. Adjudication of tuberculosis, opportunistic infections (OIs; excluding tuberculosis), malignancies (excluding non-melanoma skin cancer (NMSC)), NMSC, melanoma, lymphoma/lymphoproliferative disorders, gastrointestinal perforation events and major adverse cardiovascular events (MACEs; total MACE defined as composite of myocardial infarction, stroke and cardiovascular deaths) has been described previously.[8]

Statistical analyses

IRs for AEs, SAEs, discontinuations due to AEs, deaths and AEs of special interest were reported as the number of unique patients with events per 100 patient-years. Total follow-up time was calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cut-off date, whichever occurred earlier. Events occurring after the 28-day post-treatment period are not included in the IR calculation. Exact Poisson, adjusted for exposure, was used to calculate 95% CIs for the crude IR. Kaplan-Meier curves and cumulative probability plots were generated for analysis of time to events.

Age-adjusted and sex-adjusted standardised mortality ratios (SMRs) were calculated using the observed rates weighted by country, compared with the expected rates for the general population based on the WHO country-specific mortality rates for 2012.[12]

For malignancies, standardised incidence ratios (SIRs) were calculated as the ratio of observed adjudicated malignancies to expected malignancies, based on rates reported by the US National Cancer Institute Surveillance and Epidemiology and End Results (SEER) database, 2013–2017 (RA, PsA and UC) and 2008–2012 (PsO)[13]; 95% CIs for SIRs were calculated based on a Poisson distribution.

Patient and public involvement

Patients and the public were not involved in the design, analysis or data interpretation of this study.

RESULTS

Patients

A total of 13 567 patients received tofacitinib and were included in the analysis (RA: n=7964; PsA: n=783; UC: n=1157; PsO: n=3663). Total tofacitinib exposure (patient-years) and median (range) length of exposure by cohort were as follows: 23 497 patient-years, with median exposure of 2.1 years (0–10.5 years) for RA; 2038 patient-years, with median exposure of 3.0 years (0–4.8 years) for PsA; 2581 patient-years, with median exposure

Table 1 Baseline characteristics and demographics

Characteristics	RA (N=7964)	PsA (N=783)	UC (N=1157)	PsO (N=3663)
Age, years				
Mean (SD)	52.6 (12.1)	48.7 (12.0)	41.3 (13.9)	44.8 (12.9)
Median (range)	53.0 (18–86)	50.0 (18–78)	39.0 (18–81)	45.0 (18–82)
<65 at baseline, n (%)	6694 (84.1)	711 (90.8)	1080 (93.3)	3443 (94.0)
≥65 at baseline, n (%)	1270 (15.9)	72 (9.2)	77 (6.7)	220 (6.0)
Female, n (%)	6522 (81.9)	428 (54.7)	478 (41.3)	1117 (30.5)
Region, n (%)				
Europe	2180 (27.4)	542 (69.2)*	686 (59.3)	1563 (42.7)
USA/Canada	2021 (25.4)	158 (20.2)	241 (20.8)	1559 (42.6)
Asia	1775 (22.3)†	15 (1.9)	123 (10.6)	185 (5.1)
Latin America	1246 (15.6)	68 (8.7)	NA	356 (9.7)
Rest of the world	742 (9.3)	NA	107 (9.2)	NA
BMI (kg/m^2), mean (range)	27.1 (12.1–70.8)	29.6 (17.0–54.6)	24.8 (15.8–55.0)	29.9 (15.4–64.8)
BMI ≥30 kg/m^2, n (%)	2138 (26.8)	333 (42.5)	159 (13.8)	1544 (42.2)
Disease duration (years), mean (range)	8.1 (0.0–65.7)	7.7 (0.2–43.4)	8.2 (0.4–42.5)	18.3 (0.6–68.1)
CRP (mg/L), median (Q1–Q3)	9.2 (3.8–22.8)	4.8 (1.7–12.6)	4.5 (1.7–11.5)	2.7 (1.1–6.5)
Smoking status, n (%)				
Never smoked	4996 (62.7)	485 (61.9)	740 (64.0)	1412 (38.5)
Smoker	1366 (17.2)	140 (17.9)	59 (5.1)	1380 (37.7)
Ex-smoker	1388 (17.4)	158 (20.2)	357 (30.9)	871 (23.8)
Unknown	214 (2.7)	0 (0.0)	1 (0.1)	0 (0.0)
Prior therapy, n (%)				
Methotrexate	6657 (83.6)	725 (92.6)	NA	1157 (31.6)
Non-bDMARD (non-methotrexate)	3739 (46.9)	372 (47.5)	NA	390 (10.6)
Thiopurines	NA	NA	823 (73.2)	NA
TNFi	1245 (15.6)	377 (48.1)	612 (54.4)	580 (15.8)
Non-TNFi bDMARD	414 (5.2)	46 (5.9)	NA	214 (5.8)
Concomitant medications				
Corticosteroids, n (%)	4254 (53.4)	171 (21.8)	523 (45.2)	NA‡
Corticosteroids dose (mg/day), mean (range)	6.5 (0.01–200.0)	1.4 (0.0–20.0)	16.0 (2.0–30.0)	NA‡

