Original research

Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme

Stanley B Cohen,[1] Yoshiya Tanaka ,[2] Xavier Mariette ,[3] Jeffrey R Curtis ,[4] Eun Bong Lee ,[5] Peter Nash ,[6] Kevin L Winthrop ,[7] Christina Charles-Schoeman,[8] Lisy Wang ,[9] Connie Chen,[10] Kenneth Kwok,[10] Pinaki Biswas,[10] Andrea Shapiro,[11] Ann Madsen,[10] Jürgen Wollenhaupt[12]

ABSTRACT

Objective Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). We report the largest integrated safety analysis of tofacitinib, as of March 2017, using data from phase I, II, III, IIIb/IV and long-term extension studies in adult patients with RA.

Methods Data were pooled for patients with RA who received ≥1 tofacitinib dose. Incidence rates (IRs; patients with events/100 patient-years [PY]; 95% CIs) of first-time occurrences were obtained for adverse events (AEs) of interest.

Results 7061 patients received tofacitinib (total exposure: 22 875 PY; median [range] exposure: 3.1 [0 to 9.6] years). IRs (95% CI) for serious AEs, serious infections, herpes zoster (all), opportunistic infections (excluding tuberculosis [TB]) and TB were 9.0 (8.6 to 9.4), 2.5 (2.3 to 2.7), 3.6 (3.4 to 3.9), 0.4 (0.3 to 0.5) and 0.2 (0.1 to 0.2), respectively. IRs (95% CI) for malignancies (excluding non-melanoma skin cancer [NMSC]), NMSC and lymphomas were 0.8 (0.7 to 0.9), 0.6 (0.5 to 0.7) and 0.1 (0.0 to 0.1), respectively. IRs (95% CI) for gastrointestinal perforations, deep vein thrombosis, pulmonary embolism, venous thromboembolism, arterial thromboembolism and major adverse cardiovascular events were 0.1 (0.1 to 0.2), 0.2 (0.1 to 0.2), 0.1 (0.1 to 0.2), 0.3 (0.2 to 0.3), 0.4 (0.3 to 0.5) and 0.4 (0.3 to 0.5), respectively. IR (95% CI) for mortality was 0.3 (0.2 to 0.3). IRs generally remained consistent across 6-month intervals to >78 months.

Conclusion This represents the largest clinical dataset for a JAK inhibitor in RA to date. IRs remained consistent with previous reports from the tofacitinib RA clinical development programme, and stable over time.

Trial registration numbers NCT01262118; NCT01484561; NCT00147498; NCT00413660; NCT00550446; NCT00603512; NCT00687193; NCT01164579; NCT00976599; NCT01059864; NCT01359150; NCT02147587; NCT00960440; NCT00847613; NCT00814307; NCT00856544; NCT00853385; NCT01039688; NCT02187055; NCT00413699; NCT00661661.
For summary of phase I, phase II, phase III, phase IIIb/IV and LTE studies included in the integrated safety analysis, see online supplemental table 1.

Key messages

What is already known about this subject?
► The efficacy and safety of tofacitinib 5 and 10 mg twice daily have been demonstrated in patients with moderately to severely active rheumatoid arthritis (RA) in previous phase II, III and IIIb/IV randomised controlled trials (RCTs) and open-label, long-term extension (LTE) studies. Safety was generally similar with tofacitinib, compared with biological disease-modifying antirheumatic drugs (bDMARDs); however, an increased risk of certain types of infection (eg, herpes zoster [HZ]) was observed.
► An integrated analysis of the long-term safety of tofacitinib in patients with RA was carried out in 2015, using RCT/LTE data, with up to 8.5 years of tofacitinib exposure. Adverse events (AEs) were generally stable over time; no new safety risks were observed, compared with previous analyses of tofacitinib safety.

What does this study add?
► This integrated safety summary of completed RCTs and LTE studies, using data up to 2017, spans 9.5 years of cumulative tofacitinib exposure in >7000 patients, and represents the largest clinical dataset for a Janus kinase (JAK) inhibitor in RA to date.
► Overall, incidence rates (IRs; patients with events/100 patient-years [PY] of exposure) of AEs of special interest, discontinuations due to AEs and mortality with tofacitinib were consistent with those reported previously. With the exception of HZ (non-serious and serious), serious infections, malignancies (excluding non-melanoma skin cancer [NMSC]) and NMSC, IRs for AEs of special interest (including thromboembolic events) were <0.5/100 PY.

How might this impact on clinical practice?
► This analysis is the largest integrated safety analysis of tofacitinib to date. With the exception of HZ, rates of safety events were generally similar with tofacitinib, compared with bDMARDs and other JAK inhibitors used to treat RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and debilitating autoimmune disease affecting approximately 0.24% of the global population.[1] Current treatment guidelines recommend biological disease-modifying antirheumatic drugs (bDMARDs), such as tumour necrosis factor inhibitors (TNFi), or targeted synthetic DMARDs, such as Janus kinase (JAK) inhibitors, in patients who have failed treatment with conventional synthetic DMARDs (csDMARDs).[2 3]

Tofacitinib is an oral JAK inhibitor for the treatment of RA. The efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) administered as monotherapy or in combination with csDMARDs, mainly methotrexate (MTX), in patients with moderately to severely active RA, have been demonstrated in phase II,[4–8] phase III[9–14] and phase IIIb/IV[15] studies of up to 24 months' duration, and in long-term extension (LTE) studies with up to 114 months' observation.[16–18] Tofacitinib was first approved by the US Food and Drug Administration (FDA) in 2012 for the treatment of patients with RA.[19] In February 2019, the Data Safety Monitoring Board for tofacitinib rheumatology studies determined that the frequency of pulmonary embolism (PE) and all-cause mortality in the tofacitinib 10 mg BID arm was higher than in the TNFi comparator arm in an FDA post-marketing requirement safety study (A3921133; NCT02092467; database not locked and data have not yet been source verified or subjected to standard quality check procedures that would occur at database lock and may therefore be subject to change)[20] designed to evaluate the long-term risk of major adverse cardiovascular events (MACE) and malignancy. Study A3921133 is an ongoing, open-label, endpoint-driven study, evaluating the safety of tofacitinib 5 and 10 mg BID versus TNFi in patients with RA. To be eligible for enrolment, patients had to be ≥50 years of age, have at least one cardiovascular (CV) risk factor and be on a stable dose of MTX. Subsequently, based on the information from an ad hoc safety analysis of Study A3921133 and consideration of information pertaining to PE for other JAK inhibitors, venous thromboembolic events (deep vein thrombosis [DVT]/PE) are considered an important identified risk for treatment with tofacitinib.

While the safety profile of the JAK inhibitors to date is generally similar to that of bDMARDs, some differences have been reported, including an increased risk of certain types of infection, most notably herpes zoster (HZ),[21] and thromboembolic events.[22] A comprehensive review of the long-term safety of tofacitinib was previously carried out using a 2015 integrated analysis of data from >6000 adult patients with RA with a cumulative tofacitinib exposure of up to 8.5 years.[23] This study reported that adverse events (AEs) were generally stable over time, and no new safety risks were observed compared with those reported in previous phase I, II, III and IIIb/IV randomised controlled trials (RCTs) and open-label LTE studies in the tofacitinib RA clinical development programme.[23]

Here, we report an updated and comprehensive integrated safety summary of completed RCTs and LTE studies spanning 9.5 years of cumulative tofacitinib exposure in >7000 patients. This 2017 analysis reports the results of the largest, long-term safety database for a JAK inhibitor in RA and captures the maximum level of patient exposure to tofacitinib from the main LTE study, ORAL Sequel (NCT00413699), which was completed in March 2017. This analysis included all patients meeting individual study inclusion/exclusion criteria, irrespective of potential CV risk factors (ie, patients were not required to be ≥50 years of age or have ≥1 CV risk factor) and did not include ongoing Study A3921133.

METHODS

Patients and study design

Details of the methods have been described previously.[23]

Data, up to March 2017, were pooled from patients with RA who received ≥1 tofacitinib dose, as monotherapy or with background csDMARDs, across the completed 2 phase I, 10 phase II, 6 phase III, 1 phase IIIb/IV index studies and 2 open-label LTE studies (online supplemental table 1). Safety data are reported up to 114 months.

Adult patients (aged ≥18 years) with a diagnosis of active RA, based on the American College of Rheumatology 1987 Revised Criteria[24] and active disease at screening and baseline, were included in index studies. Patients who completed an index study were eligible for inclusion in the LTE studies. Inclusion and exclusion criteria for the index and LTE studies have been previously reported.[23]

Studies were conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines, along with applicable local country regulations and laws. The study protocols were approved by the Institutional Review Boards and/or Independent Ethics Committee at each centre. All patients provided written informed consent.

Dosing

Across the index studies, patients received tofacitinib 1, 3, 5, 10, 15 or 30 mg BID or 20 mg once daily, as monotherapy or with background csDMARDs, mainly MTX (online supplemental table 1).

Data for combined tofacitinib 5 and 10 mg BID populations (all tofacitinib doses) and average dosing are reported (full details in online supplemental methods). Tofacitinib and concomitant RA treatment dose adjustments were allowed at the investigator's discretion.

Data collection, coding and adjudication

Patients were included in the safety analysis if they had received ≥1 tofacitinib dose. Data for all treatment-emergent AEs and serious AEs (SAEs) occurring during treatment and within 28 days after discontinuation of tofacitinib (the clinical trial observation period) were collected and coded using the Medical Dictionary for

Regulatory Activities (MedDRA) v.20.0. Details of baseline comorbidities were also collected. Deaths occurring during treatment and within 28 days after discontinuation of tofacitinib are reported.

Adjudication of events has been described previously[23 25] and is summarised in the online supplemental methods.

