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## EXTENDED REPORT

# 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

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**ABSTRACT**

**Objectives** Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). We report an integrated safety summary of tofacitinib from two phase I, nine phase II, six phase III and two long-term extension studies in adult patients with active RA.

**Methods** Data were pooled for all tofacitinib-treated patients (data cut-off: 31 March 2015). Incidence rates (IRs; patients with event/100 patient-years) and 95% CIs are reported for adverse events (AEs) of interest.

**Results** 6194 patients received tofacitinib for a total 19 406 patient-years' exposure; median exposure was 3.4 patient-years. IR (95% CI) for serious AEs was 9.4 (9.0 to 9.9); IR for serious infections was 2.7 (2.5 to 3.0). IR for (all) herpes zoster was 3.9 (3.6 to 4.2); IR for disseminated or multidermatomal herpes zoster was 0.3 (0.2 to 0.4). IR for opportunistic infections (excluding tuberculosis) was 0.3 (0.2 to 0.4) and was 0.2 (0.1 to 0.3) for tuberculosis. IR for malignancies (excluding non-melanoma skin cancer (NMSC)) was 0.9 (0.8 to 1.0); NMSC IR was 0.6 (0.5 to 0.7). IR for gastrointestinal perforations was 0.1 (0.1 to 0.2). Analysis of IR for serious infections, herpes zoster and malignancies by 6-month intervals did not reveal any notable increase in IR with longer-duration tofacitinib exposure.

**Conclusion** This analysis of tofacitinib exposure up to 8.5 years allowed estimation of safety events with improved precision versus previous tofacitinib reports. AEs were generally stable over time; no new safety signals were observed compared with previous tofacitinib reports.

**Trial registration numbers** NCT01262118, NCT01484561, NCT00147498, NCT00413660, NCT00550446, NCT00603512, NCT00687193, NCT01164579, NCT00976599, NCT01059864, NCT01359150, NCT00960440, NCT00847613, NCT00814307, NCT00856544, NCT00853385, NCT01039688, NCT00413699, NCT00661661; Results.

of special interest: serious infection events (SIEs), opportunistic infections (OI; including tuberculosis (TB)), herpes zoster (HZ), malignancies, cardiovascular events and gastrointestinal (GI) perforations.

We report for the first time integrated data based on cumulative tofacitinib exposure throughout the RA development programme. This analysis extends previous safety reports for tofacitinib which focused on specific AEs and includes up to 8.5 years of tofacitinib exposure, allowing estimation of rates for safety events of interest with improved precision versus previous reports, and novel methods to examine dose-related AEs.

**PATIENTS AND METHODS****Studies**

Data were pooled from patients with RA treated with tofacitinib in phases I–III and LTE studies (see online supplementary table S1). All studies were completed by 31 March 2015 except LTE study NCT00413699. LTE data collection and analyses are ongoing (database not locked; some values may change in final locked database).

Patients (aged  $\geq 18$  years) had an active RA diagnosis based on the American College of Rheumatology 1987 revised criteria<sup>19</sup> and active disease at screening and baseline.<sup>1–18</sup> Key exclusion criteria included untreated infection with *Mycobacterium tuberculosis* or clinically significant infection, and history of malignancy except adequately treated squamous cell or basal cell skin cancer or cervical carcinoma in situ.<sup>1–18</sup>

Studies were conducted in compliance with the Declaration of Helsinki, International Council for Harmonisation Guidelines for Good Clinical Practice and local country regulations. The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each centre. Patients provided written informed consent.

**Dosing**

Patients received tofacitinib 1, 3, 5, 10, 15 or 30 mg twice daily or 20 mg once daily, as monotherapy or with background DMARDs (see online supplementary table S1). Upon entering LTE studies, patients from phase II and III studies received tofacitinib 5 and 10 mg twice daily, respectively, regardless of index study treatment.

**INTRODUCTION**

Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib has demonstrated efficacy and manageable safety in patients with active RA in phase I–III trials and long-term extension (LTE) studies.<sup>1–18</sup> Results from these studies and adverse event (AE) profiles of other disease-modifying antirheumatic drugs (DMARDs) informed the selection of safety events



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Within the LTE, tofacitinib could be increased to 10 mg twice daily for inadequate response or reduced to 5 mg twice daily for safety reasons.

Because patients could change doses between index and LTE studies and within LTE, dose was categorised using two methods. The primary analysis used the average dosing algorithm in which patients were assigned to average tofacitinib 5 or 10 mg twice daily if the average daily dose at end of enrolment up to the cut-off date was <15 or ≥15 mg, respectively. The constant dosing algorithm was used in a sensitivity analysis. Only patients exposed to a constant tofacitinib dose of 5 or 10 mg twice daily without prior exposure to a different tofacitinib dose or adalimumab were included in the algorithm.

Person-time with exposure to constant tofacitinib 5 or 10 mg twice daily would not sum to the overall exposure, because patients had exposure censored upon tofacitinib dose change.

**Data collection, coding and adjudication**

The safety database included patients receiving ≥1 tofacitinib dose.

Data were collected for all treatment-emergent AEs and serious AEs (SAEs) and coded using Medical Dictionary for Regulatory Activities (MedDRA) V.18.0. Details of comorbidities were requested at baseline.

