

Efficacy and safety of tofacitinib in older and younger patients with rheumatoid arthritis

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Abstract Objective

Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). We evaluated the efficacy and safety of tofacitinib 5 or 10 mg twice daily (BID), in patients with moderate to severe RA, aged ≥ 65 and < 65 years.

Methods

Data were pooled from five Phase 3 trials and, separately, from two open-label long-term extension (LTE) studies (data cut-off April, 2012). Patients received tofacitinib, or placebo (Phase 3 only), with/without conventional synthetic DMARDs (mainly methotrexate). Clinical efficacy outcomes from Phase 3 studies were evaluated at Month 3. Safety evaluations using pooled Phase 3 data (Month 12) and pooled LTE data (Month 24) compared exposure-adjusted incidence rates (IRs; with 95% confidence intervals [CIs]), in older versus younger patients.

Results

In Phase 3 and LTE studies, 15.3% (475/3111) and 16.1% (661/4102) of patients, respectively, were aged ≥ 65 years. Consequently, exposure to tofacitinib was lower in older versus younger patients in Phase 3 (259.2 vs. 1554.9 patient years [pt-yrs]) and LTE (962.1 vs. 5071.7 pt-yrs) studies. Probability ratios for ACR responses and HAQ-DI improvement from baseline ≥ 0.22 (Month 3) favoured tofacitinib and were similar in older and younger patients, with overlapping CIs.

IRs for SAEs and discontinuations due to AEs were generally numerically higher in older versus younger patients, irrespective of treatment.

Conclusion

Older patients receiving tofacitinib 5 or 10 mg BID had a similar probability of ACR20 or ACR50 response and, due to comorbidities, a numerically higher risk of SAEs and discontinuations due to AEs compared with younger patients.

Key words

age, efficacy, rheumatoid arthritis, safety, risk, benefit, tofacitinib, elderly, geriatric

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Introduction

Although the median age of onset of rheumatoid arthritis (RA) is in the fifth decade of life, the rate of new onset of RA is highest among people in their sixties (1). As the population ages, a greater proportion of patients will have RA at an advanced age. Current RA guidelines do not differentiate treatment options by age category (2–4). However, successful treatment of RA may be more difficult in older (≥ 65 years) than in younger (< 65 years) patients for several reasons. Older patients with and without RA are more likely than younger patients to have comorbid conditions (e.g. cardiovascular disease, diabetes, infections and malignancies) since the incidence and prevalence of these conditions tends to increase with age, regardless of the treatment received (5, 6). Older patients are also at increased risk of certain treatment side effects compared with younger patients (7). Perhaps consequently, the likelihood of an older patient receiving a conventional synthetic (cs) or biologic (b) disease-modifying anti-rheumatic drug (DMARD) therapy for RA appears to be lower than for younger patients (8, 9). Additionally, given any level of disease activity, older patients with RA appear to receive less aggressive treatment (10–12). Thus, it is important that differences in treatment response or safety outcomes be evaluated in the context of age. Understanding age-associated differences in outcomes may aid treatment decision-making, particularly in understanding the role of new therapies in the treatment algorithm.

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of RA. Tofacitinib works at the intracellular level to partially and reversibly inhibit JAK-dependent inflammatory cytokine signalling involving IL-6 and IFN β pathways that are critical to the pathogenesis of RA and thus modulate the immune response (13). The efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) has been demonstrated in adult patients with moderate to severe active RA in randomised, double-blind studies of up to 24 months' duration (14–24) and in ongoing open-label, long-term extension (LTE) studies of

up to 96 months' observation (25). The Phase 3 RA clinical development programme for tofacitinib enrolled more than 400 patients aged ≥ 65 years. At the time of this analysis, the LTE studies enrolled more than 600 patients aged ≥ 65 years. The aim of this post-hoc pooled analysis was to describe the efficacy and safety of tofacitinib 5 and 10 mg BID *versus* placebo in older (≥ 65 years) and younger (< 65 years) patients with RA, who participated in any of five, Phase 3, double-blind, randomised controlled trials or two open-label LTE studies. In addition, the potential effects of selected baseline demographics and characteristics on treatment response, serious adverse events (SAEs) and other safety events of special interest, were explored to inform clinical decision-making for the use of tofacitinib in older patients with RA.