*Also includes Australia and Russia.
†East/South Asia.
‡Concomitant corticosteroid use was not permitted in the PsO studies.
bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; CRP, C-reactive protein; N, number of patients in the disease cohort (note that N varies for some variables); n, number of patients with each characteristic; NA, not applicable; PsA, psoriatic arthritis; PsO, psoriasis; Q, Quarter; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor; UC, ulcerative colitis.

of 1.7 years (0–6.8 years) for UC; and 8950 patient-years, with median exposure of 2.4 years (0–5.7 years) for PsO.

Baseline characteristics and demographics for each disease are shown in table 1. The RA cohort had a higher proportion of females than other cohorts (81.9% vs 54.7%, 41.3% and 30.5% in the PsA, UC and PsO cohorts, respectively) and an approximately twofold to fivefold higher proportion of patients who had enrolled at centres in Asia. Patients with RA were also older than those in the other cohorts, with 15.9% of patients aged ≥65 years, vs 6.0%–9.2% for the other cohorts. Approximately 40% of patients in the PsA and PsO cohorts had body mass index ≥30 kg/m^2, and a ≥2-fold higher proportion of patients with PsO were current smokers versus other cohorts. Mean disease duration was approximately 8 years for all cohorts except for PsO, for which the mean duration was 18.3 years. C-reactive protein levels were highest in the RA cohort; there was a wide range of C-reactive protein concentrations for all diseases. The range of permitted concomitant medications administered was as expected for each disease, except for PsO, for which the study protocols did not permit background corticosteroid

Table 2 IRs (95% CI) of AEs and SAEs (all cause)

	RA (N=7964)	PsA (N=783)	UC (N=1157)	PsO (N=3663)
Total tofacitinib exposure, patient-years	23 497	2038	2581	8950
Median exposure, years	2.1	3.0	1.7	2.4
Discontinuations due to AEs, IR (95% CI) (n)	7.2 (6.9 to 7.6) (1705)	3.8 (3.0 to 4.8) (80)	4.1 (3.3 to 4.9) (108)	5.7 (5.3 to 6.3) (530)
SAEs,* IR (95% CI) (n)	9.0 (8.6 to 9.4) (1913)	7.0 (5.8 to 8.2) (135)	8.5 (7.4 to 9.8) (210)	5.5 (5.0 to 6.0) (484)
Mortality,* IR (95% CI) (n)	0.2 (0.2 to 0.3) (59)	0.1 (0.0 to 0.3) (2)	0.1 (0.0 to 0.3) (2)	0.2 (0.1 to 0.3) (17)

*Within 28 days of the last dose of study drug.
AE, adverse event; IR, incidence rate (unique patients with events per 100 patient-years); n, unique number of patients with event; N, number of patients in the disease cohort; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SAE, serious adverse event; UC, ulcerative colitis.

use. Almost all patients in the RA and PsA cohorts had previously received methotrexate, and approximately half of patients in the PsA and UC cohorts had previously received tumour necrosis factor inhibitors (TNFi). Mean corticosteroid dose was highest in the UC cohort (16.0 mg/day) and lowest in the PsA cohort (1.4 mg/day), in which only 21.8% of patients were receiving concomitant corticosteroids.

AEs, SAEs, discontinuations and deaths

For details of AEs, see the online supplemental material.