An external, independent committee of infectious disease experts blindly adjudicated and classified all SIEs and all events of possible OIs occurring in the tofacitinib RA development

**Table 1** Patient demographics and baseline disease characteristics

	All tofacitinib doses N=6194	Average tofacitinib 5 mg twice daily* N=2239	Average tofacitinib 10 mg twice daily* N=3955	Constant tofacitinib 5 mg twice daily† N=2342	Constant tofacitinib 10 mg twice daily† N=2814
Age, mean (range)	52.9 (18–86)	53.3 (18–86)	52.7 (18–86)	53.3 (18–86)	52.6 (18–86)
Female, %	82.7	83.2	82.5	82.6	83.0
Race, n (%)					
White	3895 (62.9)	1177 (52.6)	2718 (68.7)	1418 (60.5)	1817 (64.6)
Black	182 (2.9)	55 (2.5)	127 (3.2)	75 (3.2)	88 (3.1)
Asian	1486 (24.0)	800 (35.7)	686 (17.3)	626 (26.7)	605 (21.5)
Other	631 (10.2)	207 (9.2)	424 (10.7)	223 (9.5)	304 (10.8)
Regions, n (%)					
North America	1505 (24.3)	405 (18.1)	1100 (27.8)	482 (20.6)	835 (29.7)
Latin America	1037 (16.7)	400 (17.9)	637 (16.1)	405 (17.3)	426 (15.1)
Europe	2065 (33.3)	632 (28.2)	1433 (36.2)	791 (33.8)	887 (31.5)
Asia	1587 (25.6)	802 (35.8)	785 (19.8)	664 (28.4)	666 (23.7)
Mean duration of RA since first diagnosis, years (range)	8.0 (0.0–65.0)	8.2 (0.0–50.1)	7.9 (0.0–65.0)	7.9 (0.0–55.0)	7.7 (0.0–49.4)
Mean DAS28-4(ESR) (SD)	6.4 (1.0) [n=5487]	6.3 (1.0) [n=1923]	6.4 (1.0) [n=3564]	6.4 (1.0) [n=2182]	6.3 (1.1) [n=2562]
Mean swollen joint count (of 66 joints) (SD)	15.4 (9.1) [n=6140]	15.3 (9.2) [n=2222]	15.4 (9.1) [n=3918]	15.5 (9.2) [n=2324]	15.2 (9.2) [n=2779]
Mean tender joint count (of 68 joints) (SD)	24.9 (14.7) [n=6140]	23.6 (14.4) [n=2222]	25.6 (14.8) [n=3918]	25.7 (14.9) [n=2324]	24.8 (14.9) [n=2779]
Mean BMI (SD), kg/m <sup>2</sup>	27.0 (6.4) [n=6192]	26.2 (6.1) [n=2239]	27.4 (6.5) [n=3953]	26.6 (6.3) [n=2342]	27.4 (6.5) [n=2813]
Diabetes mellitus, n (%)	264 (4.3)	121 (5.4)	143 (3.6)	110 (4.7)	110 (3.9)
COPD, n (%)	115 (1.9)	36 (1.6)	79 (2.0)	47 (2.0)	60 (2.1)
History of TB, n (%)	34 (0.5)	16 (0.7)	18 (0.5)	15 (0.6)	13 (0.5)
Therapy prior to enrolment, n (%)					
Methotrexate	4869 (78.6)	1877 (83.8)	2992 (75.7)	1876 (80.1)	2041 (72.5)
Traditional DMARDs other than methotrexate	3263 (52.7)	1220 (54.5)	2043 (51.7)	1300 (55.5)	1401 (49.8)
TNFi	1026 (16.6)	279 (12.5)	747 (18.9)	428 (18.3)	493 (17.5)
Non-TNFi biological DMARDs	273 (4.4)	71 (3.2)	202 (5.1)	114 (4.9)	141 (5.0)
Concomitant therapy, n (%)					
Glucocorticoids	3468 (56.0)	1304 (58.2)	2164 (54.7)	1359 (58.0)	1487 (52.8)
Any DMARD‡	3456 (55.8)	1268 (56.6)	2188 (55.3)	1394 (59.5)	1554 (55.2)
Hydroxychloroquine	251 (4.1)	86 (3.8)	165 (4.2)	112 (4.8)	123 (4.4)
Leflunomide	219 (3.5)	96 (4.3)	123 (3.1)	104 (4.4)	112 (4.0)
Methotrexate	3161 (51.0)	1163 (51.9)	1998 (50.5)	1260 (53.8)	1408 (50.0)

All groups are based on tofacitinib exposure data (not tofacitinib patient-level data).

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

†Constant dosage without prior exposure to another tofacitinib dose or adalimumab during the study; patients who switched doses were not included in this group.

‡Most common DMARDs are listed.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; DAS28-4(ESR), disease activity score in 28 joints, erythrocyte sedimentation rate; DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; TB, tuberculosis; TNFi, tumour necrosis factor inhibitor.

programme. SIEs were defined as requiring hospitalisation or parenteral antimicrobial therapy, or otherwise meeting SAE criteria; patients with SIEs were discontinued from the study. HZ involving >2 adjacent dermatomes or with disseminated disease were considered OIs. TB screening was performed as previously described.<sup>20</sup>

Malignancy data were adjudicated as previously described.<sup>21</sup>

GI perforations were blindly adjudicated by two sponsor-independent reviewers (US board-certified practising gastroenterologists). SAEs in the clinical and safety databases that might reflect a GI perforation (see online supplementary appendix) were reviewed. Status was determined by two reviewers, with any differences resolved by a third reviewer. Clinical events reflecting an opening in the GI tract, including those associated with appendicitis and diverticulitis, were classified as confirmed GI perforations. Incidence rate (IR) of deaths occurring within 30 days after tofacitinib discontinuation was calculated.

### Statistical analysis

Safety analyses were based on observed cases. Crude IRs per 100 patient-years were calculated for patients receiving tofacitinib and those in average or constant 5 or 10 mg twice daily groups. IRs for each AE were obtained by dividing the number of first-time occurrences of the AE over a time interval, by the total duration of study treatment exposure censored at time of first event, death or discontinuation from study time interval. An exact Poisson 95% CI adjusted for exposure time was calculated for IRs.

Standardised incidence ratios (SIRs) were calculated as the ratio of observed AEs to those in the US National Cancer Institute Surveillance and Epidemiology and End Results (SEER) database, 1992–2011<sup>22</sup>; 95% CIs for SIRs were calculated following a Poisson distribution.