Methods

Patients

At enrolment, all patients were aged ≥ 18 years, with a diagnosis of active RA, based upon the American College of Rheumatology (ACR) revised criteria (1987) (26). Patients had ≥ 6 tender or painful joints and ≥ 6 swollen joints, except for those in the ORAL Sync study, who had ≥ 4 tender or painful joints and ≥ 4 swollen joints. All patients had an erythrocyte sedimentation rate (Westergren method) > 28 mm/h, or C-reactive protein level > 7 mg/L, and a previous inadequate response or intolerance to one or more csDMARDs (mainly methotrexate) or bDMARDs (mainly tumour necrosis factor inhibitors [TNFi]).

Studies included

Data were included from five Phase 3, double-blind, randomised controlled trials of 6 to 24 months' duration (ORAL Step [NCT00960440] (20), ORAL Sync [NCT00856544] (21), ORAL Scan [NCT00847613] (22), ORAL Solo [NCT00814307] (23), ORAL Standard [NCT00853385] (24)), and two open-label LTE studies (A3921024, global [NCT00413699], and A3921041, Japan [NCT00661661] (27)). Patients from qualifying Phase 1, Phase 2 and Phase 3 index studies were

eligible to participate in open-label LTE studies.

Study treatment

In Phase 3 studies, patients received placebo or tofacitinib (5 or 10 mg BID) as monotherapy (ORAL Solo), or with stable doses of background csDMARD (ORAL Scan, ORAL Step, ORAL Standard and ORAL Sync). Patients randomised to placebo were blindly advanced to a pre-specified dose of tofacitinib at Month 3 or Month 6 as per study protocol.

In LTE studies, patients from Phase 2 index studies initiated treatment with tofacitinib 5 mg BID, while those from Phase 3 initiated with tofacitinib 10 mg BID except patients from China and Japan who initiated treatment with tofacitinib 5 mg BID. The dose of tofacitinib could be reduced from 10 to 5 mg BID, or temporarily discontinued, for safety reasons. In cases of inadequate response, the dose of tofacitinib could be increased from 5 to 10 mg BID at the discretion of the investigator. Patients were classified based on the highest dose of tofacitinib received during the first 135 days of treatment in the LTE studies. All LTE study data captured, up to and including 19 April 2012, were included in this analysis. At the time of the analysis, LTE study data collection was ongoing (*i.e.* LTE study databases were not locked and some values may change *versus* the final locked database).

Efficacy outcomes

Efficacy outcomes, including ACR 20%, 50% and 70% response rates (ACR20, ACR50 and ACR70) and improvement from baseline in Health Assessment Questionnaire-Disability Index score (HAQ-DI) ≥ 0.22 , were evaluated at Month 3 (*i.e.* before any patient randomised to the placebo group advanced to tofacitinib) using pooled Phase 3 data. The number needed to treat (NNT) was calculated for the same outcomes (28).

After the publication of one of the Phase 3 studies (ORAL Standard) (24), one of the sites for this study (nine patients randomised) was found to be non-compliant with study procedures.

These nine patients were excluded from the efficacy analyses presented here.

Safety outcomes

Safety was evaluated in the Phase 3 study population (up to Month 12) and, separately, in the LTE study population (up to Month 24). Safety endpoints, assessed using exposure estimates, incidence rates (IRs; patients with events per 100 patient-years [pt-yrs] of exposure) and IR differences (older *vs.* younger patients) included: SAEs; discontinuations due to adverse events (AEs); serious infections; serious and non-serious herpes zoster (HZ); opportunistic infections (OIs; including tuberculosis); major adverse cardiovascular events (MACE); and all malignancies (excluding non-melanoma skin cancer [NMSC]). Serious infections were defined as any infection that required hospitalisation or parenteral antimicrobial therapy, or was otherwise considered to be an SAE. The number needed to harm (NNH) was calculated for the same outcomes (28).

Additional exploratory analyses

The probability of ACR20 (Month 3) and occurrence of SAEs (up to Month 12) were compared, using probability ratios (PRs), in older and younger patients in Phase 3 studies, according to selected baseline demographics and characteristics, including: gender; body mass index (BMI; >30 *vs.* ≤ 30); smoking status; duration of RA (<5 years *vs.* ≥ 5 years); and presence of other health conditions of clinical interest such as diabetes, chronic obstructive pulmonary disease (COPD), asthma or depression. The use of specific, relevant, concomitant medications (such as antidepressants) was taken as a surrogate indicator of a comorbid health condition under treatment (*e.g.* depression/anxiety).