The IRs for SAEs and discontinuations due to AEs for the all tofacitinib groups were highest for the RA cohort (SAEs: 9.0 vs 5.5–8.5; discontinuations due to AEs: 7.2 vs 3.8–5.7 for the other diseases; table 2).

All-cause mortality risk was similar across cohorts (table 2) and tofacitinib doses (online supplemental figures S1A,B). The most common cause of death within the 28-day risk period (by MedDRA System Organ Class) was cardiac, for both RA (n/N=20/7964; 0.3%) and PsO (n/N=7/3663; 0.2%). Two deaths occurred within the 28-day risk period in the PsA (cardiac arrest and chronic obstructive pulmonary disease) and UC (aortic dissection and pulmonary embolism (PE)) cohorts. Age-adjusted and sex-adjusted SMRs (95% CI) were as follows: 0.2 (0.2–0.3) for RA, 0.2 (0.0–0.4) for PsA, 0.1 (0.0–0.5) for UC and 0.2 (0.1–0.4) for PsO.

Infections and serious infection events (SIEs)

The SIEs IR was highest for the RA cohort (2.5; 95% CI 2.3 to 2.7; table 3). The five most common SIEs per cohort were pneumonia (n=131), herpes zoster (HZ; n=44), urinary tract infection (n=31), cellulitis (n=31) and gastroenteritis (n=24) for RA; pneumonia (n=4), gastroenteritis (n=3), appendicitis, cellulitis and influenza (all n=2) for PsA; HZ (n=8), anal abscess (n=4), appendicitis (n=4), gastroenteritis (n=3), and cellulitis, sinusitis and *Clostridium difficile* (all n=2) for UC; and pneumonia (n=27), appendicitis (n=11), HZ (n=10), diverticulitis (n=9) and cellulitis (n=7) for PsO. Subanalyses of SIEs, according to age and by concomitant corticosteroid use, are shown in table 4. Across cohorts, the SIEs IR was highest in the ≥65 years age group; within this age group, the IR was higher in the RA versus PsA, UC and PsO cohorts. The IR for SIEs with concomitant corticosteroid use was higher in the RA versus PsA and UC cohorts. When no concomitant corticosteroids were used, IRs for SIEs were similar between the RA and UC cohorts, and lower in the PsA cohort.

HZ IRs (non-serious and serious) ranged from 1.8 for PsA to 3.6 and 3.5 for RA and UC, respectively (table 3). Adjudicated HZ infection types included 49 multidermatomal (ie, non-adjacent dermatomes or >2 adjacent dermatomes) and 8 disseminated (ie, >6 dermatomes or other organ involvement) cases out of 795 HZ cases for RA; 4 multidermatomal and 2 disseminated cases out of 36 HZ cases for PsA; 17 multidermatomal and 7 disseminated cases out of 87 HZ cases for UC; and 23 multidermatomal and 3 disseminated cases out of 209 HZ cases for the PsO cohort.

Cases of adjudicated active tuberculosis were observed in the RA (n=38; IR: 0.2) and PsO (n=1; IR: 0.0) cohorts only (table 3). Eighteen patients in the RA cohort had extrapulmonary/disseminated tuberculosis within the 28-day risk period. Most cases of tuberculosis among patients with RA occurred in patients receiving the average 10 mg two times per day dose and in regions of high prevalence of tuberculosis. Four patients in the RA cohort with a positive test for tuberculosis at screening who were receiving adequate prophylactic treatment went on to develop active tuberculosis infection. The single case of adjudicated tuberculosis in the PsO cohort was reported in a patient receiving the average tofacitinib 10 mg two times per day dose and was a de novo infection.

The IR for adjudicated OIs (excluding tuberculosis) was fourfold to fivefold higher in the UC cohort (1.6 vs 0.3 (PsA and PsO) and 0.4 (RA); table 3), and this was largely accounted for by adjudicated HZ events.

For additional details on SIEs, HZ and adjudicated OIs, see online supplemental figures S1C–F, S2 and table S2.