TB rates were stratified by geographical background rates using the WHO incidence categorisation of low, intermediate and high.<sup>23</sup>

To assess whether IRs increased over time, rates were examined within 6-month intervals of tofacitinib exposure. To investigate whether the hazard for developing a malignancy was constant over time, the probability distribution of time to first event was analysed using a Kaplan-Meier curve and cumulative hazard function. Patients were censored at their last day of tofacitinib exposure.

A Cox regression model evaluated risk factors for SIEs, HZ and OIs excluding TB; backward selection (stay fixed at 15%) was used to screen baseline factors: age, gender, region, body mass index (BMI), smoking history, RA disease duration, line of therapy, diabetes, chronic obstructive pulmonary disease (COPD), DAS-4(CRP), methotrexate use, glucocorticoid dose groups, absolute lymphocyte count (ALC), rheumatoid factor and Health Assessment Questionnaire-Disability Index (HAQ-DI) score to model the time to event from the first tofacitinib dose.

## RESULTS

### Patients and tofacitinib exposure

Six thousand one hundred and ninety-four patients received tofacitinib. Overall, 4794 (77.4%), 4032 (65.1%), 3351 (54.1%) and 2489 (40.2%) patients received tofacitinib for >12, 24, 36 and 48 months; overall median exposure was 3.38 patient-years. Demographics and disease characteristics were similar between groups (table 1).

### AEs and SAEs

The most common AEs (all causality) were nasopharyngitis, upper respiratory tract infection and urinary tract infection (UTI); the most common System Organ Class of SAEs was infections and infestations.

IRs for AEs, discontinuations due to AEs, SAEs and deaths were similar for average and constant tofacitinib 5 and 10 mg twice daily (table 2). The most common causes of death were infections, cardiovascular events and malignancies.

### Serious infections

The most common types were pneumonia, HZ, UTI and cellulitis. IRs did not increase with longer treatment (figure 1A). IRs of SIEs and deaths due to infections by average and constant dose had overlapping 95% CIs (table 3).

Based on Cox regression analysis, baseline glucocorticoid dose >0–<7.5 and ≥7.5 mg/day (selected based on clinical relevance and sample size) were associated with increased risk of SIEs (HRs (95% CI) 1.6 (1.3 to 2.0) and 1.7 (1.3 to 2.2), respectively, vs no glucocorticoid use; p=0.0001) (figure 2A). Other significant baseline risk factors were higher age, presence of COPD, higher HAQ-DI score, higher BMI, prior confirmed post-baseline lymphopenia (<500 cells/μL), diabetes, female

**Table 2** IRs (patients with events/100 patient-years; 95% CI) of AEs and SAEs (all-cause)

	All tofacitinib doses N=6194	Average tofacitinib twice daily* N=2239	Average tofacitinib 10 mg twice daily* N=3955	Constant tofacitinib 5 mg twice daily† N=2342	Constant tofacitinib 10 mg twice daily† N=2814
Total patient-years of exposure, years	19 406	6870	12 536	3623	6702
Median patient-years of exposure	3.4	3.0	3.5	1.0	2.0
AEs (n=5545)	136.9 (133.3 to 140.5)	136.1 (130.2 to 142.3)	137.3 (132.8 to 141.8)	153.1 (146.1 to 160.4)	157.9 (151.7 to 164.3)
Discontinuations due to AEs (n=1446)	7.5 (7.1 to 7.8)	8.6 (7.9 to 9.3)	6.8 (6.4 to 7.3)	7.2 (6.4 to 8.2)	7.8 (7.1 to 8.5)
SAEs (n=1649)	9.4 (9.0 to 9.9)	10.1 (9.4 to 11.0)	9.1 (8.5 to 9.7)	9.2 (8.2 to 10.3)	9.3 (8.6 to 10.1)
Mortality‡ (n=51)	0.3 (0.2 to 0.3)	0.4 (0.3 to 0.6)	0.2 (0.1 to 0.3)	0.3 (0.2 to 0.5)	0.2 (0.1 to 0.3)