Statistical analyses

Rates of ACR20, ACR50 and ACR70 at Month 3, and improvement from baseline in HAQ-DI of ≥ 0.22 points at Month 3, were reported as PRs (proportion of responders in tofacitinib group divided by proportion of responders in the placebo group) with 95% confidence

intervals (CIs). The PR was estimated as a Mantel-Haenszel adjusted relative risk – interpreted in the same way as for relative risk – with 95% CIs based on a log-normal assumption for the PR. PRs were then compared in older and younger patients. Efficacy and NNT calculations used the full analysis set (all patients who received ≥ 1 dose of study medication). All patients with data at Month 3 were counted in the denominator. For each combination of the three variables – age group, tofacitinib dose and efficacy measure – the NNT was calculated as the reciprocal of the difference in percent of responders between tofacitinib and placebo. Similarly, for the safety outcomes, the NNH was calculated as the reciprocal of the difference in IRs between tofacitinib and placebo.

IR differences with 95% CIs, and exposure-adjusted IRs, were calculated for safety endpoints at Month 12 in Phase 3 studies and at Month 24 in LTE studies, based on first occurrence of safety events. Patients randomised to placebo (Phase 3 studies only) were counted in the placebo group until advancement, then in the tofacitinib group (5 or 10 mg BID according to randomisation) after advancement. IRs were compared in older *versus* younger patients using the full analysis set. SAEs occurring after the end of treatment were counted in the numerator and full treatment exposure was included in the denominator.

The probability of achieving ACR20 or reporting an SAE at Month 3 was estimated based on a logistic regression of the outcome on gender, BMI, smoking status (ever smoked/never smoked), diabetes status (yes/no), duration of RA (<2 , 2–5, 5–10 and ≥ 10 years), antibody status (rheumatoid factor [RF] + and/or anti-cyclic citrullinated peptide [CCP] +, RF– and anti-CCP–), use of systemic corticosteroids at baseline (yes/no), use of non-steroidal anti-inflammatory drugs/COX-2 inhibitors at baseline (yes/no), use of antidepressants at baseline (yes/no) and use of COPD/asthma medications at baseline (yes/no). Correlation plots were generated by plotting the estimated probability of clinical response (ACR20 at Month 3) on the x axis, with estimated

Table I. Demographic data and baseline clinical characteristics in five Phase 3 and two long-term extension studies of tofacitinib, by age group (<65 years and ≥65 years) and treatment.