Statistical analyses

All safety analyses were based on observed data. Incidence rates (IRs) and 95% CIs (calculated via the Exact Poisson method adjusted for exposure time) were based on the number of unique patients (per 100 patient-years [PY] of exposure) with first events during the time between the first and last dose plus 28 days, divided by the time accrued during the risk period (ie, between the first and last dose plus 28 days, or the time accrued to the first event, whichever occurred earlier). Events reported after the 28-day post-treatment final visit (study conclusion) were not included in the IR analysis but were presented in the data listings.

To assess changes in IRs over time, rates were examined within 6-month intervals of tofacitinib exposure.

Additional details on the statistical methods used to analyse risk factors are provided in the online supplemental methods.

The large number of participants in the tofacitinib RA clinical development programme accrued a substantial amount of exposure time. Therefore, to enable future comparison to the AE rates from other RA clinical trial programmes (eg, indirect standardisation), highly stratified distributions of exposure time according to age group, geographical region, prior bDMARD exposure and combination therapy versus monotherapy are provided in the online supplemental data.

RESULTS
Patients

This analysis included 7061 patients, representing 22 875 PY of tofacitinib exposure, with a median exposure of 3.1 years. Overall, 4895 (69.3%), 4055 (57.4%), 3543 (50.2%) and 2740 (38.8%) patients received tofacitinib for ≥12, 24, 36 and 48 months, respectively. Patient baseline demographics and disease characteristics were generally similar between all groups (table 1).

Adverse events and serious adverse events

The most common treatment-emergent AE by MedDRA system organ class (SOC) was infection and infestations (56.2% [3970/7061]), and the four most common treatment-emergent AEs by preferred term were viral upper respiratory tract infection (17.3% [1221/7061]), upper respiratory tract infection (17.2% [1214/7061]), urinary tract infection (11.8% [832/7061]) and bronchitis (11.3% [800/7061]). A total of 1857 (26.3%) patients experienced SAEs (IR 9.0 [95% CI 8.6 to 9.4]). A total of 1634 (23.1%) patients discontinued due to AEs (IR 7.1 [95% CI 6.8 to 7.5]) (table 2). A total of 59 deaths were

reported (0.8%; IR 0.3 [95% CI 0.2 to 0.3]) (table 2). The most common causes of death by MedDRA SOC were cardiac disorders (n=20, 0.28%), infections and infestations (n=18, 0.25%) and respiratory, thoracic and mediastinal disorders (n=16, 0.23%) (full details in the online supplemental results).

Serious infections

Serious infection events (SIEs) occurred in 576 (8.2%) patients with an IR (95% CI) of 2.5 (2.3 to 2.7). The most common SIEs were pneumonia (n=124), HZ (n=43), urinary tract infection (n=31) and cellulitis (n=31). The IR (95% CI) of SIEs (excluding serious HZ) was 2.3 (2.1 to 2.5). The IRs of SIEs gradually decreased over time with longer exposure to tofacitinib (figure 1A). IRs of SIEs were similar for average tofacitinib 5 and 10 mg BID (table 3). When stratified by prior confirmed lymphocyte counts (two sequential observations), the IRs (95% CI) for SIEs were 7.1 (2.6 to 15.5) for <500 cells/μL, 2.9 (2.5 to 3.5) for ≥500–<1000 cells/μL, 2.4 (2.1 to 2.7) for ≥1000–<1500 cells/μL and 2.3 (2.0 to 2.8) for ≥1500–<2000 cells/μL.

A Cox regression analysis revealed that factors showing a significantly elevated hazard ratio (HR) for risk of SIEs were tofacitinib dose, higher age, male sex, geographical region (in particular Asia and Australia/New Zealand/rest of world vs USA/Canada), increasing baseline Health Assessment Questionnaire-Disability Index score, prior confirmed post-baseline lymphopenia (defined as prior confirmed cases <1000 cells/μL), baseline glucocorticoid use (all doses vs no use), increasing body mass index, diabetes mellitus and chronic obstructive pulmonary disease (COPD) (all p<0.05) (figure 2A).

Herpes zoster

Overall, 782 (11.1%) patients developed HZ, with an IR (95% CI) of 3.6 (3.4 to 3.9). The majority of cases (90.2%) involved a single dermatome. Disseminated HZ was reported in 8 patients (1% of all patients with HZ; all cutaneous, except one case of ocular disease), multidermatomal HZ in 43 patients (5.5% of all patients with HZ) and serious HZ in 57 patients (7.3% of all patients with HZ; 0.8% of the total population). Baseline factors with a significant increase in HR for risk of HZ were tofacitinib dose, higher age, geographical region (in particular, Asia vs USA/Canada), smoking (ex-smoker vs never smoked) and baseline glucocorticoid doses (all doses vs no use) (all p<0.05) (figure 2B; online supplemental figure 1A). The crude IRs for HZ were similar for average tofacitinib 5 and 10 mg BID (table 3), but after multivariable adjustment and considering tofacitinib dose as exposed (ie, time-varying), there was a 40% increase in relative risk for HZ associated with an increase of every 5 mg BID dose (figure 2B). Analysis of IRs over 6-month intervals did not show any increase in HZ with longer exposure to tofacitinib (figure 1B). IRs (95% CI) for HZ were higher in Asia than in non-Asian regions (USA/Canada, Europe, Latin America) (5.6 [5.0 to 6.3] vs

Table 1 Patient baseline demographics and disease characteristics

	All tofacitinib doses N=7061	Average tofacitinib 5 mg BID* N=3066	Average tofacitinib 10 mg BID* N=3995
Age (years), mean (range)	52.1 (18–86)	52.2 (18–86)	52.0 (18–85)
Female, n (%)	5829 (82.6)	2543 (82.9)	3286 (82.3)
Race, n (%)			
White	4576 (64.8)	1823 (59.5)	2753 (68.9)
Black	219 (3.1)	88 (2.9)	131 (3.3)
Asian	1566 (22.2)	880 (28.7)	686 (17.2)
Other	700 (9.9)	275 (9.0)	425 (10.6)
Regions, n (%)			
North America	1745 (24.7)	599 (19.5)	1146 (28.7)
Latin America	1221 (17.3)	586 (19.1)	635 (15.9)
Europe	2382 (33.7)	951 (31.0)	1431 (35.8)
Asia	1673 (23.7)	890 (29.0)	783 (19.6)
ROW	40 (<1.0)	40 (1.3)	0 (0)
Duration of RA since first diagnosis (years), mean (range)	8.0 (0.0–65.0)	8.3 (0.0–50.1)	7.8 (0.0–65.0)
DAS28-4(ESR), mean (SD)	6.4 (1.0) (n=6238)	6.4 (1.0) (n=2688)	6.4 (1.0) (n=3550)
Swollen joint count, mean (SD)	14.9 (8.9) (n=7007)	14.2 (8.5) (n=3049)	15.4 (9.1) (n=3958)
Tender joint count, mean (SD)	23.3 (14.5) (n=7007)	20.4 (13.7) (n=3049)	25.5 (14.8) (n=3958)
HAQ-DI, mean (SD)	1.5 (0.7) (n=6952)	1.5 (0.7) (n=3037)	1.5 (0.7) (n=3915)
BMI (kg/m^2), mean (SD)	27.1 (6.4) (n=7056)	26.7 (6.3) (n=3063)	27.5 (6.5) (n=3993)
Comorbidities, n (%)			
Diabetes mellitus	562 (8.0)	276 (9.0)	286 (7.2)
Coronary heart disease	28 (<1.0)	11 (<1.0)	17 (1.0)
Myocardial infarction	84 (1.2)	3.4 (1.1)	50 (1.3)
Hypertension	2460 (34.8)	1046 (34.1)	1414 (35.4)
COPD	478 (6.8)	172 (5.6)	306 (7.7)
Positive for latent TB by lab testing (QuantiFERON Gold), n (%)	236 (3.3)	73 (2.4)	163 (4.1)
Positive for latent TB by PPD skin test, n (%)	57 (0.8)	36 (1.2)	21 (0.5)
Therapy prior to enrolment, n (%)			
MTX	5758 (81.5)	2711 (88.4)	3047 (76.3)
csDMARD other than MTX	3587 (50.8)	1503 (49.0)	2084 (52.2)
TNFi	1138 (16.1)	356 (11.6)	782 (19.6)
Non-TNFi biological DMARDs	355 (5.0)	118 (3.8)	237 (5.9)
Concomitant corticosteroids, n (%)	3972 (56.3)	1778 (58.3)	2184 (54.7)

Data are based on index study baseline assessments. All studies were completed by March 2017, including the LTE study ORAL Sequel (NCT00413699; study database was locked at the time of analysis).

*Average dosing was based on average daily dose: patients receiving <15 mg/day were assigned to the tofacitinib 5 mg BID group; patients receiving ≥15 mg/day were assigned to the tofacitinib 10 mg BID group, except for patients from China and Japan who initiated tofacitinib 5 mg BID per protocol.

BID, twice daily; BMI, body mass index; COPD, chronic obstructive pulmonary disease; csDMARD, conventional synthetic DMARD; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; DMARD, disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; LTE, long-term extension; MTX, methotrexate; N, number of patients in the treatment group; n, number of unique patients with event; PPD, purified protein derivative; RA, rheumatoid arthritis; ROW, rest of world; TB, tuberculosis; TNFi, tumour necrosis factor inhibitor.