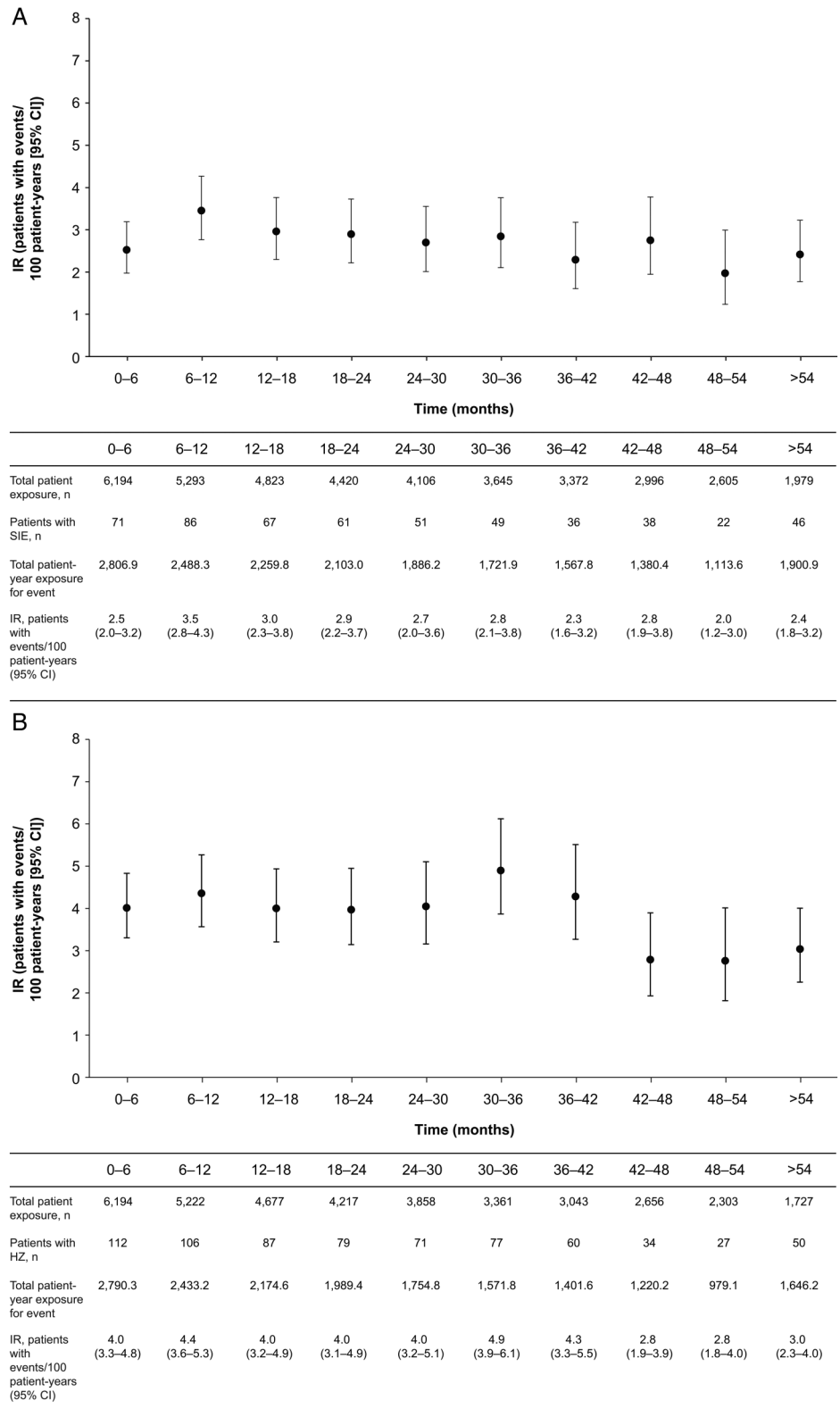
\*Average dosing was based on average daily dose: patients receiving <15 mg/day were assigned to the 5 mg twice daily group; patients receiving ≥15 mg/day were assigned to the 10 mg twice daily group.

†Constant dosage without prior exposure to another tofacitinib dose or adalimumab during the study; patients who switched doses were not included in this group.

‡Within 30 days of last dose of study drug.

AE, adverse event; IR, incidence rate; n, unique number of patients with event; SAE, serious AE.

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

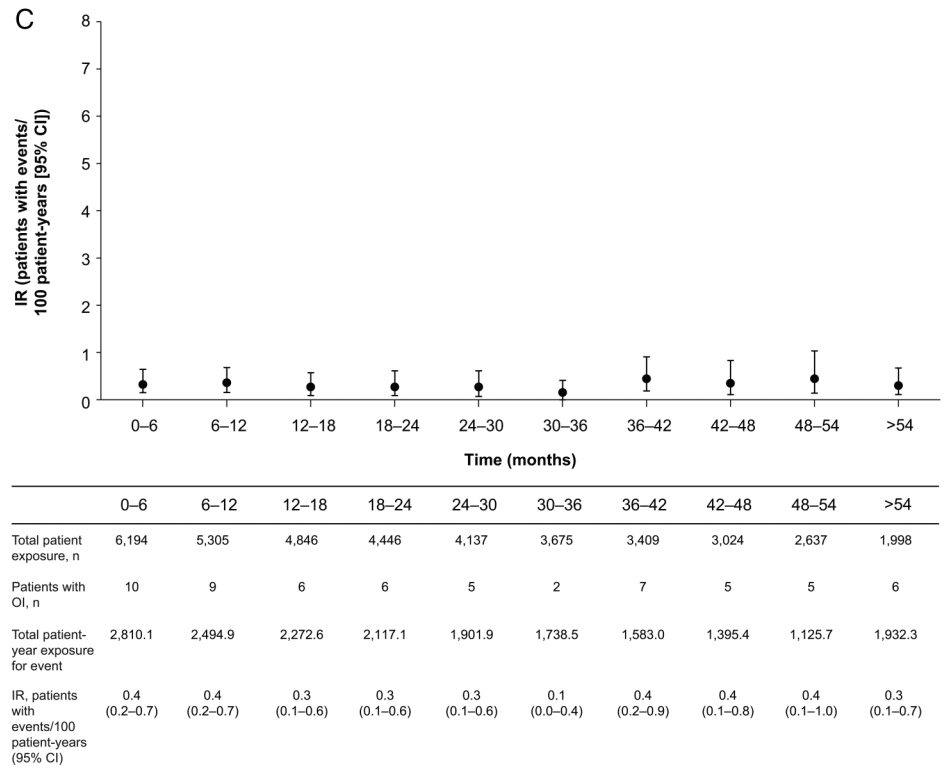


gender, line of therapy (3rd vs 2nd line), geographical region (Asia, Europe and Latin America, each vs US/Canada) and time-varying tofacitinib dose (referent to 5 mg twice daily) (all  $p < 0.05$ ) (figure 2A).

Six patients had lymphopenia  $< 500$  cells/ $\mu$ L, with a crude IR (95% CI) for SIEs of 8.3 (3.0 to 18.1), and 115 patients had lymphopenia  $\geq 500$ – $< 1000$  cells/ $\mu$ L, with a crude IR (95% CI) of

3.4 (2.8 to 4.1). Inclusion of confirmed ALC  $< 500$  cells/ $\mu$ L as a time-varying categorical covariate in a multivariable Cox regression model showed an increased risk of SIEs in the period following confirmed ALC  $< 500$  cells/ $\mu$ L (HR (95% CI) 2.5 (1.1 to 5.7)) versus the period before confirmed ALC  $< 500$  cells/ $\mu$ L. Evaluation of a threshold of ALC  $< 1000$  cells/ $\mu$ L (exposure period prior to lymphopenia  $< 1000$  cells/ $\mu$ L vs

Figure 1 Continued



exposure period after lymphopenia  $<1000$  cells/ $\mu$ L) showed a HR (95% CI) of 1.3 (1.0 to 1.6) ( $p=0.02$ ), suggesting a trend towards increasing risk with lower lymphocyte counts. The 500 cells/ $\mu$ L threshold is recommended in the product label as the discontinuation criterion.