	Phase 3 studies						LTE studies			
	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Placebo		Tofacitinib 5 mg BID		Tofacitinib 10 mg BID	
	<65 years (n=1026)	≥65 years (n=190)	<65 years (n=1030)	≥65 years (n=184)	<65 years (n=580)	≥65 years (n=101)	<65 years (n=1189)	≥65 years (n=232)	<65 years (n=2252)	≥65 years (n=429)
Female (%)	84.8	82.6	85.0	84.8	82.1	76.2	84.5	78.0	83.3	80.2
Age, mean (range)	50.1 (18.0–64.0)	70.2 (65.0–86.0)	49.5 (18.0–64.0)	69.2 (65.0–85.0)	49.4 (18.0–64.0)	70.1 (65.0–82.0)	49.6 (18.0–64.0)	69.3 (65.0–81.0)	50.4 (18.0–64.0)	69.5 (65.0–86.0)
Ethnicity (%)										
Caucasian	58.3	73.2	59.3	70.7	62.2	77.2	43.7	56.5	67.0	79.2
Black	3.9	2.6	2.6	4.3	3.8	2.0	1.6	1.3	3.7	3.0
Asian	28.7	17.4	27.5	16.8	26.2	13.9	45.7	36.2	20.2	12.5
Other	9.2	6.8	10.6	8.2	7.8	6.9	9.0	6.0	9.1	5.3
Geographical location (%)										
US/Canada	215 (21.0)	51 (26.8)	218 (21.2)	57 (31.0)	361 (62.2)	32 (21.7)	156 (13.1)	42 (18.1)	703 (31.3)	149 (34.7)
Europe	323 (31.5)	82 (43.2)	331 (32.1)	67 (36.4)	22 (3.8)	44 (43.6)	269 (22.6)	71 (30.6)	744 (33.1)	179 (41.7)
Latin America	173 (16.9)	16 (8.4)	165 (16.0)	20 (10.9)	152 (26.2)	9 (8.9)	227 (19.1)	35 (15.1)	330 (14.7)	29 (6.8)
Asia	315 (30.7)	41 (21.6)	316 (30.7)	40 (21.7)	45 (7.8)	16 (15.8)	537 (45.2)	84 (36.2)	471 (21.0)	72 (16.8)
Concomitant corticosteroids (%)	57.3	54.7	55.8	52.7	56.4	47.5	53.7	51.7	50.0	50.1
No. prior bDMARDs (mean)	1.6	1.5	1.5	1.7	1.6	1.6	1.0	1.0	1.3	1.0
≥1 cardiac disorder (%)	5.2	16.8	6.7	19.0	6.4	14.9	4.3	13.8	6.5	17.5
Diabetes (%)	7.7	15.3	7.2	15.8	5.9	13.9	4.4	11.6	6.2	9.8
Smoking status (%)										
Never smoked	67.3	61.6	65.6	71.7	62.9	59.4	63.0	62.9	62.3	62.5
Smoker	14.7	7.9	19.8	4.3	20.0	13.9	18.3	10.3	19.4	10.3
Ex-smoker	17.9	30.5	14.6	23.9	16.7	26.7	13.4	22.0	18.0	27.0
Missing	–	–	–	–	<1.0	–	5.3	4.7	<1.0	<1.0

bDMARDs: biologic disease-modifying anti-rheumatic drugs; BID: twice daily; LTE: long-term extension.

probability of an SAE (up to Month 3) on the y axis.

Results

Patients

The pooled, Phase 3 data set included 3111 patients, of whom 1216 received tofacitinib 5 mg BID, 1214 received tofacitinib 10 mg BID and 681 received placebo (Table I). In total, 475 patients (15.3%) were aged ≥65 years: 15.6% (190/1216), 15.2% (184/1214) and 14.8% (101/681) patients in the tofacitinib 5 mg BID, tofacitinib 10 mg BID and placebo groups, respectively (Table I). The total exposure to tofacitinib (5 mg and 10 mg BID, not including patients initially randomised to placebo) in Phase 3 studies was 259.2 pt-yrs in patients aged ≥65 years and 1554.9 pt-yrs in patients aged <65 years. The mean duration of exposure to tofacitinib in Phase 3 studies was 0.55 yrs and 0.59 yrs in older and younger patients, respectively. The pooled LTE data set included

4102 patients, of whom 1421 received tofacitinib 5 mg BID and 2681 received tofacitinib 10 mg BID. In total, 661 (16.1%) were aged ≥65 years: 16.3% (232/1421) and 16.0% (429/2681) patients in the tofacitinib 5 mg and 10 mg BID groups, respectively (Table I). The corresponding total exposure in LTE studies was 962.1 pt-yrs and 5071.7 pt-yrs, in the older (≥65 years) and younger (<65 years) patient groups, respectively. The mean duration of exposure to tofacitinib in LTE studies was 1.46 yrs and 1.47 yrs in older and younger patients, respectively. The total exposure to placebo in Phase 3 studies was limited due to study design and randomisation: 28.9 pt-yrs and 173.7 pt-yrs in older and younger patients, respectively.

As global studies, the Phase 3 and LTE studies had good representation of patients from US/Canada, Europe, Asia and Latin America (Table I). However, in the LTE studies, a significant portion of patients receiving tofacitinib

5 mg BID were located in Asia while those receiving tofacitinib 10 mg BID were located in Europe and US/Canada (Table I). The proportion of Caucasians was generally higher for older *versus* younger patients (Table I). Similarly, the proportion with cardiac disorders or diabetes was higher in older than in younger patients. Among patients who had ever smoked, there was a higher proportion of current smokers among younger patients, while older patients tended to be ex-smokers (Table I).