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

	All tofacitinib doses N=7061	Average tofacitinib 5 mg BID* N=3066	Average tofacitinib 10 mg BID* N=3995
	22 874.5 PY	8171.3 PY	14 703.2 PY
Median PY of exposure	3.1	1.4†	4.0
AEs	130.3 (127.0 to 133.6) (n=6117)	129.7 (124.7 to 134.9) (n=2484)	130.7 (126.5 to 135.0) (n=3633)
Discontinuations due to AEs	7.1 (6.8 to 7.5) (n=1634)	8.0 (7.4 to 8.7) (n=664)	6.6 (6.2 to 7.0) (n=970)
SAEs	9.0 (8.6 to 9.4) (n=1857)	9.6 (8.9 to 10.3) (n=717)	8.6 (8.1 to 9.1) (n=1140)
Mortality‡	0.3 (0.2 to 0.3) (n=59)	0.3 (0.2 to 0.5) (n=29)	0.2 (0.1 to 0.3) (n=30)

IRs are presented as the unit of patients with events per 100 PY.

*Average dosing was based on average daily dose: patients receiving <15 mg/day were assigned to the tofacitinib 5 mg BID group; patients receiving ≥15 mg/day were assigned to the tofacitinib 10 mg BID group.

†Exposure was lower than previously reported due to the addition of data from two studies using the tofacitinib 5 mg BID dose (protocols A3921187 and A3921237), which led to an increase in the proportion of patients having <1 year exposure in the average tofacitinib 5 mg BID group.

‡Within 28 days of last dose of study drug.

AE, adverse event; BID, twice daily; IR, incidence rate; N, number of patients in the treatment group; n, number of unique patients with event; PY, patient-years; SAE, serious adverse event.

3.0 [2.8 to 3.3]), respectively; online supplemental table 2), mainly due to elevated IRs in Japan and the Republic of Korea.

Sixty-two (7.9%) patients had recurrence of HZ (IR 3.7 [95% CI 2.8 to 4.7]), comprising 18 (6.7%; IR 3.0 [95% CI 1.8 to 4.7]) in the tofacitinib 5 mg BID group and 44 (8.6%; IR 4.1 [95% CI 3.0 to 5.5]) in the tofacitinib 10 mg BID group.

Opportunistic infections

Opportunistic infections (OIs; excluding TB) were reported in 90 (1.3%) patients, with an IR (95% CI) of 0.4 (0.3 to 0.5). IRs for average tofacitinib 5 and 10 mg BID were similar and are presented in table 3. IRs for OIs (excluding TB) remained stable with increasing tofacitinib exposure (figure 1C). A list of all OIs (excluding TB) are provided in online supplemental table 3. Most OIs were HZ (57 of 90 cases). There were five cryptococcosis cases: four cryptococcal pneumonia cases and one cryptococcal meningitis case, which resolved.

A Cox regression analysis showed that factors with a significant increase in HR for risk of OIs (excluding TB) were tofacitinib dose, higher age, geographical region (Asia vs USA/Canada), COPD and prior confirmed post-baseline lymphopenia <1000 cells/μL (figure 2C; online supplemental figure 1B).

Tuberculosis

Tuberculosis (TB) is reported separately from other OIs given varying background rates based on geographical region. Active TB was reported in 38 (0.5%) patients, with an IR (95% CI) of 0.2 (0.1 to 0.2). IRs

for TB were similar for average tofacitinib 5 and 10 mg BID (table 3). Extrapulmonary/disseminated TB occurred in 19 patients (one of these events was not included in the IR calculation as it occurred outside the 28-day risk period window). The majority of cases (28/38) occurred in geographical regions with a high prevalence of TB (online supplemental table 4). Latent TB was reported in 130 and 190 patients receiving tofacitinib 5 and 10 mg BID, respectively; of these, 121 and 173 patients, respectively, were reported to have been adequately treated with prophylaxis. Four patients who had completed prophylaxis and were randomised to tofacitinib 10 mg BID developed TB during the study period; of these, one patient still had active TB at study completion.

Malignancies

Malignancies (excluding non-melanoma skin cancer [NMSC]) occurred in 177 (2.5%) patients (IR [95% CI] of 0.8 [0.7 to 0.9]) and NMSC in 129 (1.8%) patients (IR 0.6 [95% CI 0.5 to 0.7]); IRs for both were similar regardless of tofacitinib dose (table 3). An analysis of IRs for malignancies (excluding NMSC) and NMSC at 6-month intervals showed that they were generally consistent over time with the overall IRs (figure 3A and B). Outside the 28-day risk period window, where patients were no longer followed in the study and could be receiving alternative therapy, 28 cases of malignancies (excluding NMSC) were reported (not included in the IR calculation) and no cases of NMSC were reported.
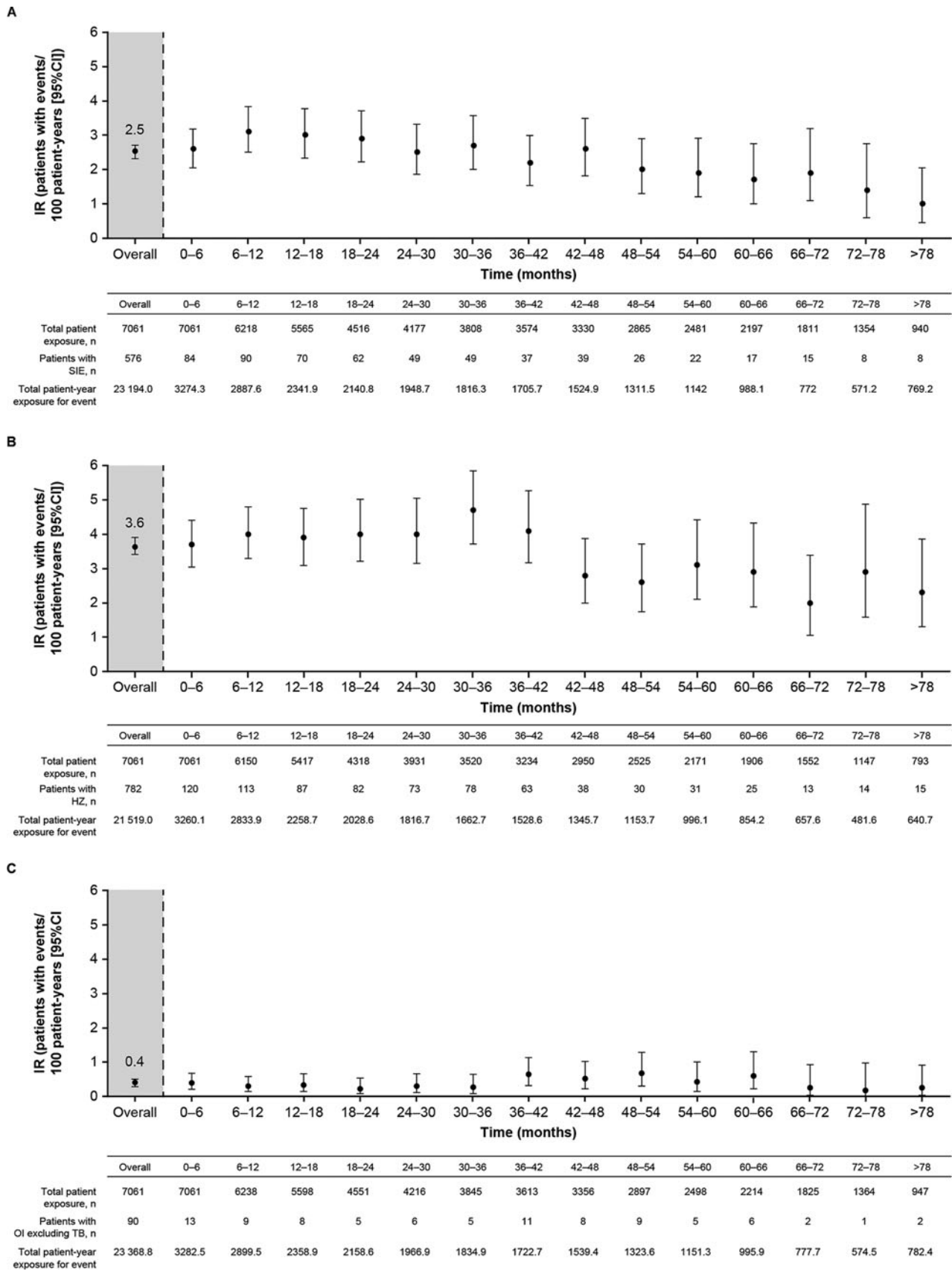
A

	Overall	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	54–60	60–66	66–72	72–78	>78
Total patient exposure, n	7061	7061	6218	5565	4516	4177	3808	3574	3330	2865	2481	2197	1811	1354	940
Patients with SIE, n	576	84	90	70	62	49	49	37	39	26	22	17	15	8	8
Total patient-year exposure for event	23 194.0	3274.3	2887.6	2341.9	2140.8	1948.7	1816.3	1705.7	1524.9	1311.5	1142	988.1	772	571.2	769.2

B

	Overall	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	54–60	60–66	66–72	72–78	>78
Total patient exposure, n	7061	7061	6150	5417	4318	3931	3520	3234	2950	2525	2171	1906	1552	1147	793
Patients with HZ, n	782	120	113	87	82	73	78	63	38	30	31	25	13	14	15
Total patient-year exposure for event	21 519.0	3260.1	2833.9	2258.7	2028.6	1816.7	1662.7	1528.6	1345.7	1153.7	996.1	854.2	657.6	481.6	640.7

C

	Overall	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	54–60	60–66	66–72	72–78	>78
Total patient exposure, n	7061	7061	6238	5598	4551	4216	3845	3613	3356	2897	2498	2214	1825	1364	947
Patients with OI excluding TB, n	90	13	9	8	5	6	5	11	8	9	5	6	2	1	2
Total patient-year exposure for event	23 368.8	3282.5	2899.5	2358.9	2158.6	1966.9	1834.9	1722.7	1539.4	1323.6	1151.3	995.9	777.7	574.5	782.4

Figure 1 IRs for (A) SIEs, (B) HZ (non-serious and serious) and (C) OIs (excluding TB) over time, for all tofacitinib doses (first events). HZ, herpes zoster; IR, incidence rate; OI, opportunistic infection; SIE, serious infection event; TB, tuberculosis.