### Herpes zoster

Overall, 703 patients developed HZ; IRs for the first occurrence of non-serious or serious HZ had overlapping 95% CIs for average and constant tofacitinib 5 and 10 mg twice daily (table 3). IR analysis by 6-month intervals did not reveal increasing IRs with longer exposure (figure 1B).

Most HZ cases (92%) involved one dermatome; IR (95% CI) of disseminated/multidermatomal HZ was 0.3 (0.2 to 0.4). Serious HZ was reported in 53 patients. HZ IRs (95% CI) were higher in Asia (5.9 (5.2 to 6.6)) than other regions (see online supplementary table S2).

Baseline glucocorticoid doses  $>0$ – $<7.5$  mg/day and  $\geq 7.5$  mg/day were associated with increased HZ (HR (95% CI) 1.5 (1.3 to 1.9) and 1.4 (1.1 to 1.8), respectively, vs no glucocorticoid use;  $p<0.0001$ ) (figure 2B). Other significant risk factors were baseline age, geographical region, smoking history (ex-smoker and smoker, each vs never smoked) and time-varying tofacitinib dose (all  $p<0.05$ ) (figure 2B).

### Opportunistic infections

OIs excluding TB were reported in 61 patients (see online supplementary table S3), and OIs including TB in 97 patients; 95% CIs for IRs with average and constant tofacitinib 5 and 10 mg twice daily overlapped (table 3). IRs of OIs excluding TB did not increase with longer exposure (figure 1C). Thirty-one OI events were serious.

Baseline age, geographical region and time-varying tofacitinib dose were associated with increased OIs excluding TB (all  $p<0.05$ ) (figure 2C).

### Tuberculosis

Active TB was reported in 36 patients, four had latent TB at screening with a history of adequate treatment. TB IRs were similar for average and constant tofacitinib 5 and 10 mg twice daily (table 3). Pulmonary and non-pulmonary TB occurred in 17 and 19 patients, respectively. Most cases (28/36) occurred in geographical regions endemic for TB (see online supplementary table S4). At screening, 301 patients had latent TB in the phase I–III studies. Of these, 23 had untreated or inadequately treated latent TB, and were treated with isoniazid and permitted to enrol in the study after  $\geq 1$  month of treatment. None of these 301 patients developed active TB.

### Malignancies

Malignancies (excluding non-melanoma skin cancer, NMSC) occurred in 173 patients and NMSC in 118 patients; analysis of IRs by dose revealed widely overlapping 95% CIs (table 3).

Geographical variation in the NMSC distribution was observed (see online supplementary table S5). Analyses of IRs by 6-month intervals did not reveal any trend (figure 3A, B). A constant hazard over time for developing a malignancy was seen before month 60 (see online supplementary figure S1). Estimation beyond month 60 was less precise due to small patient numbers and limited patient-years of exposure.

Age-adjusted and sex-adjusted SIR (95% CI) for all malignancies (excluding NMSC) versus SEER among tofacitinib-treated patients was 1.0 (0.8 to 1.1). SIRs (95% CI) for lymphoma, lung cancer and breast cancer were 2.6 (1.6 to 4.1), 1.4 (1.0 to 2.0) and 0.5 (0.3 to 0.7), respectively.

### GI perforations

Twenty-two patients experienced GI perforations. IRs (95% CI) were 0.11 (0.07 to 0.17) overall (0.07 (0.02 to 0.17) and 0.14 (0.08 to 0.22) for average 5 and 10 mg twice daily; 0.00 (0.00 to 0.10) and 0.15 (0.07 to 0.27) for



**Table 3** IRs of infections or malignancies, patients with events/100 patient-years (95% CI)

	All tofacitinib doses N=6194	Average tofacitinib 5 mg twice daily * N=2239	Average tofacitinib 10 mg twice daily * N=3955	Constant tofacitinib 5 mg twice daily † N=2342	Constant tofacitinib 10 mg twice daily † N=2814
Total patient-years of exposure, years	19 406	6870	12 536	3623	6702
<i>Infections</i>					
Serious infections (n=527)‡	2.7 (2.5 to 3.0)	3.1 (2.7 to 3.5)	2.6 (2.3 to 2.9)	2.3 (1.8 to 2.8)	2.7 (2.3 to 3.1)
HZ (non-serious and serious) (n=703)	3.9 (3.6 to 4.2)	3.8 (3.3 to 4.3)	4.0 (3.6 to 4.4)	3.5 (2.9 to 4.1)	4.1 (3.6 to 4.7)
HZ (serious‡) (n=53)	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.5)	0.2 (0.2 to 0.4)	0.3 (0.1 to 0.5)	0.2 (0.1 to 0.3)
Disseminated/multidermatomal HZ (n=53)	0.3 (0.2 to 0.4)	NA	NA	0.1 (0.0 to 0.2)	0.2 (0.1 to 0.4)
Opportunistic infection, excluding TB (n=61)	0.3 (0.2 to 0.4)	0.4 (0.2 to 0.6)	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.5)	0.3 (0.1 to 0.4)
Opportunistic infection, including TB (n=97)	0.5 (0.4 to 0.6)	0.5 (0.4 to 0.7)	0.5 (0.4 to 0.6)	0.3 (0.2 to 0.6)	0.5 (0.4 to 0.7)
TB (n=36)	0.2 (0.1 to 0.3)	0.1 (0.07 to 0.3)	0.2 (0.1 to 0.3)	0.08 (0.02 to 0.2)	0.3 (0.2 to 0.4)
Mortality due to infections (n=23)	0.1 (0.08 to 0.2)	0.2 (0.1 to 0.4)	0.1 (0.0 to 0.1)	0.2 (0.1 to 0.4)	0.05 (0.009 to 0.1)
<i>Malignancies</i>					
Malignancy excluding NMSC (n=173)	0.9 (0.8 to 1.0)	1.0 (0.8 to 1.3)	0.8 (0.7 to 1.0)	0.8 (0.5 to 1.2)	0.9 (0.7 to 1.2)
NMSC (n=118)	0.6 (0.5 to 0.7)	0.5 (0.4 to 0.7)	0.7 (0.5 to 0.8)	0.4 (0.3 to 0.7)	0.6 (0.5 to 0.9)
Lung (n=32)	0.2 (0.1 to 0.2)	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.4)	0.1 (0.1 to 0.2)
Breast (n=25)§	0.2 (0.1 to 0.2)	0.2 (0.1 to 0.3)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.4)	0.2 (0.1 to 0.3)
Lymphoma (n=19)¶	0.1 (0.1 to 0.2)	0.09 (0.0 to 0.2)	0.1 (0.1 to 0.2)	0.1 (0.0 to 0.3)	0.1 (0.1 to 0.2)