Efficacy in older and younger patients

The PRs (95% CI) for clinical responses at Month 3 with tofacitinib 5 mg BID (vs. placebo) in older and younger patients, respectively, were as follows: for ACR20, 1.84 (1.36, 2.49) and 2.06 (1.81, 2.35); for ACR50, 2.70 (1.48, 4.95) and 3.42 (2.65, 4.42); for ACR70, 2.36 (0.95, 5.90) and 5.35 (3.21, 8.93); and for improvement from baseline in HAQ-DI (≥0.22), 1.13 (0.91, 1.39) and

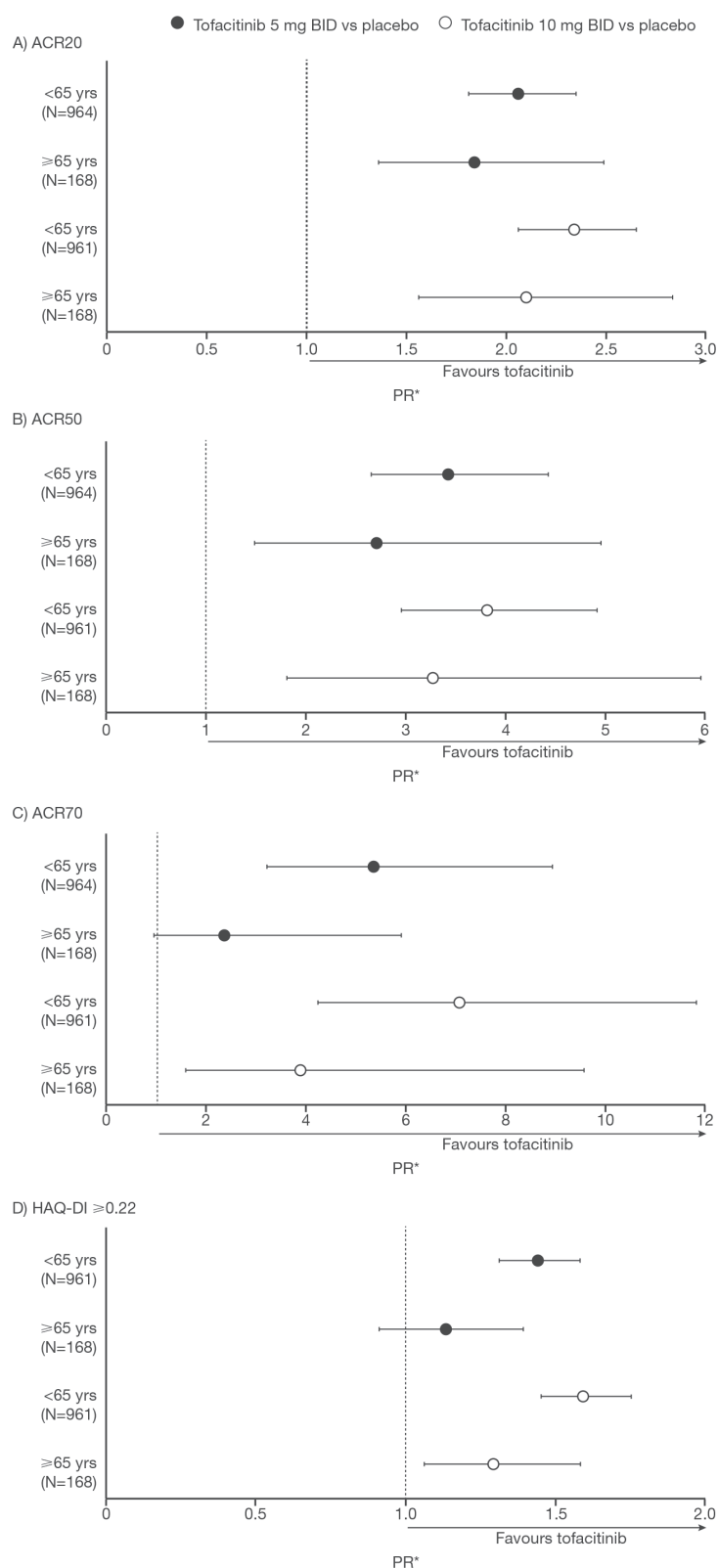


Fig. 1. Probability ratios (with 95% confidence intervals) for A) ACR20, B) ACR50, C) ACR70, and D) HAQ-DI improvement ≥ 0.22 from baseline at Month 3 in five Phase 3 studies of tofacitinib in older (≥ 65 years) versus younger patients (< 65 years).