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

	All tofacitinib doses N=7061	Average tofacitinib 5 mg BID* N=3066	Average tofacitinib 10 mg BID* N=3995
	22 874.5 PY	8171.3 PY	14 703.2 PY
Serious infection events[†]	2.5 (2.3 to 2.7) (n=576)	2.8 (2.5 to 3.2) (n=233)	2.3 (2.1 to 2.6) (n=343)
HZ (non-serious and serious)	3.6 (3.4 to 3.9) (n=782)	3.5 (3.1 to 3.9) (n=269)	3.7 (3.4 to 4.1) (n=513)
HZ (serious)	0.2 (0.2 to 0.3) (n=57)	0.3 (0.2 to 0.4) (n=23)	0.2 (0.2 to 0.3) (n=34)
Opportunistic infection (excluding TB)	0.4 (0.3 to 0.5) (n=90)	0.3 (0.2 to 0.5) (n=28)	0.4 (0.3 to 0.5) (n=62)
TB	0.2 (0.1 to 0.2) (n=38)	0.1 (0.1 to 0.2) (n=11)	0.2 (0.1 to 0.3) (n=27)
Malignancy (excluding NMSC)	0.8 (0.7 to 0.9) (n=177)	0.8 (0.6 to 1.0) (n=64)	0.8 (0.6 to 0.9) (n=113)
NMSC	0.6 (0.5 to 0.7) (n=129)	0.4 (0.3 to 0.6) (n=36)	0.6 (0.5 to 0.8) (n=93)
Breast cancer (female patients)	0.2 (0.1 to 0.2) (n=30)	0.2 (0.1 to 0.3) (n=12)	0.1 (0.1 to 0.2) (n=18)
Lung cancer	0.1 (0.1 to 0.2) (n=30)	0.1 (0.1 to 0.3) (n=12)	0.1 (0.1 to 0.2) (n=18)
Lymphoma[‡]	0.05 (0.03 to 0.09) (n=12)	0.01 (0.00 to 0.07) (n=1)	0.07 (0.04 to 0.13) (n=11)
GI perforations	0.1 (0.1 to 0.2) (n=28)	0.1 (0.0 to 0.2) (n=6)	0.2 (0.1 to 0.2) (n=22)
DVT	0.2 (0.1 to 0.2) (n=36)	0.2 (0.1 to 0.3) (n=13)	0.2 (0.1 to 0.2) (n=23)
PE	0.1 (0.1 to 0.2) (n=28)	0.1 (0.0 to 0.2) (n=8)	0.1 (0.1 to 0.2) (n=20)
VTE[§]	0.3 (0.2 to 0.3) (n=59)	0.2 (0.1 to 0.4) (n=19)	0.3 (0.2 to 0.4) (n=40)
ATE	0.4 (0.3 to 0.5) (n=84)	0.3 (0.2 to 0.5) (n=28)	0.4 (0.3 to 0.5) (n=56)
MACE	0.4 (0.3 to 0.5) (n=85)	0.4 (0.3 to 0.6) (n=31)	0.4 (0.3 to 0.5) (n=54)

*Average dosing was based on average daily dose: patients receiving <15 mg/day were assigned to the tofacitinib 5 mg BID group; patients receiving ≥15 mg/day were assigned to the tofacitinib 10 mg BID group.
†Defined as requiring hospitalisation or parenteral antimicrobial therapy, or otherwise meeting SAE criteria.
‡Lymphoproliferative disorders/lymphoma. In total, 11/12 events were classified as non-Hodgkin lymphoma.
§Patients with a DVT event, a PE event, or both DVT and PE events. A total of five patients experienced a DVT and a PE event (may not have occurred at the same time).
IRs are presented as the unit of patients with events per 100 PY.
AE, adverse event; ATE, arterial thromboembolism; BID, twice daily; DVT, deep vein thrombosis; GI, gastrointestinal; HZ, herpes zoster; IR, incidence rate; MACE, major adverse cardiovascular events; N, number of patients in the treatment group; n, number of unique patients with event; NMSC, non-melanoma skin cancer; PE, pulmonary embolism; PY, patient-years; SAE, serious adverse event; TB, tuberculosis; VTE, venous thromboembolism.

The age- and sex-adjusted standardised incidence ratio (SIR) (95% CI) for all malignancies (excluding NMSC) was 0.8 (0.7 to 1.0) using US National Cancer Institute Surveillance and Epidemiology and End Results (SEER) and 1.4 (1.2 to 1.6) using Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) estimates.

In total, 12 lymphoma events were reported within the 28-day risk period, 1 event in patients receiving an average tofacitinib dose of 5 mg BID (IR 0.01 [95% CI 0.00 to 0.07]) and 11 events occurring in patients receiving an average tofacitinib dose of 10 mg BID (IR 0.07 [95% CI 0.04 to 0.13]) in the main analysis (table 3). Outside the 28-day risk period window used in the calculation of IRs, as a supplemental analysis, a total of 19 lymphoma events occurred, 6 events in patients receiving an average tofacitinib dose of 5 mg BID (IR 0.07 [95% CI 0.03 to 0.16])
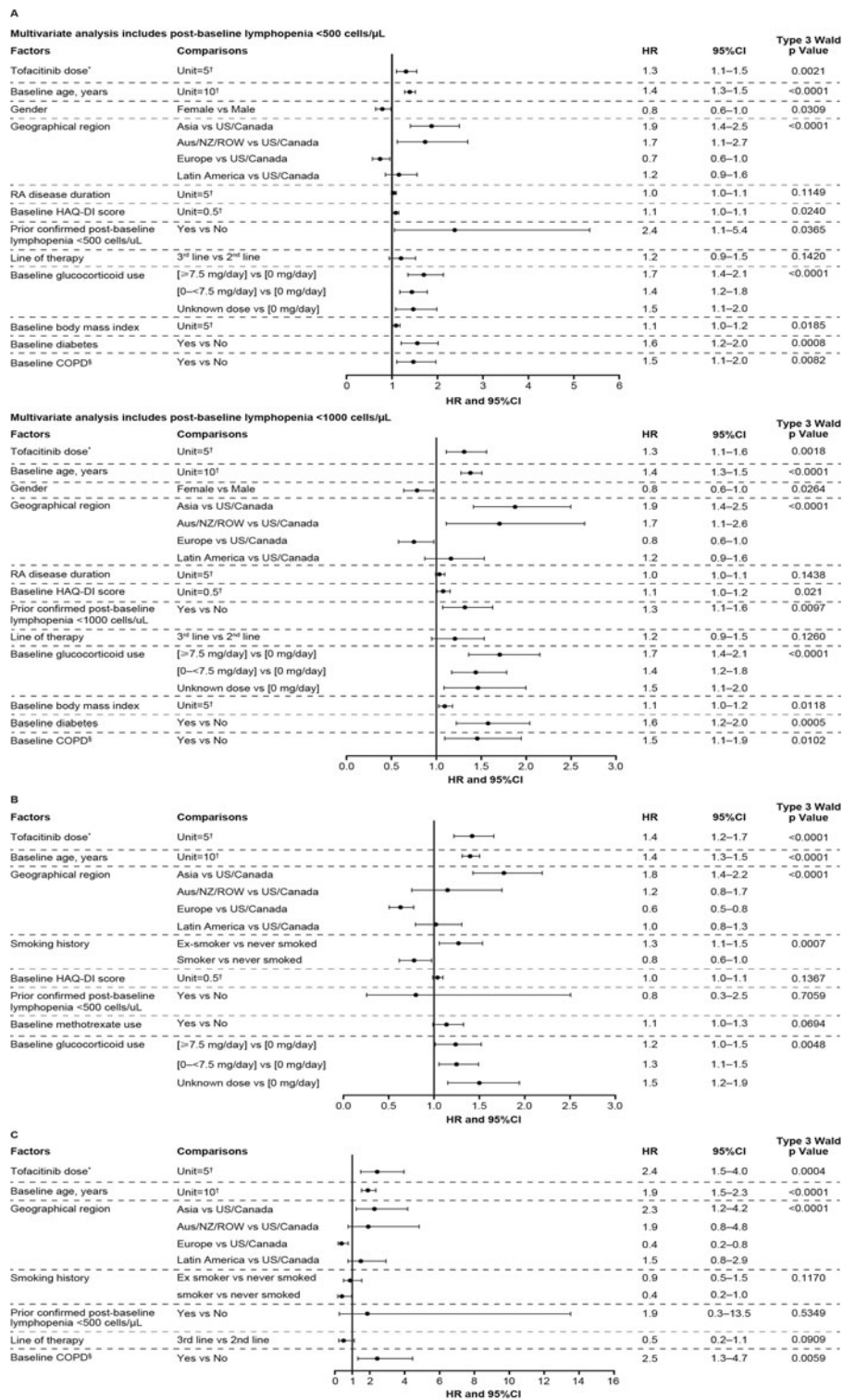
Figure 2 HRs of potential risk factors for (A) SIEs (including post-baseline lymphopenia <500 and <1000 cells/μL), (B) HZ (non-serious and serious; including post-baseline lymphopenia <500 cells/μL) and (C) OIs (excluding TB; including post-baseline lymphopenia <500 cells/μL), for all tofacitinib doses. Results from multivariable Cox regression models in the phase I, II, III, IIIb/IV and open-label LTE studies. *This is a time-varying continuous variable (ie, a patient's dose could be varied during the course of the analysis). †In Unit=x, 'x' is the change in the continuous variable corresponding to which the change in hazards is observed. §Medical history and/or complication of COPD. Aus, Australia; COPD, chronic obstructive pulmonary disease; HAQ-DI, Health Assessment Questionnaire-Disability Index; HR, hazard ratio; HZ, herpes zoster; LTE, long-term extension; NZ, New Zealand; OI, opportunistic infection; ROW, rest of world; SIE, serious infection event; TB, tuberculosis.
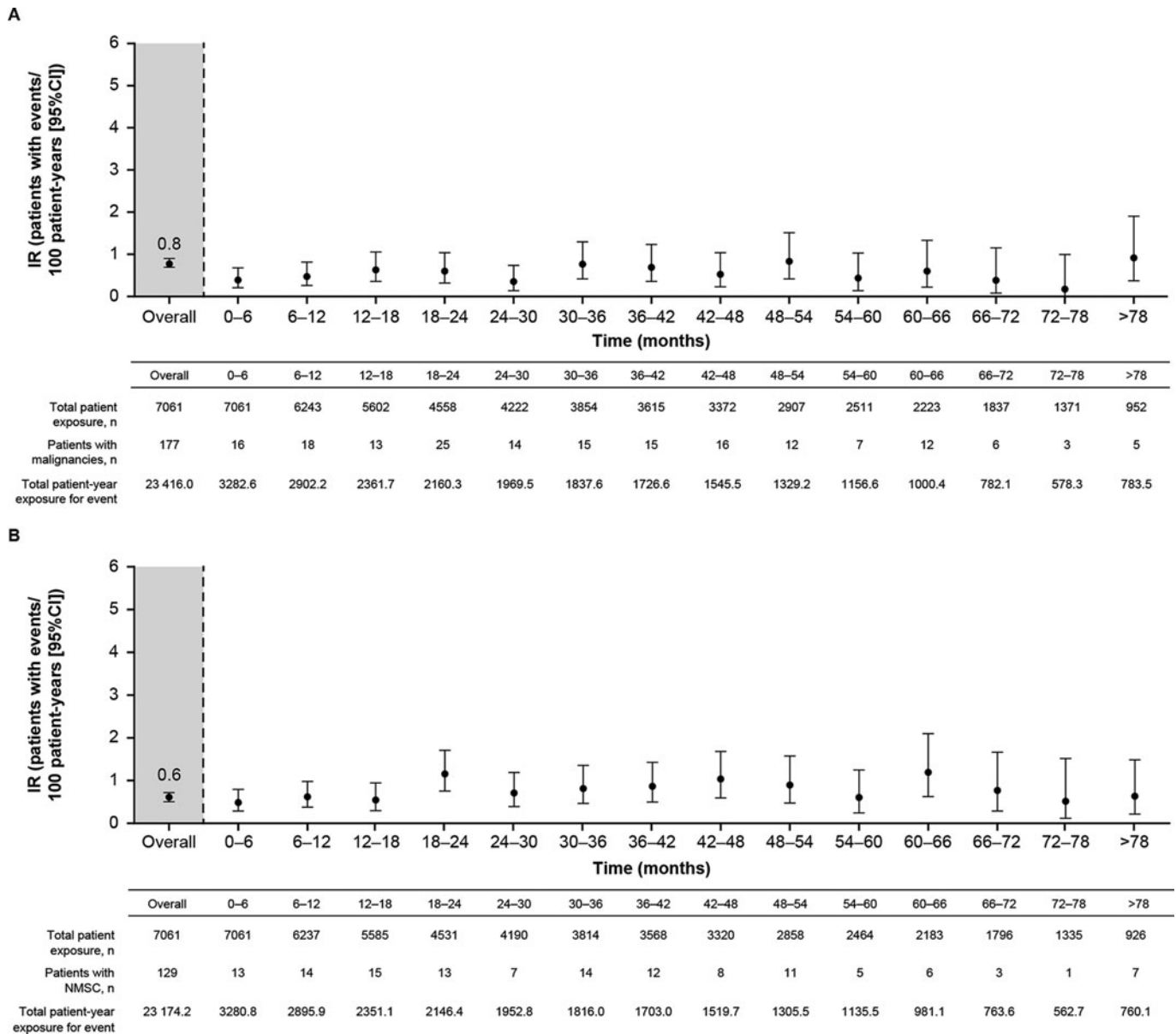
Figure 3 IRs for (A) malignancies (excluding NMSC) and (B) NMSC over time, for all tofacitinib doses. IR; incidence rate; NMSC, non-melanoma skin cancer.