Malignancies

IRs for adjudicated malignancies (excluding NMSC), NMSC, melanoma and lymphoma/lymphoproliferative disorders were similar across cohorts (table 3). The

Table 3 IRs (95% CI) for AEs of special interest

	RA (N=7964)	PsA (N=783)	UC (N=1157)	PsO (N=3663)
Total tofacitinib exposure, patient-years	23497	2038	2581	8950
Serious infections, IR (95% CI) (n)	2.5 (2.3 to 2.7) (592)	1.2 (0.7 to 1.7) (24)	1.7 (1.2 to 2.3) (45)	1.3 (1.1 to 1.5) (119)
All HZ (non-serious and serious), IR (95% CI) (n)	3.6 (3.3 to 3.8) (795)	1.8 (1.2 to 2.4) (36)	3.5 (2.8 to 4.3) (87)	2.4 (2.0 to 2.7) (209)
Adjudicated OIs excluding tuberculosis, IR (95% CI) (n)	0.4 (0.3 to 0.5) (95)	0.3 (0.1 to 0.7) (7)	1.6 (1.1 to 2.1) (40)*	0.3 (0.2 to 0.5) (29)
Adjudicated tuberculosis, IR (95% CI) (n)	0.2 (0.1 to 0.2) (38)	0.0 (0.0 to 0.2) (0)	0.0 (0.0 to 0.1) (0)*	0.0 (0.0 to 0.1) (1)
Adjudicated malignancies excluding all NMSC, IR (95% CI) (n) n1 (%)	0.7 (0.6 to 0.9) (179) 211 (2.6)	0.7 (0.4 to 1.2) (15) 18 (2.3)	0.6 (0.3 to 1.0) (16)* 20 (1.8)*	0.7 (0.5 to 0.8) (60) 74 (2.0)
Adjudicated NMSC, IR (95% CI) (n) n1 (%)	0.6 (0.5 to 0.7) (133) 135 (1.7)	0.8 (0.4 to 1.3) (16) 16 (2.0)	0.7 (0.4 to 1.1) (19)* 19 (1.7)*	0.7 (0.5 to 0.9) (63) 67 (1.8)
Adjudicated melanoma, IR (95% CI) (n) n1 (%)	0.1 (0.0 to 0.1) (14) 14 (0.2)	0.0 (0.0 to 0.2) (0) 0 (0.0)	0.1 (0.0 to 0.3) (2)* 2 (0.2)*	0.1 (0.0 to 0.1) (5) 5 (0.1)
Adjudicated lymphoma/lymphoproliferative disorders, IR (95% CI) (n) n1 (%)	0.1 (0.0 to 0.1) (12) 19 (0.2)	0.1 (0.0 to 0.3) (1) 1 (0.1)	0.1 (0.0 to 0.3) (2)* 2 (0.2)*	0.02 (0.0 to 0.1) (2) 4 (0.1)
Adjudicated gastrointestinal perforation, IR (95% CI) (n)	0.1 (0.1 to 0.2) (27)	0.1 (0.0 to 0.3)(1)	0.2 (0.1 to 0.5) (6)*	0.1 (0.0 to 0.2) (7)
Adjudicated MACE,† IR (95% CI) (n)	0.4 (0.3 to 0.5) (85)‡	0.3 (0.1 to 0.6) (6)	0.3 (0.1 to 0.5) (7)*	0.3 (0.2 to 0.4) (23)
DVT,§ IR (95% CI) (n)	0.2 (0.1 to 0.2) (37)	0.1 (0.0 to 0.3) (1)	0.0 (0.0 to 0.2) (1)	0.1 (0.0 to 0.1) (6)
PE,§ IR (95% CI) (n)	0.1 (0.1 to 0.2) (31)	0.1 (0.0 to 0.3) (1)	0.2 (0.0 to 0.4) (4)	0.1 (0.0 to 0.2) (9)

*N=1124.
†Composite MACE defined as any myocardial infarction, stroke or cardiovascular death.
‡N=7311.
§Previously reported in Mease *et al*[40] (excludes Study A3921133) and Sandborn *et al*.[44]
AE, adverse event; DVT, deep vein thrombosis; HZ, herpes zoster; IR, incidence rate (unique patients with events per 100 patient-years); MACE, major adverse cardiovascular events; N, number of patients in the disease cohort; n, unique number of patients with event (events are counted up to 28 days beyond the last dose or to the data cut-off date, and are included in the calculation of IR); n1, all events, including those occurring outside the 28-day risk period; NMSC, non-melanoma skin cancer; OI, opportunistic infection; PE, pulmonary embolism; PsA, psoriatic arthritis; PsO psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis.