*PR is the proportion of responders in the tofacitinib group divided by the proportion of responders in the placebo group at Month 3. A PR > 1 favours tofacitinib.

ACR: American College of Rheumatology; BID: twice daily; HAQ-DI: Health Assessment Questionnaire-Disability Index; PR: probability ratio; yrs: years.

1.44 (1.31, 1.58). The 95% CIs overlapped for all of the efficacy measures between the older and younger cohorts (Fig. 1). Similarly, PRs for clinical responses with tofacitinib 10 mg BID (vs. placebo) in older and younger patients, respectively, were as follows: for ACR20, 2.10 (1.56, 2.83) and 2.34 (2.06, 2.65); for ACR50, 3.27 (1.80, 5.95) and 3.81 (2.95, 4.91); for ACR70, 3.88 (1.58, 9.54) and 7.07 (4.23, 11.81); and for improvement from baseline in HAQ-DI (≥ 0.22), 1.29 (1.06, 1.58) and 1.59 (1.45, 1.75). As with tofacitinib 5 mg BID, the CIs overlapped between the older and younger groups receiving tofacitinib 10 mg BID (Fig. 1).

At Month 3, ACR20 and ACR50 rates were very similar in older and younger patients who received tofacitinib 5 and 10 mg BID (Table II). Comparisons of ACR70 rates should be interpreted with caution due to the limited number of patients achieving this response (Table II). Rates of HAQ-DI change from baseline in HAQ-DI ≥ 0.22 appeared to be somewhat lower for older patients than for younger patients in both tofacitinib groups at Month 3 (Table II). The NNTs for clinical responses can be found in Table II.

When data were stratified by geographic region, there were limited patient numbers in various regions resulting in no clear trends or significant differences in the probability of ACR20 and HAQ-DI responses between older and younger patients receiving tofacitinib; CIs generally overlapped and included 1.0 (data not shown).

Analysis of ACR20 response rates by age group and selected baseline characteristics

There were no clear trends or significant differences in the probability of ACR20 response between older and younger patients according to baseline characteristics. CIs generally overlapped and included 1.0 (Supplementary Fig. 1).

Safety in older and younger patients

• Phase 3 studies

Differences in IRs between older versus younger patients for AEs of special interest are presented by tofacitinib

Table II. Number needed to treat for key efficacy outcomes at Month 3 in five Phase 3 studies of tofacitinib, by age group (<65 years and ≥65 years) and treatment.

	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Placebo	
	<65 years (n=964)	≥65 years (n=168)	<65 years (n=961)	≥65 years (n=168)	<65 years (n=532)	≥65 years (n=86)
ACR20						
Response rate (%)	60.0	56.0	67.0	64.3	28.6	29.1
NNT (95% CI)	3.2 (2.7, 3.7)	3.7 (2.0, 5.4)	2.6 (2.3, 2.9)	2.8 (1.9, 3.8)	–	–
ACR50						
Response rate (%)	31.7	27.4	35.8	33.3	9.8	10.5
NNT (95% CI)	4.6 (3.7, 5.4)	5.9 (2.6, 9.2)	3.8 (3.3, 4.4)	4.4 (2.5, 6.2)	–	–
ACR70						
Response rate (%)	12.8	9.5	16.6	16.7	2.4	5.8
NNT (95% CI)	9.7 (7.4, 12.0)	27.0 (-21.3, 75.2)	7.0 (5.7, 8.4)	9.2 (2.8, 15.6)	–	–
HAQ-DI ≥0.22*						
Response rate (%)	64.5	57.1	71.1	64.3	44.0	51.2
NNT (95% CI)	4.9 (3.6, 6.1)	15.8 (-16.6, 48.2)	3.7 (3.0, 4.4)	7.6 (0.2, 15.1)	–	–

Number used to calculate NNT included all patients who were treated and eligible for the FAS population: for tofacitinib 5 mg BID, n=1012 (<65 years) and n=188 (≥65 years); for tofacitinib 10 mg BID, n=1017 (<65 years) and n=181 (≥65 years); and for placebo, n=574 (<65 years) and n=99 (≥65 years). Patients with missing results were not considered as failures.