and 13 events occurring in patients receiving an average tofacitinib dose of 10 mg BID (IR 0.09 [95% CI 0.05 to 0.15]).

Gastrointestinal perforations

Gastrointestinal (GI) perforations were reported in 28 (0.4%) patients with an IR (95% CI) of 0.1 (0.1 to 0.2). One additional patient reported a GI perforation outside the 28-day risk period (not included in the IR calculation). IRs for GI perforations with average doses of 5 and 10 mg BID were similar. IRs remained stable with increasing tofacitinib exposure (online supplemental figure 2). In the majority of cases, GI perforations occurred in the lower GI tract (n=22), and all except two occurred in patients with underlying risk factors. Twenty-six patients

received concomitant therapy with one or more non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids. Thirteen patients had at least one of the following underlying relevant diseases and/or surgeries: history of gastric perforation with peritonitis, diverticulitis, irritable bowel syndrome, colon polyp, gastroenteritis or gastric ulcer; current event of spastic colon, gastritis, gastroduodenitis or diverticulitis; history of cholecystectomy and/or appendectomy with or without gastric ulcer.

Thromboembolic events

Venous thromboembolism (ie, DVT and/or PE) was reported in 59 (0.8%) patients with an IR (95% CI) of 0.3 (0.2 to 0.3) (table 3). DVT was reported in 36 (0.5%) patients (IR 0.2 [95% CI 0.1 to 0.2]) and PE in 28 (0.4%)

patients (IR 0.1 [95% CI 0.1 to 0.2]). Seventeen patients with DVT events (47.2%) and 24 patients with PE events (85.7%) were hospitalised. IR analysis of DVT or PE by 6-month intervals showed that they were generally consistent over time with the overall IR (online supplemental figure 3). Arterial thromboembolism was reported in 84 (1.2%) patients (IR 0.4 [95% CI 0.3 to 0.5]). IRs for all thromboembolic events were similar for both tofacitinib doses in this patient population (table 3). These events were not adjudicated.

Major adverse cardiovascular events

Adjudicated MACE, including myocardial infarction, stroke and/or CV death, was reported in 85 (1.3%) patients (IR [95% CI] of 0.4 [0.3 to 0.5]). MACE IRs were similar for both tofacitinib doses. The IR analysis by 6-month intervals demonstrated that IRs were generally stable with longer tofacitinib exposure (online supplemental figure 4). The most common cardiac disorders reported as SAEs were atrial fibrillation (n=27), myocardial infarction (n=24) and coronary artery disease (n=17).

Laboratory variables of interest

Low-density lipoprotein and high-density lipoprotein cholesterol remained generally stable with tofacitinib treatment over time (online supplemental figure 5).

During the index studies, 10.2% of patients treated with tofacitinib were receiving a statin at baseline, which increased to 15.9% by Month 24 (data truncated at study end in studies <24 months; 14.3% in patients receiving tofacitinib 5 mg BID and 17.9% in patients receiving tofacitinib 10 mg BID). Upon entry into the LTE studies, 12.9% of patients were taking statins, which gradually increased to 25.0% by Months 90–96 (25.1% in patients receiving tofacitinib 5 mg BID and 24.2% in patients receiving tofacitinib 10 mg BID). The use of concomitant statins was at the investigator's discretion and the specific reason for patients initiating statins was not reported.

Overall, 878 (12.4%) patients had hypertension (IR 4.2 [95% CI 3.9 to 4.5]) and 209 (3.0%) patients had hyperlipidaemia (IR 0.9 [95% CI 0.8 to 1.1]).

Persistent serum creatine kinase elevations were infrequent; these are summarised in the online supplemental results.

DISCUSSION

This long-term integrated safety summary of tofacitinib with up to 9.5 years of follow-up in >7000 patients with RA worldwide, with a combined tofacitinib exposure of 22 875 PY, represents the largest clinical dataset for a JAK inhibitor in RA to date. This 2017 analysis includes cumulative safety data from completed studies in the RA clinical development programme and captures the maximum level of patient exposure to tofacitinib from the main LTE study, ORAL Sequel.

Overall, the crude 2017 IRs of safety events of interest, discontinuations due to AEs and mortality were consistent with those reported in the previous integrated safety analysis of 19 406 PY of tofacitinib exposure and 8.5 years of follow-up,[23] and with those observed in the individual phase II,[4–8] phase III[9–14] and phase IIIb/IV[15] RCTs and LTE studies.[16–18] IRs for safety events of interest were <0.5/100 PY, with the exception of HZ (all), SIEs, malignancies (excluding NMSC) and NMSC. The crude IRs for safety events of interest were comparable between the two tofacitinib average dosing groups. IRs for SIEs, HZ, OIs (excluding TB), GI perforations, DVT, PE, MACE, malignancies (excluding NMSC) and NMSC remained generally stable with longer exposure to tofacitinib over time. The Cox regression analyses found that increasing tofacitinib doses (based on time-varying dosing in units of 5 mg) could have a higher relative risk of SIEs, HZ and OIs (excluding TB) (HR 1.3, 1.4 and 2.4, respectively).