Table 4 IRs (95% CI) for serious infections according to age and concomitant corticosteroid use

	RA	PsA	UC	PsO
Age				
<65 years, IR (95% CI)	N=6694 2.2 (2.0 to 2.4) (n=452)	N=711 1.1 (0.7 to 1.7) (n=21)	N=1080 1.7 (1.2 to 2.3) (n=41)	N=3443 1.2 (1.0 to 1.5) (n=108)
≥65 years, IR (95% CI)	N=1270 4.6 (3.8 to 5.4) (n=140)	N=72 1.7 (0.3 to 4.8) (n=3)	N=77 2.1 (0.6 to 5.3) (n=4)	N=220 2.2 (1.1 to 3.9) (n=11)
Corticosteroid use				
Yes, IR (95% CI)	N=4254 3.0 (2.7 to 3.3) (n=390)	N=171 1.6 (0.7 to 3.4) (n=7)	N=523 1.3 (0.7 to 2.2) (n=14)	–*
No, IR (95% CI)	N=3710 1.9 (1.6 to 2.1) (n=202)	N=612 1.0 (0.6 to 1.6) (n=17)	N=634 2.0 (1.4 to 2.8) (n=31)	–*

*Concomitant corticosteroid use was not permitted in the PsO studies.
IR, incidence rate (unique patients with events per 100 patient-years); n, number of patients with the event (events are counted up to 28 days beyond the last dose or to the data cut-off date); N, number of patients per category in the disease cohort; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis.

most common malignancies, including those reported outside the 28-day risk period, are summarised in the online supplemental material, a listing of malignancies is provided in online supplemental table S3, and time to malignancies, NMSC, melanoma and lymphoma/lymphoproliferative disorders data are shown in online supplemental figure S1G–N.

Age-adjusted and sex-adjusted SIRs based on SEER data for malignancies (excluding NMSC), melanoma and lymphoma are shown in figure 1. The 95% CI for most SIRs included 1.0. SIRs for all malignancies (excluding NMSC) were ≤1.0 for the RA and PsA cohorts. SIRs were generally highest for the UC cohort; however, comparisons are limited by the small number of events and wide CIs.

Other AEs of special interest

IRs for adjudicated gastrointestinal perforation were similar across diseases (table 3) and in patients receiving concomitant non-steroidal anti-inflammatory drugs or corticosteroids (online supplemental table S4).

Adjudicated MACE was reported at similar incidence across the different diseases (table 3). Additional details on MACE for tofacitinib are provided in the online supplemental material.

IRs for DVT ranged from 0.0 (UC) to 0.2 (RA), and IRs for PE ranged from 0.1 (RA, PsA and PsO) to 0.2 (UC) (table 3).

DISCUSSION

This analysis of tofacitinib safety across RA, PsA, UC and PsO demonstrates a generally consistent long-term safety profile, despite differences in patient populations for each cohort in terms of age, region of study enrolment, smoking status, tofacitinib dosing, concomitant use of corticosteroids and prior use of bDMARDs and immunosuppressants. Age-adjusted and sex-adjusted mortality rates indicated no excess mortality, and the overall safety profile was consistent compared with previous analyses for each indication. Additionally, the average tofacitinib 5 and 10 mg two times per day doses were similar in terms of time to mortality, SIEs, all HZ (non-serious and serious) and malignancies (online supplemental figures S1 and S2).