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

†Constant dosage without prior exposure to another tofacitinib dose or adalimumab during the study; patients who switched doses were not included in this group.

‡Defined as requiring hospitalisation or parenteral antimicrobial therapy, or otherwise meeting SAE criteria.

§IR calculated for female patients only; N [total patient-years' exposure]: N=5125 [16 077] (all tofacitinib); N=1863 [5701] (average tofacitinib 5 mg twice daily); N=3262 [10 377] (average tofacitinib 10 mg twice daily); N=1935 [2984] (constant tofacitinib 5 mg twice daily); N=2335 [5608] (constant tofacitinib 10 mg twice daily).

¶Lymphoproliferative disorders/lymphoma.

HZ, herpes zoster; IR, incidence rate; n, unique number of patients with event; NA, not available; NMSC, non-melanoma skin cancer; SAE, serious adverse event; TB, tuberculosis.

constant 5 and 10 mg twice daily). Perforations occurred in the large bowel, excluding anus and rectum (n=13), gastroduodenal area (n=3), small bowel (n=1), anus and rectum (n=2) and undetermined locations (n=3). All received concomitant therapy with non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. Ten patients received NSAIDs and corticosteroids; nine NSAIDs alone and three chronic corticosteroid therapy alone. Thirteen patients had a history of diverticulitis or diverticulosis and two additional patients had a history of gastric ulcers.

## DISCUSSION

This analysis presents an integrated view of safety data across the tofacitinib RA development programme. Types and rates of AEs were similar to those observed in phase III trials, with no evidence of directional trends with longer-term tofacitinib exposure through 8.5 years.

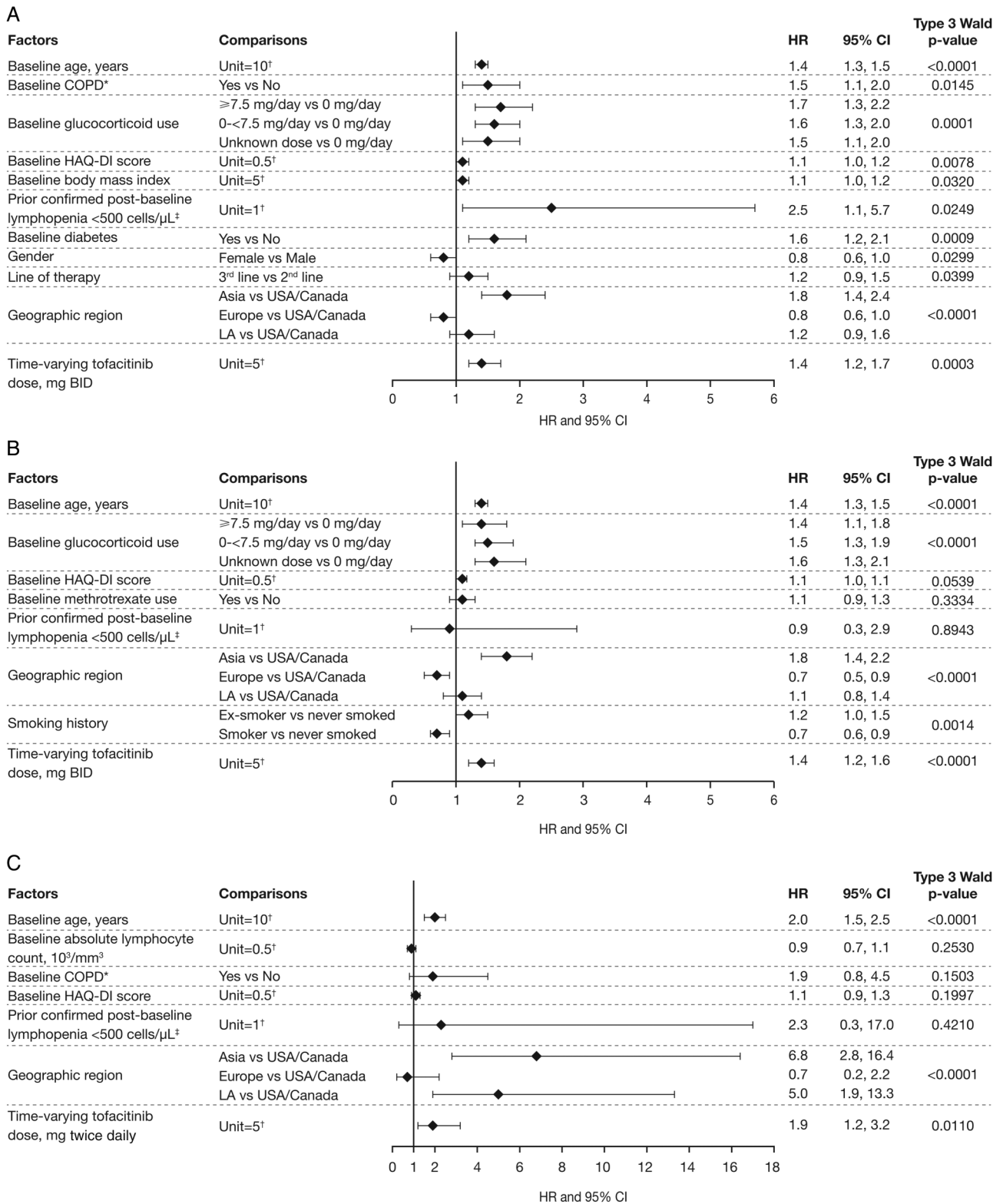
SIEs are an identified risk with immunomodulatory medications in RA, including tofacitinib and biological DMARDs (bDMARDs). IRs were consistent with those reported in phase III tofacitinib trials.<sup>12–17 24</sup> SIE IRs for bDMARDs in RA clinical trials range from 3.0 to 5.5 per 100 patient-years,<sup>25</sup> and are similar to those reported with tumour necrosis factor inhibitors (TNFi) in RA registries (3.2–4.6 per 100 patient-years).<sup>26–28</sup> IRs with tofacitinib were generally consistent with IRs with bDMARDs.<sup>25–28</sup> Previous studies of registry data revealed a decrease in SIEs with TNFi over time, likely due to discontinuation in patients at increased risk of SIEs,