CV events and SIEs were the most common causes of death; this updated analysis reported that respiratory disorders were the next most common cause of death, whereas the prior integrated safety analysis reported that malignancies were the next most common cause of death.[23] The reason for this difference is that the IR calculation used in this study was based on the number of patients with incident events during the time between the first and last dose plus 28 days, which was the clinical trial observation period; the previous integrated safety summary of tofacitinib included events, but not person time, outside the observation period.[23]

Infections and infestations are typically the most common AEs by SOC reported for tofacitinib.[4–18 23 26] Rates of SIEs previously reported in tofacitinib-treated patients with RA were generally comparable with those for patients treated with bDMARDs, baricitinib and upadacitinib.[27–31] In this analysis, the most common types of SIEs were pneumonia, HZ, urinary tract infection and cellulitis, which is consistent with the prior analysis[23] and those reported for baricitinib and upadacitinib.[27 32] Notably, there was an increased risk of SIEs with lymphopenia <500 cells/µL (HR 2.4), which was observed previously,[23] and also with lymphopenia <1000 cells/µL (HR 1.3). As noted in the Results section, when stratified by lymphocyte count, the IRs for SIEs were numerically higher for lymphopenia <500 cells/µL versus lymphopenia ≥500–<1000 cells/µL. When assessing the benefit:risk profile of tofacitinib in patients with lymphocyte counts between 500 cells/µL and 1000 cells/µL, consideration is warranted for the magnitude of increase in SIEs and the relatively low frequency of prior confirmed lymphopenia (<500 cells/µL, 76/7061 patients; ≥500–<1000 cells/µL, 1835/7061 patients; note that categories are not mutually exclusive and some patients are included in more than one), as well as the contribution of other risk factors for SIEs in patients that may be more prevalent and have a greater relative impact on risk, such as older age and diabetes.

These results were confirmed in a recent post hoc analysis of combined data from RA tofacitinib phase III and

LTE studies, which recommended absolute lymphocyte count monitoring in patients with RA since rates of SIEs are recognised to be increased with lymphopenia.[33 34] This is consistent with the requirement in the prescribing information for monitoring of lymphocyte counts at baseline and every 3 months thereafter during tofacitinib therapy.[19]

The risk of HZ is elevated in patients with RA,[35] with further increases in patients treated with JAK inhibitors.[23 36–38] Rates of HZ were generally similar to the published rates for baricitinib and upadacitinib,[29–31 38] and higher than rates reported for bDMARDs.[21] The majority of HZ cases were non-serious, with a low proportion of patients developing disseminated or multidermatomal HZ, and were clinically manageable. Results were consistent with previous reports that older patients and those from Japan or Korea had a higher risk for HZ.[23 35] The contribution of tofacitinib to an increased risk of HZ in RA is complicated by the fact that over half of patients in the index studies were taking concomitant glucocorticoid therapy. Recent reports suggest that concomitant treatment with glucocorticoids with or without csDMARDs further increases the risk of HZ in patients with RA using tofacitinib[39 40]; glucocorticoid use was also identified as a risk factor in our multivariate analysis within the present study. A previous analysis of data from the tofacitinib RA clinical development programme demonstrated a trend for numerically higher IR of HZ when tofacitinib was administered with concomitant csDMARDs.[39] Consistent with this and other reports, concomitant MTX did not significantly increase the risk of HZ in our analysis.[39 40] Lymphopenia was not found to be a significant risk factor for HZ, which is consistent with the previous report.[23]

The risk of TB and other OIs in patients with RA compared with the general population is increased further in patients treated with bDMARDs[41–43] and tofacitinib.[44] In our analysis, rates of OIs (excluding TB) were similar to those reported for bDMARDs.[45–49] However, between-study comparison of overall rates of OIs with other studies is difficult due to heterogeneous study designs and differences in the definition of OIs.[44] Similar to the prior integrated safety analysis of tofacitinib, risk factors for OIs (excluding TB) included higher age, geographical region and increased tofacitinib dose.[23] COPD was identified as an additional potential risk factor for OIs (excluding TB) in this analysis. The IR of TB in this study was consistent with previous reports of tofacitinib,[17 23 44] with the majority of cases occurring in geographical regions with a high prevalence of TB per prior research, indicating that risk of TB with tofacitinib treatment directly varies with background TB prevalence.[44] IR data for TB reported here are comparable with those reported in clinical trials of bDMARDs,[50 51] baricitinib and upadacitinib.[27 30 31 52] IRs of interstitial lung disease are reported in a separate publication.[53]

Patients with RA are at a higher risk of developing lung and lymphoma malignancies compared with the general population,[54] and continued long-term monitoring of immunomodulatory treatments, such as tofacitinib, is necessary to evaluate any potential malignancy risk.[25] There were 12 lymphoma events reported in the main analysis. Of these, 11/12 events were classified as non-Hodgkin lymphoma, and the majority (11/12) occurred in patients receiving an average tofacitinib dose of 10 mg BID. Outside the 28-day risk period window, a total of 19 lymphoma events were reported, 6 events (IR 0.07 [95% CI 0.03 to 0.16]) and 13 events (IR 0.09 [95% CI 0.05 to 0.15]) in patients receiving an average tofacitinib dose of 5 and 10 mg BID, respectively. These results are similar to a previous analysis of lymphoma incidence in the tofacitinib RA clinical development programme, where six lymphoma events were reported in patients receiving an average tofacitinib dose of 5 mg BID, compared with 13 events in those receiving an average tofacitinib dose of 10 mg BID; the majority (17/19 events) were classified as non-Hodgkin lymphoma.[55] The risk of malignancies with tofacitinib in this analysis was similar to that reported previously.[17 23] It should be noted that estimation beyond 78 months was less precise due to small patient numbers and limited PY of exposure. The IRs and SIRs of malignancies (excluding NMSC) and IRs for NMSC reported here are within a range similar to those reported in RA populations treated with bDMARDs,[45 47 56–59] baricitinib and upadacitinib.[27 29] Consistent with other studies,[59 60] SIRs using GLOBOCAN were higher than those using SEER, potentially due to differences in cancer-screening practices or surveillance systems. However, the need for caution remains over the long-term risk of cancer with any immunomodulator.[60]

GI perforations are a known risk in patients with RA, and treatment with NSAIDs or glucocorticoids elevates this risk further.[61] The IR of GI perforations observed here for tofacitinib was slightly lower than the published rate for tocilizumab,[62] slightly higher than the rates reported in the integrated safety studies of certolizumab pegol[60] and baricitinib,[27] and comparable with the rate reported for upadacitinib.[52] However, these variations may be influenced by different exclusion criteria regarding GI medical history between clinical trials.

There is an increased risk of thromboembolic events in patients with RA compared with the general population,[63 64] and this risk is increased further with JAK inhibitor treatment.[22 27] In contrast to findings in an ad hoc safety analysis of ongoing Study A3921133 described previously in this paper, an increased risk of thromboembolic events was not evident in this 2017 analysis of tofacitinib. A post hoc analysis performed using combined data from phase II/III studies from the RA clinical development programme, which included 5368 patients (representing 4440 PY), did not find a link between tofacitinib treatment and DVT or PE events.[65] However, based on the information from Study A3921133, and consideration of information pertaining to PE for other JAK inhibitors, venous thromboembolic events (DVT/PE) are considered an important identified

risk for treatment with tofacitinib. The current integrated safety analysis included all patients meeting individual study inclusion/exclusion criteria, irrespective of potential CV risk factors (ie, patients were not required to be ≥50 years of age or have ≥1 CV risk factor) and did not include Study A3921133.

Based on pooled data from RCTs and LTEs, the IR of MACE reported with tofacitinib appears similar to that reported with bDMARDs, such as certolizumab pegol (0.62/100 PY)[60] and tocilizumab (0.34/100 PY),[66] and with baricitinib (0.8/100 PY)[67] and upadacitinib (0.6/100 PY).[29] Head-to-head studies, such as Study A3921133 described earlier, are necessary to identify any differences in CV risk between treatments.

Older patients had an increased risk of SIEs, HZ and OIs. The safety of tofacitinib in patients aged <65 years versus ≥65 years has been evaluated previously in post hoc analyses of data pooled from clinical studies. Incidence of SAEs and discontinuations due to AEs were generally higher in older versus younger patients in a post hoc analysis of data from phase III and LTE studies.[68] In addition, a recent analysis of tofacitinib studies that included an adalimumab control/comparator arm reported that IRs of overall infection events and SIEs were higher with tofacitinib 5 mg BID, tofacitinib 10 mg BID and adalimumab in patients aged ≥65 years versus <65 years. The risk of SIEs or overall infection events was similar for tofacitinib and adalimumab, with the exception of a numerically higher rate of SIEs with tofacitinib 10 mg BID versus adalimumab in patients aged ≥65 years.[69] Duration of RA is an important factor in predicting response to treatment; however, duration of RA was not a significant risk factor for SIEs, HZ or OIs in the present analysis. A previous post hoc analysis of patients with RA duration of <1 year versus ≥1 year receiving tofacitinib monotherapy in the phase III ORAL Start study found no difference in safety profiles with longer versus shorter RA duration.[70] In addition, a post hoc analysis of data from patients receiving tofacitinib in the phase IIIb/IV ORAL Strategy study found that rates of AEs were generally similar in those with early RA (duration ≤2 years) compared with established RA (duration >2 years).[71] Use of glucocorticoids at baseline was associated with a higher risk of SIEs and HZ. A previous post hoc analysis of data pooled from phase I, phase II, phase III and LTE studies of tofacitinib also found that risk of HZ was higher in those receiving tofacitinib with glucocorticoids at baseline, versus tofacitinib monotherapy.[39] However, a separate post hoc analysis of data from a phase IIIb/IV study found no difference in rates of AEs with glucocorticoid use; therefore, the effect of glucocorticoids on safety endpoints in patients with RA receiving tofacitinib may require further study.[72]