Infections and infestations were the most common treatment-emergent AEs observed across the cohorts, a finding consistent with data for other therapies approved across multiple indications, for example, bDMARDs (eg, adalimumab, etanercept, infliximab, tocilizumab)[14–17] and for other JAK inhibitors approved for the treatment of RA.[18 19] The SIEs IR (2.5) for the RA cohort in this analysis was slightly higher compared with the other disease cohorts, consistent with a long-term safety analysis of adalimumab across these indications.[14] In the RA cohort, the SIEs IR was higher in patients aged ≥65 years versus younger patients, and also higher in those taking concomitant corticosteroids, compared with those not. It is therefore possible that patient characteristics may have contributed to the higher rate of SIEs in the RA cohort compared with the other cohorts (eg, the higher proportion of patients aged ≥65 years in the RA cohort, with prior methotrexate use and with concomitant corticosteroids and/or csDMARDs), although formal statistical analyses of the relationships between baseline characteristics and risk of events were not conducted. Another recent pooled analysis of tofacitinib RA clinical trials identified a higher incidence of SIEs for patients aged ≥65 versus <65 years receiving tofacitinib, consistent with the TNFi comparator arm, and with patients receiving bDMARDs in an RA registry.[20] The SIEs IR in the RA cohort is observed to be similar to that reported in an integrated safety analysis of baricitinib[18 21] and lower than that reported for upadacitinib.[19]

Across diseases, most HZ infections were monodermatomal, consistent with previous studies.[22–24] Rates of all HZ (non-serious and serious) were higher in the RA and UC cohorts versus PsA and PsO. The higher HZ rate in these cohorts is not unexpected, as patients with RA or UC are at increased risk of HZ, compared with the general population.[25] The RA and UC cohorts had the