and reduction in risk associated with improvement in function and decreased glucocorticoid use.<sup>29–31</sup> In contrast, analyses of data from open-label LTE studies suggest that the SIE risk remains stable over time.<sup>32 33</sup>

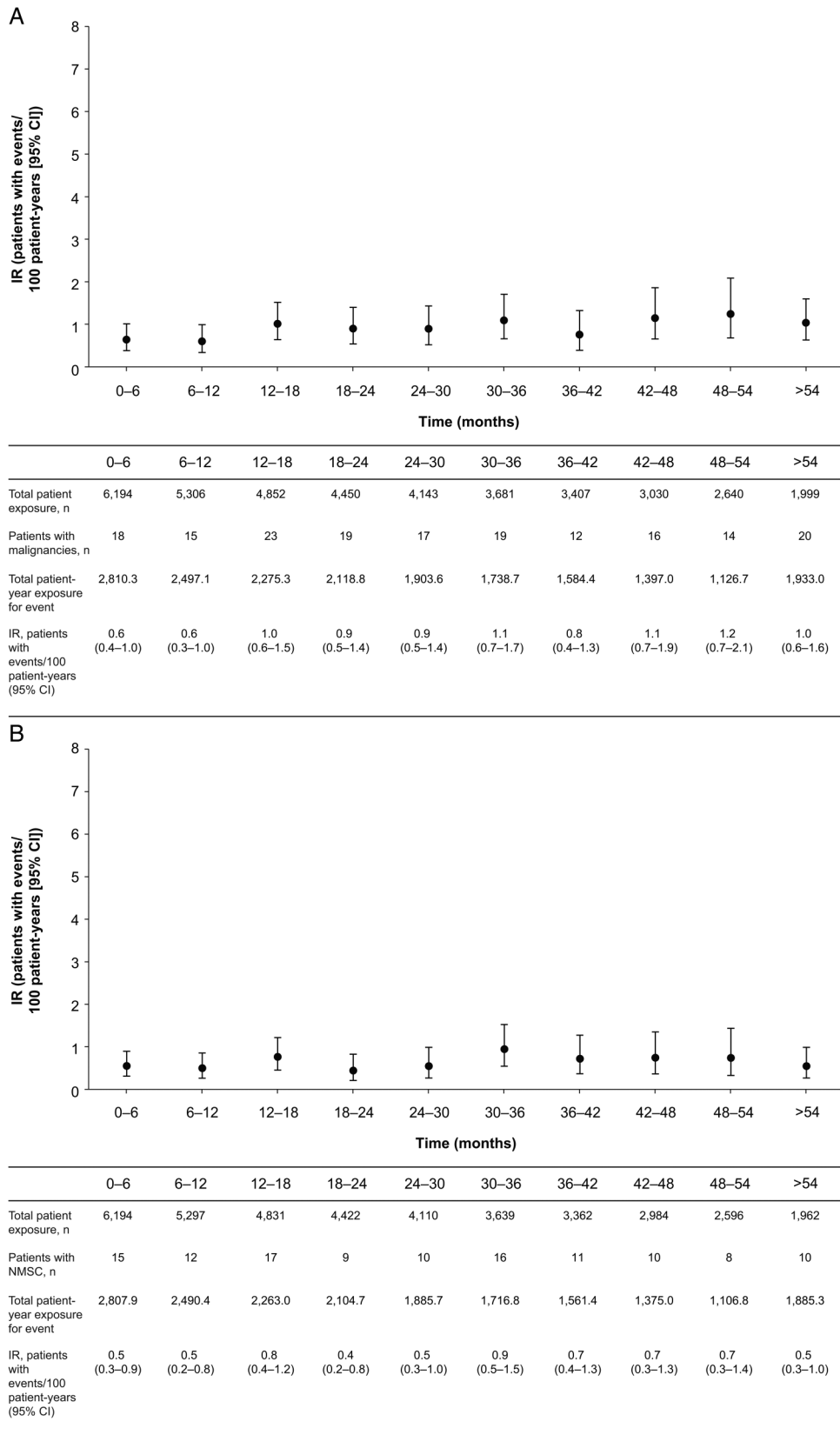
Although an increase in SIEs was not detected here, the studies discontinued patients who developed SAEs, which may have depleted patients at risk of recurrent SAEs. Only time to first event, and not second and subsequent events were analysed.