As reported previously, there were limitations to this integrated analysis.[23] Although analysis of crude IRs did not account for the imbalance and potential dose switching between 5 mg and 10 mg BID doses and the different dosing requirements for different geographical regions, the majority (76.4%) of patients remained on their start dose in the LTE studies. As a pertinent limitation to the dose-related analyses, the use of average daily dose estimated at the end of the study, rather than in a time-varying fashion, may have attenuated any safety differences between tofacitinib doses. Throughout the course of the trial, 23.6% of the patients changed dose at any time. Additionally, while the average dose approach categorises patients into either tofacitinib 5 or 10 mg BID, the Cox regression model takes into account the actual dose from the index studies (ie, some patients were treated with >10 mg BID and others with <5 mg BID). Therefore, it is not possible to reconcile the results from the Cox regression model with the crude IRs since the method used to classify dose was dissimilar between the two approaches. Caution should also be taken when interpreting results for patients with the shortest and longest tofacitinib exposure due to differences in patient numbers, which are fewer in later months, and reporting AEs as counts or rates assume a constant hazard (risk) over time. Another limitation was that changes in rates of SAEs over time and recurring SAEs could not be analysed because patients who developed certain SAEs were discontinued and censored at the time of first event. This restricts the patient population to those in which tofacitinib was well tolerated, restricting full benefit:risk profile evaluation, although this also reflects clinical practice where patients experiencing SAEs would discontinue therapy. Our analysis found that IRs for AEs of interest remained stable with longer tofacitinib exposure. It should be noted that this is common in any long-term safety study of treatments for RA, or other treatments, and is likely partially due to the survival bias (ie, depletion of susceptibles), as those who tolerate therapy without AEs are more likely to continue such therapy.[73] Another potential limitation is that, with the exception of assessment of lymphoma events, this analysis used an updated IR calculation that classified exposure based on treatment received plus 28 days after discontinuation versus the method used in the previous analysis that included events, but not person time, outside the observation period,[23] which must be considered when making comparisons. While this means that events recorded beyond the observation period were not included in the calculation of IRs, as they had been in the previous analysis, this updated approach is a more systematic method of event recording versus the previous method as it ensures no differential follow-up for case ascertainment for any patients at risk.

Comparisons with placebo were not included because treatment duration with placebo was short, thus limiting the PY of placebo exposure. The analysis is also limited by the difficulty in accurately assessing the frequency of events of long latency, as they may not have occurred during the study period.

CONCLUSIONS

This 2017 long-term integrated safety analysis represents the largest and longest clinical dataset for a JAK inhibitor for RA and captures the maximum level of patient exposure to tofacitinib from the main LTE study, ORAL Sequel, which is now completed. Rates of important safety events, including infections and malignancies, were stable across data cuts. In this analysis, with the exception of higher HZ rates than those reported for bDMARDs, particularly among patients from Japan and Korea, the rates of safety events were generally similar to those reported for bDMARDs and other JAK inhibitors used to treat RA.

Studies collecting patient safety data on tofacitinib beyond clinical trials are currently ongoing. For example, the prospective study using data from the US Corrona RA registry is evaluating tofacitinib safety in a US real-world population,[74] while the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis, the Antirheumatic Therapies in Sweden and the Rheumatoide Arthritis: Beobachtung der Biologika-Therapie registers are collecting long-term data on real-world use of tofacitinib and other drugs used to treat RA in Europe.

Author affiliations

[1]Metroplex Clinical Research Center and University of Texas Southwestern Medical Center, Dallas, Texas, USA
[2]University of Occupational and Environmental Health, Kitakyushu, Japan
[3]Paris-Saclay University, AP-HP, INSERM, Le Kremlin Bicêtre, France
[4]University of Alabama at Birmingham, Birmingham, Alabama, USA
[5]Seoul National University, Seoul, Korea (the Democratic People's Republic of)
[6]Department of Medicine, Griffith University, Brisbane, Australia
[7]Oregon Health and Science University, Portland, Oregon, USA
[8]University of California, Los Angeles, California, USA
[9]Pfizer Inc, Groton, Connecticut, USA
[10]Pfizer Inc, New York, New York, USA
[11]Pfizer Inc, Peapack, New Jersey, USA
[12]Struenseehaus Centre for Rheumatology and Clinical Immunology, Hamburg, Germany

ORCID iDs

Yoshiya Tanaka http://orcid.org/0000-0002-0807-7139
Xavier Mariette http://orcid.org/0000-0002-4244-5417
Jeffrey R Curtis http://orcid.org/0000-0002-8907-8976
Eun Bong Lee http://orcid.org/0000-0003-0703-1208
Peter Nash http://orcid.org/0000-0002-2571-788X
Kevin L Winthrop http://orcid.org/0000-0002-3892-6947
Lisy Wang http://orcid.org/0000-0003-1096-0868

REFERENCES

1. Cross M, Smith E, Hoy D, *et al*. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis* 2014;73:1316–22.
2. Singh JA, Saag KG, Bridges JSL, *et al*. American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2015;2016:1–26.
3. Smolen JS, Landewé R, Bijlsma J, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960–77.
4. Fleischmann R, Cutolo M, Genovese MC, *et al*. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab

monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum* 2012;64:617–29.

5 Kremer JM, Bloom BJ, Breedveld FC, *et al.* The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum* 2009;60:1895–905.

6 Kremer JM, Cohen S, Wilkinson BE, *et al.* A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum* 2012;64:970–81.

7 Tanaka Y, Suzuki M, Nakamura H, *et al.* Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res (Hoboken)* 2011;63:1150–8.

8 Tanaka Y, Takeuchi T, Yamanaka H, *et al.* Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. *Mod Rheumatol* 2015;25:514–21.

9 Burmester GR, Blanco R, Charles-Schoeman C, *et al.* Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet* 2013;381:451–60.

10 Fleischmann R, Kremer J, Cush J, *et al.* Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012;367:495–507.

11 Kremer J, Li Z-G, Hall S, *et al.* Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2013;159:253–61.

12 Lee EB, Fleischmann R, Hall S, *et al.* Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med* 2014;370:2377–86.

13 van der Heijde D, Tanaka Y, Fleischmann R, *et al.* Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum* 2013;65:559–70.

14 van Vollenhoven RF, Fleischmann R, Cohen S, *et al.* Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508–19.

15 Fleischmann R, Mysler E, Hall S, *et al.* Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet* 2017;390:457–68.

16 Yamanaka H, Tanaka Y, Takeuchi T, *et al.* Tofacitinib, an oral Janus kinase inhibitor, as monotherapy or with background methotrexate, in Japanese patients with rheumatoid arthritis: an open-label, long-term extension study. *Arthritis Res Ther* 2016;18:34.

17 Wollenhaupt J, Lee EB, Curtis JR, *et al.* Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. *Arthritis Res Ther* 2019;21:89.

18 Wollenhaupt J, Silverfield J, Lee EB, *et al.* Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. *J Rheumatol* 2014;41:837–52.

19 US Food and Drug Administration. XELJANZ (tofacitinib): highlights of prescribing information. 2019. Available http://labeling.pfizer.com/ShowLabeling.aspx?id=959 (accessed 2 Mar 2020)

20 US Food and Drug Administration. Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate. 2019. Available https://www.fda.gov/media/120485/download (accessed 11 Mar 2020)

21 Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat Rev Rheumatol* 2017;13:320.

22 Scott IC, Hider SL, Scott DL. Thromboembolism with Janus kinase (JAK) inhibitors for rheumatoid arthritis: how real is the risk? *Drug Saf* 2018;41:645–53.

23 Cohen SB, Tanaka Y, Mariette X, *et al.* Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. *Ann Rheum Dis* 2017;76:1253–62.

24 Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.

25 Curtis JR, Lee EB, Kaplan IV, *et al.* Tofacitinib, an oral Janus kinase inhibitor: analysis of malignancies across the rheumatoid arthritis clinical development programme. *Ann Rheum Dis* 2016;75:831–41.

26 Wollenhaupt J, Silverfield J, Lee EB, *et al.* Tofacitinib, an oral Janus kinase inhibitor, in the treatment of rheumatoid arthritis: safety and efficacy in open-label, long-term extension studies over 8 years [abstract]. *Arthritis Rheumatol* 2016;68(Suppl 10):1647.

27 Smolen JS, Genovese MC, Takeuchi T, *et al.* Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. *J Rheumatol* 2019;46:7–18.

28 Strand V, Ahadieh S, DeMasi R, *et al.* THU0211 Meta-analysis of serious infections with baricitinib, tofacitinib and biologic DMARDs in rheumatoid arthritis [abstract]. *Ann Rheum Dis* 2017;76(Suppl 2):THU0211. Available https://ard.bmj.com/content/76/Suppl_2/284.1

29 Cohen S, van Vollenhoven R, Winthrop K, *et al.* Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase 3 clinical program [abstract]. *Arthritis Rheumatol* 2019;71(Suppl 10):509. Available https://acrabstracts.org/abstract/safety-profile-of-upadacitinib-in-rheumatoid-arthritis-integrated-analysis-from-the-select-phase-3-clinical-program/

30 Genovese MC, Smolen JS, Takeuchi T, *et al.* FRI0123 Safety profile of baricitinib for the treatment of rheumatoid arthritis up to 8.4 years: an updated integrated safety analysis [abstract]. *Ann Rheum Dis* 2020;79 (Suppl 1):FRI0123. Available https://ard.bmj.com/content/79/Suppl_1/642.1

31 Cohen SB, Van Vollenhoven R, Curtis JR, *et al.* THU0197 Safety profile of upadacitinib up to 3 years of exposure in patients with rheumatoid arthritis [abstract]. *Ann Rheum Dis* 2020;79(Suppl 1):THU0197. Available https://ard.bmj.com/content/79/Suppl_1/319.info

32 US Food and Drug Administration. RINVOQ (upadacitinib): highlights of prescribing information. 2019. Available https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211675s000lbl.pdf (accessed 27 Apr 2020)

33 European Medicines Agency. Xeljanz (tofacitinib citrate) - summary of product characteristics, 2020. Available https://www.medicines.org.uk/emc/medicine/33167 (accessed 7 Feb 2020)

34 van Vollenhoven R, Lee EB, Strengholt S, *et al.* Evaluation of the short-, mid-, and long-term effects of tofacitinib on lymphocytes in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2019;71:685–95.