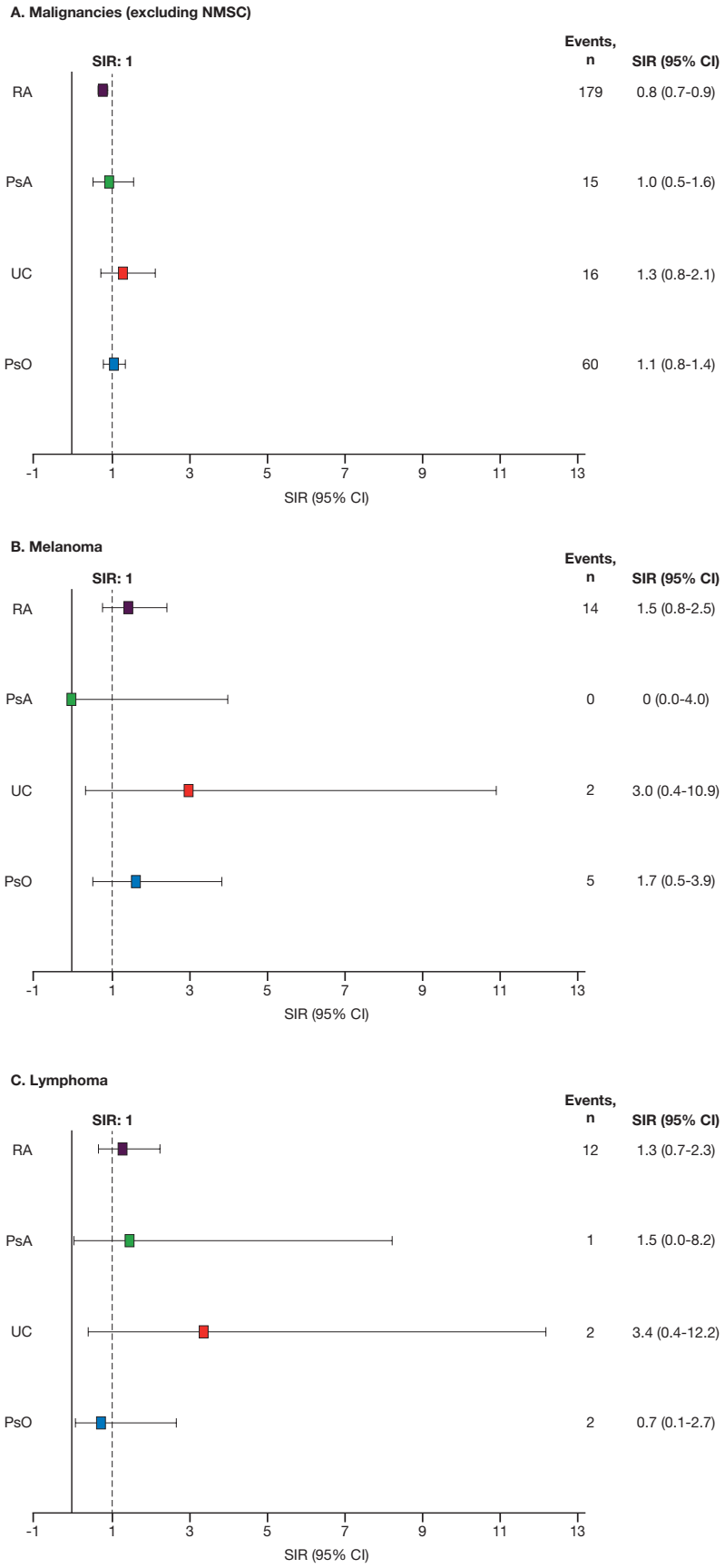

Figure 1 Age-adjusted and sex-adjusted SIRs (95% CI) using SEER registry data for (A) malignancies excluding NMSC, (B) melanoma and (C) lymphoma. n, unique number of patients with event; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SEER, Surveillance, Epidemiology, and End Results; SIR, standardised incidence ratio; UC, ulcerative colitis.

highest proportions of patients who were enrolled at sites in Asia, or were receiving concomitant corticosteroids, characteristics that were associated with an elevated risk of HZ, compared with placebo, in the global tofacitinib clinical development programme and in studies of other JAK inhibitors (enrolment in Asia only).[21–24 26] The HZ IR with tofacitinib reported in this analysis is observed to be similar to that reported for baricitinib and upadacitinib in a meta-analysis of infection risk with JAK inhibitors in RA.[27] However, expression of HZ is reduced with available vaccines, and clinical practice guidelines for rheumatologists and gastroenterologists recommend immunisation before initiating bDMARD or JAK inhibitor treatment.[28–30] The IR for adjudicated OI was several-fold higher for the UC cohort, but this was accounted for by higher incidence of adjudicated OI of HZ among those patients, compared with other cohorts, which may also have been related to the higher mean dose of concomitant corticosteroids for the UC cohort. Adjudicated events of tuberculosis were only reported in the RA and PsO cohorts, and IRs for adjudicated tuberculosis were <1.0 and similar to those previously reported for adalimumab across inflammatory conditions and for baricitinib in RA.[14 18 21] Consistent with a previous analysis,[31] the majority (76%) of tuberculosis AEs reported in the RA cohort occurred in countries with high background prevalence, that is, Brazil, China, India, Korea, the Philippines and Thailand,[32] and most (71%) occurred with the average 10 mg two times per day dose (10 mg two times per day is not the approved dose for RA in most countries). There were no adjudicated events of active tuberculosis in the UC cohort, in which more patients received the average tofacitinib 10 mg two times per day dose than the 5 mg two times per day dose, although smaller cohort sizes and differences in geographical distribution may have also accounted for differences in tuberculosis events between the RA and other cohorts.

Factors that contribute to an increased risk of developing malignancies include age, obesity and immune-mediated inflammatory conditions.[13 33 34] Overall, the age-adjusted and sex-adjusted SIRs based on the SEER registry did not indicate an increasing risk for malignancy with tofacitinib relative to the general USA population, even though numerical differences in baseline risk factors (eg, age, smoking and obesity) were apparent between cohorts. However, the number of patients, length of follow-up and number of events for the PsA, UC and PsO cohorts were substantially less than that for the RA cohort, particularly for UC and PsA; continued surveillance is required to determine the risk of malignancies in patients receiving tofacitinib. SIRs for tofacitinib in this analysis were generally consistent with those reported in previous integrated safety analyses of adalimumab (malignancies excluding NMSC (95% CI): RA 0.84 (0.73 to 0.96), PsA 0.68 (0.22 to 1.59), UC 1.47 (0.95 to 2.17), PsO 0.86 (0.58 to 1.22); lymphoma: RA 2.97 (2.05 to 4.17), PsA 5.88 (0.66 to 21.2), UC 3.52 (0.71 to 10.3), PsO 0.58 (0.01 to 3.22)) and baricitinib (malignancies excluding NMSC (95% CI): RA 1.04 (0.79 to 1.36)), which also used the SEER registry for comparison, but differed in drug exposure and length of follow-up.[14 18] Real-world evidence from the Corrona RA registry has also demonstrated comparable rates of malignancies for tofacitinib and bDMARDs.[35]