Previous analyses of the tofacitinib RA development programme identified increased rates of HZ with tofacitinib versus placebo, with greater age and Asian locations identified as risk factors.<sup>34</sup> Here, most HZ cases remained non-serious allowing study continuation; approximately 8% of patients with HZ experienced disseminated/multidermatomal HZ. HZ risk is elevated in patients with RA versus the general population;<sup>35</sup> reports are conflicting regarding risk with bDMARDs.<sup>36 37</sup> Rate comparisons between tofacitinib and bDMARDs are limited by lack of directly comparable data, but indirect comparisons indicate that IRs appear higher with tofacitinib versus other agents.<sup>37</sup> However, rates of disseminated/multidermatomal HZ and serious HZ were low and comparable with rates of multidermatomal and ophthalmic HZ reported with bDMARDs or conventional DMARDs.<sup>37</sup>

Rates of fungal and viral OIs were similar to those previously reported,<sup>20</sup> suggesting OIs are a risk with tofacitinib, although it is unclear whether risk differs from that associated with



**Figure 2** HRs of potential risk factors for events of serious infection (A), herpes zoster (B) and opportunistic infections excluding tuberculosis (C)—results from multivariable Cox regression models in the phases I–III and LTE studies \*Medical history and/or complication of COPD. <sup>†</sup>In Unit=x, 'x' is the change in the continuous variable corresponding to which the change in hazards is observed. <sup>‡</sup>Based on exposure period before lymphopenia <500 cells/μL versus exposure period after lymphopenia <500 cells/μL. COPD, chronic obstructive pulmonary disease; HAQ-DI, Health Assessment Questionnaire-Disability Index; LA, Latin America; LTE, long-term extension.



**Figure 3** IRs for malignancies excluding NMSC (A) and (B) NMSC over time for all tofacitinib doses. IR, incidence rate; NMSC, non-melanoma skin cancer.



bDMARDs. Precise estimations of differences in OI risk among RA therapies are limited by heterogeneous definitions of OIs,<sup>38</sup> geographical variability and lack of head-to-head studies with sufficient power to detect differences.

A higher incidence of TB has been observed in patients with RA versus the general population, and in those receiving TNFi.<sup>39–40</sup> Here, the elevation in TB IR with tofacitinib was within the range for bDMARDs.<sup>33–41</sup> TB rates reflected geographical background TB prevalence.

IR of malignancies (excluding NMSC) here was 0.89, similar to those observed in previous tofacitinib studies.<sup>18–21</sup> Patients with RA are at higher risk of developing some malignancies than the general population.<sup>42–43</sup> IRs and SIRs for malignancies (excluding NMSC) reported here are in the range reported with bDMARDs.<sup>33–44–46</sup> Analysis of IR of malignancies by 6-month interval exposure revealed variability, whereas analysis of the probability distribution of time to first malignancy event revealed a constant hazard over time. Of note, no real dose difference was observed. Although SIRs for malignancies (excluding NMSC) by 6-month interval exposure were not evaluated, SIRs were stable over time in an analysis of malignancy data (to 10 April 2013) from 14 tofacitinib studies.<sup>21</sup> Despite this, vigilance should be exercised when evaluating malignancy risk with long-term exposure.

Cardiovascular safety data for tofacitinib pooled from phase III and LTE studies (data cut-off: 10 April 2013) have been published.<sup>47</sup> Similar findings were reported in this analysis of pooled data from phases I–III and LTE studies (data cut-off: 31 March 2015; see online supplementary appendix).

GI perforations are a known risk in patients with RA, especially in patients treated with NSAIDs or glucocorticoids.<sup>48</sup> GI perforations with tocilizumab had an IR of 0.3 events/100 patient-years,<sup>49</sup> and an observational study revealed an IR of 0.1 events/100 patient-years for TNFi.<sup>50</sup> Another study showed higher GI perforation rates with bDMARDs and concomitant glucocorticoids (0.1 events/100 patient-years), versus bDMARDs without glucocorticoids (0.05 events/100 patient-years), indicating glucocorticoid use as a risk factor.<sup>51</sup> GI perforations IRs here are within the range reported; most patients with GI perforations had underlying risk factors (eg, glucocorticoids and/or NSAIDs).

Comparison of IRs by dose is limited by several factors. One factor is the imbalance between the tofacitinib 5 and 10 mg twice daily doses in the LTE studies, due to the fact that patients were not randomised to treatment. Instead, patients from phase II and III studies were transitioned into the LTE on 5 and 10 mg twice daily, respectively, except for patients from China and Japan who initiated treatment with tofacitinib 5 mg twice daily per protocol. Therefore, differences in the chronology of LTE study initiation and patient numbers from phase II versus phase III led to a longer median duration of exposure with 5 mg twice daily, but higher overall patient-years' exposure with 10 mg twice daily. This, coupled with differences in geographical regions between trials, preclude definitive dose comparisons. This analysis is also limited by exclusion of patients upon development of a SAE and censoring at time of first event, meaning healthier patients remain at later time points. This limits our ability to evaluate potential changes in SAE rates over time with greater cumulative tofacitinib exposure. Furthermore, the average dosing approach used in the primary analysis did not consider the actual dose at the time of AE. As any method of dose categorisation in this population would have drawbacks, we used constant dosing in a sensitivity analysis to give a more

complete picture. Comparisons with placebo were reported for the placebo-controlled phases II and III tofacitinib index studies;<sup>3–7 12–16</sup> however, duration of treatment with placebo was short, and patient-years of exposure to placebo was limited, therefore we have not included placebo data in our analysis.

This report describes the tofacitinib safety profile across the RA clinical programme to 31 March 2015, with >6000 patients treated for ≤8.5 years. These data represent the most comprehensive view of long-term safety to date, and reveal a stable AE profile versus controlled studies and earlier analyses of LTE data. Ongoing comparative clinical studies and post-marketing surveillance will provide further information on the tofacitinib risk profile in the clinical trial and real-world settings.

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