35 Winthrop KL, Yamanaka H, Valdez H, *et al.* Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2014;66:2675–84.

36 Winthrop KL, Valdez H, Mortensen E, *et al.* Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis [abstract]. *Arthritis Rheum* 2013;65(Suppl):2490. Available https://acrabstracts.org/abstract/herpes-zoster-and-tofacitinib-therapy-in-patients-with-rheumatoid-arthritis/

37 Genovese MC, Kremer J, Zamani O, *et al.* Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med* 2016;374:1243–52.

38 Winthrop KL, Lindsey S, Weinblatt M, *et al.* Herpes zoster in patients with moderate to severe rheumatoid arthritis treated with baricitinib [abstract]. *Arthritis Rheumatol* 2016;68(Suppl 10):3027. Available https://acrabstracts.org/abstract/herpes-zoster-in-patients-with-moderate-to-severe-rheumatoid-arthritis-treated-with-baricitinib/

39 Winthrop KL, Curtis JR, Lindsey S, *et al.* Herpes zoster and tofacitinib: clinical outcomes and the risk of concomitant therapy. *Arthritis Rheumatol* 2017;69:1960–8.

40 Curtis JR, Xie F, Yang S, *et al.* Risk for herpes zoster in tofacitinib-treated rheumatoid arthritis patients with and without concomitant methotrexate and glucocorticoids. *Arthritis Care Res (Hoboken)* 2019;71:1249–54.

41 Arkema EV, Jonsson J, Baecklund E, *et al.* Are patients with rheumatoid arthritis still at an increased risk of tuberculosis and what is the role of biological treatments? *Ann Rheum Dis* 2015;74:1212–17.

42 Baronnet L, Barnetche T, Kahn V, *et al.* Incidence of tuberculosis in patients with rheumatoid arthritis. a systematic literature review. *Joint Bone Spine* 2011;78:279–84.

43 Novosad SA, Winthrop KL. Beyond tumor necrosis factor inhibition: the expanding pipeline of biologic therapies for inflammatory diseases and their associated infectious sequelae. *Clin Infect Dis* 2014;58:1587–98.

44 Winthrop KL, Park SH, Gul A, *et al.* Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. *Ann Rheum Dis* 2016;75:1133–8.

45 Weinblatt ME, Moreland LW, Westhovens R, *et al.* Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. *J Rheumatol* 2013;40:787–97.

46 Keystone EC, van der Heijde D, Kavanaugh A, *et al.* Clinical, functional, and radiographic benefits of longterm adalimumab plus methotrexate: final 10-year data in longstanding rheumatoid arthritis. *J Rheumatol* 2013;40:1487–97.

47 Bykerk VP, Cush J, Winthrop K, *et al.* Update on the safety profile of certolizumab pegol in rheumatoid arthritis: an integrated analysis from clinical trials. *Ann Rheum Dis* 2015;74:96–103.

48 Kay J, Fleischmann R, Keystone E, *et al.* Five-year safety data from 5 clinical trials of subcutaneous golimumab in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol* 2016;43:2120–30.

49 Schiff MH, Kremer JM, Jahreis A, *et al.* Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011;13:R141.

50 Alten R, Kaine J, Keystone E, *et al.* Long-term safety of subcutaneous abatacept in rheumatoid arthritis: integrated analysis of clinical trial data representing more than four years of treatment. *Arthritis Rheumatol* 2014;66:1987–97.

51 Schiff MH, Burmester GR, Kent JD, *et al.* Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;65:889–94.

52 Fleischmann RM, Genovese MC, Enejosa JV, *et al.* Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. *Ann Rheum Dis* 2019;78:1454–62.

53 Citera G, Mysler E, Madariaga H, *et al.* Low interstitial lung disease event rate in patients with rheumatoid arthritis: pooled post hoc analysis of data from the tofacitinib clinical development program [abstract]. *Arthritis Rheumatol* 2018;70(Suppl 10):525. Available https://acrabstracts.org/abstract/low-interstitial-lung-disease-event-rate-in-patients-with-rheumatoid-arthritis-pooled-post-hoc-analysis-of-data-from-the-tofacitinib-clinical-development-program/

54 Simon TA, Thompson A, Gandhi KK, *et al.* Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Res Ther* 2015;17:212.

55 Mariette X, Chen C, Biswas P, *et al.* Lymphoma in the tofacitinib rheumatoid arthritis clinical development program. *Arthritis Care Res (Hoboken)* 2018;70:685–94.

56 Burmester GR, Panaccione R, Gordon KB, *et al.* Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis* 2013;72:517–24.

57 Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum* 2007;56:2886–95.

58 Gomez-Reino JJ, Checchio T, Geier J, *et al.* THU0196 Systematic review and meta-analysis of malignancies, excluding non-melanoma skin cancer, in patients with rheumatoid arthritis treated with tofacitinib or biologic disease-modifying antirheumatic drugs [abstract]. *Ann Rheum Dis* 2017;76(Suppl 2):THU0196. Available https://ard.bmj.com/content/76/Suppl_2/277.1

59 Rubbert-Roth A, Sebba A, Brockwell L, *et al.* Malignancy rates in patients with rheumatoid arthritis treated with tocilizumab. *RMD Open* 2016;2:e000213.

60 Curtis JR, Mariette X, Gaujoux-Viala C, *et al.* Long-term safety of certolizumab pegol in rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis and Crohn's disease: a pooled analysis of 11 317 patients across clinical trials. *RMD Open* 2019;5:e000942.

61 Curtis JR, Lanas A, John A, *et al.* Factors associated with gastrointestinal perforation in a cohort of patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:1819–28.

62 Monemi S, Berber E, Sarsour K, *et al.* Incidence of gastrointestinal perforations in patients with rheumatoid arthritis treated with tocilizumab from clinical trial, postmarketing, and real-world data sources. *Rheumatol Ther* 2016;3:337–52.

63 Ogdie A, Kay McGill N, Shin DB, *et al.* Risk of venous thromboembolism in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a general population-based cohort study. *Eur Heart J* 2018;39:3608–14.

64 Kim SC, Schneeweiss S, Liu J, *et al.* Risk of venous thromboembolism in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2013;65:1600–7.

65 Mease PJ, Kremer J, Cohen S, *et al.* Incidence of thromboembolic events in the tofacitinib rheumatoid arthritis, psoriasis, psoriatic arthritis and ulcerative colitis development programs [abstract]. *Arthritis Rheumatol* 2017;69(Suppl 10):16L. Available https://acrabstracts.org/abstract/incidence-of-thromboembolic-events-in-the-tofacitinib-rheumatoid-arthritis-psoriasis-psoriatic-arthritis-and-ulcerative-colitis-development-programs/

66 Rao VU, Pavlov A, Klearman M, *et al.* An evaluation of risk factors for major adverse cardiovascular events during tocilizumab therapy. *Arthritis Rheumatol* 2015;67:372–80.

67 Taylor PC, Weinblatt ME, Burmester GR, *et al.* Cardiovascular safety during treatment with baricitinib in rheumatoid arthritis. *Arthritis Rheumatol* 2019;71:1042–55.

68 Curtis JR, Schulze-Koops H, Takiya L, *et al.* Efficacy and safety of tofacitinib in older and younger patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2017;35:390–400. Available https://pubmed.ncbi.nlm.nih.gov/28079500/

69 Winthrop K, Gold D, Henrohn D, *et al.* SAT0139 age-based (<65 vs ≥65 years) incidence of infections and serious infections in tofacitinib-, adalimumab- and placebo-treated patients with rheumatoid arthritis: a post hoc analysis of phase 2, phase 3 and phase 3b/4 tofacitinib studies [abstract]. *Ann Rheum Dis* 2020;79 (Suppl 1):SAT0139. Available https://ard.bmj.com/content/79/Suppl_1/1007.info

70 Fleischmann RM, Huizinga TWJ, Kavanaugh AF, *et al.* Efficacy of tofacitinib monotherapy in methotrexate-naive patients with early or established rheumatoid arthritis. *RMD Open* 2016;2:e000262.

71 Takeuchi T, Tanaka Y, Sugiyama N, *et al.* THU0193 efficacy of tofacitinib monotherapy, tofacitinib with methotrexate and adalimumab with methotrexate in patients with early (≤2 years) vs established (>2 years) rheumatoid arthritis: a post hoc analysis of data from ORAL strategy [abstract]. *Ann Rheum Dis* 2019;78:THU0193.

72 Fleischmann R, Wollenhaupt J, Cohen S, *et al.* SAT0247 Impact of glucocorticoids on efficacy and safety of tofacitinib with and without methotrexate and adalimumab with methotrexate for rheumatoid arthritis: results from a phase 3b/4 randomised trial [abstract]. *Ann Rheum Dis* 2018;77(Suppl 2):SAT0247. Available https://ard.bmj.com/content/77/Suppl_2/985.2

73 Choi HK, Nguyen U-S, Niu J, *et al.* Selection bias in rheumatic disease research. *Nat Rev Rheumatol* 2014;10:403–12.

74 Kremer J, Cappelli LC, Etzel CJ, *et al.* Real-world data from a post-approval safety surveillance study of tofacitinib vs biologic DMARDS and conventional synthetic DMARDS: five-year results from a US-based rheumatoid arthritis registry [abstract]. *Arthritis Rheumatol* 2018;70(Suppl 10):1542. Available https://acrabstracts.org/abstract/real-world-data-from-a-post-approval-safety-surveillance-study-of-tofacitinib-vs-biologic-dmards-and-conventional-synthetic-dmards-five-year-results-from-a-us-based-rheumatoid-arthritis-registry/