Rates of gastrointestinal perforation were <0.3 and were consistent across the tofacitinib RA, PsA, UC and PsO cohorts. The corresponding rate reported in the integrated safety analysis of baricitinib in RA was 0.05 per 100 patient-years (95% CI 0.01 to 0.13),[18] and the IR from clinical trials of tocilizumab in RA was 0.19 per 100 patient-years (95% CI 1.3 to 2.7).[36] However, comparison across study cohorts is limited due to variation in factors known to increase the risk of gastrointestinal perforation, including smoking, non-steroidal anti-inflammatory drug use, corticosteroids and older age.[36 37]

IRs for adjudicated MACE in this analysis were also <0.5 across all cohorts and were consistent with rates reported for bDMARDs[38 39] and other JAK inhibitors.[18 19] Comprehensive analyses of thromboembolic events with tofacitinib treatment across the RA, PsA, UC and PsO clinical programmes are published elsewhere.[40 41] Importantly, data from a large, randomised, prospective, post-authorisation safety study (Study A3921133; NCT02092467) comparing tofacitinib with TNFi in patients with RA who were aged ≥50 years and had ≥1 additional cardiovascular risk factor showed an increased rate for tofacitinib relative to TNFi regarding VTE, MACE and malignancies.[42 43] Given that the underlying mechanism(s) for these AEs remain unknown, the effect of JAK inhibitors on cardiovascular disease and malignancy risk requires further research.

These findings provide the opportunity to compare the long-term safety profile of tofacitinib in different immune-mediated inflammatory diseases. The results of this analysis also reinforce the recommendations given in the tofacitinib prescribing information regarding testing and monitoring for infections (including latent tuberculosis), ensuring that all patients are up to date with HZ and pneumococcal vaccination before initiating tofacitinib in line with current immunisation guidelines, and using tofacitinib with caution in patients at risk of gastrointestinal perforations.[2]

Limitations of the analysis include the shorter exposure time and relatively small tofacitinib treatment groups in patients with PsA, UC and PsO, compared with the larger safety database available for RA. This limits the precision and interpretation of the IRs determined for events with long latency, that is, malignancies. An additional limitation is the lack of placebo comparison due to the designs of some studies in which patients were exposed to placebo for a short period of 3 months before advancing to tofacitinib. Also, use of the average daily dose is not the best way to show a dose relationship for AEs and does not account for dose switching during individual studies, or a change in dose between the index studies and LTEs. Finally, the use of the WHO and SEER data for calculation

of SMRs and SIRs, respectively, may be confounded even after adjusting for age and gender. Longer term follow-up in the UC LTE study, and real-world data in patients with RA, PsA and UC, will provide further information on the safety profile of tofacitinib across indications.

CONCLUSIONS

The tofacitinib safety database used for this analysis provides the largest clinical database for a JAK inhibitor to date, with >13 000 tofacitinib-treated patients across four diseases, including >7000 patients with RA with exposure to tofacitinib for up to 10.5 years and accounting for 37 066 patient-years of tofacitinib exposure. This analysis is the first presentation of tofacitinib safety across RA, PsA, UC and PsO, providing the opportunity to compare long-term safety in different inflammatory diseases. The safety profile of tofacitinib in this analysis was consistent with previous analyses from the individual tofacitinib clinical programmes. An increased risk of certain AEs, such as HZ, was evident, consistent with current tofacitinib prescribing recommendations on screening and prevention of infections in patients considered to be at risk. AEs of special interest occurred at comparable rates across diseases, except for SIEs, which were more common in the RA cohort, and HZ, which was more common in the RA and UC cohorts. The variation of risk factors across diseases, such as age and concomitant corticosteroid and/or csDMARD use, may have contributed to this, and clinicians should take these risk factors into consideration when treating patients. This has also been observed for VTE, which has been identified as an important risk of treatment with tofacitinib. Prescribers should review information pertaining to VTE and tofacitinib in their current local product labelling and individualise treatment decisions by considering risk factors for VTE. In conclusion, this analysis demonstrates a generally consistent safety profile for tofacitinib across indications, and highlights the importance of determining the risk–benefit profile on an individual patient basis before initiating tofacitinib therapy.

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Data availability statement On request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the USA and/or EU, or (2) in programmes that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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