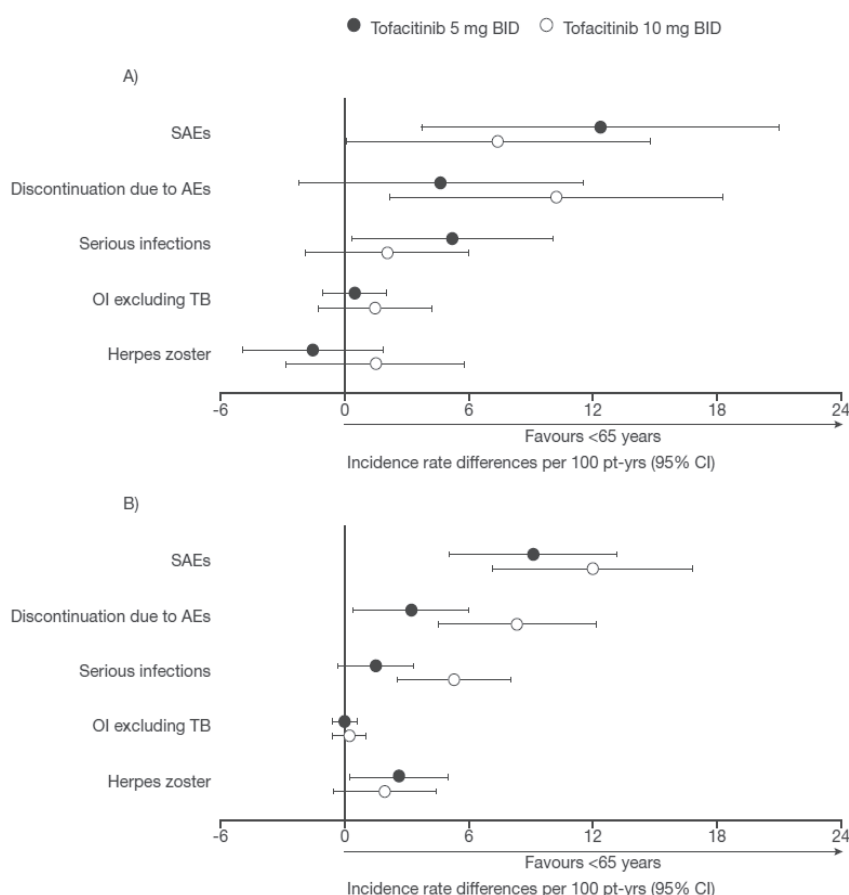
*n=961 for patients in the tofacitinib 5 mg BID group evaluable for HAQ-DI ≥0.22.

ACR: American College of Rheumatology; BID: twice daily; CI: confidence interval; FAS: full analysis set; HAQ-DI: Health Assessment Questionnaire-Disability Index; NNT: number needed to treat.

dose in Figure 2A. For each parameter, similar results were observed between tofacitinib 5 mg BID and 10 mg BID, as shown by overlapping CIs. Significant differences in IR were in favour of younger patients compared with older patients for SAEs (both tofacitinib doses), serious infections (tofacitinib 5 mg BID) and discontinuations due to AEs (tofacitinib 10 mg BID).

MACE or malignancies did not occur in older patients who received placebo in any of the Phase 3 studies and were infrequent in patients from either age group who received tofacitinib, either initially or after advancement from placebo: adjudicated MACE was reported in 12 patients and malignancies (excluding NMSC) in 13 patients. Therefore, due to the limited data, conclusions about these safety endpoints in older *versus* younger patients cannot be made.

Corresponding IRs for AEs of interest with NNH for each outcome are presented in Figure 3. NNH was not calculated for SAEs and OI in older or younger patients, or for discontinuations due to AEs in younger patients, as the IR for placebo-treated patients in each case was higher than the IR for tofacitinib-treated patients.

**Fig. 2.** Incidence rate differences (<65 years *vs.* ≥65 years; with 95% CI) for adverse events of interest in A) Phase 3 studies (Month 12), and B) LTE studies (Month 24).

AE: adverse event; BID: twice daily; CI: confidence interval; LTE: long-term extension; OI: opportunistic infection; pt-yrs: patient-years of exposure; SAE: serious adverse event; TB: tuberculosis.

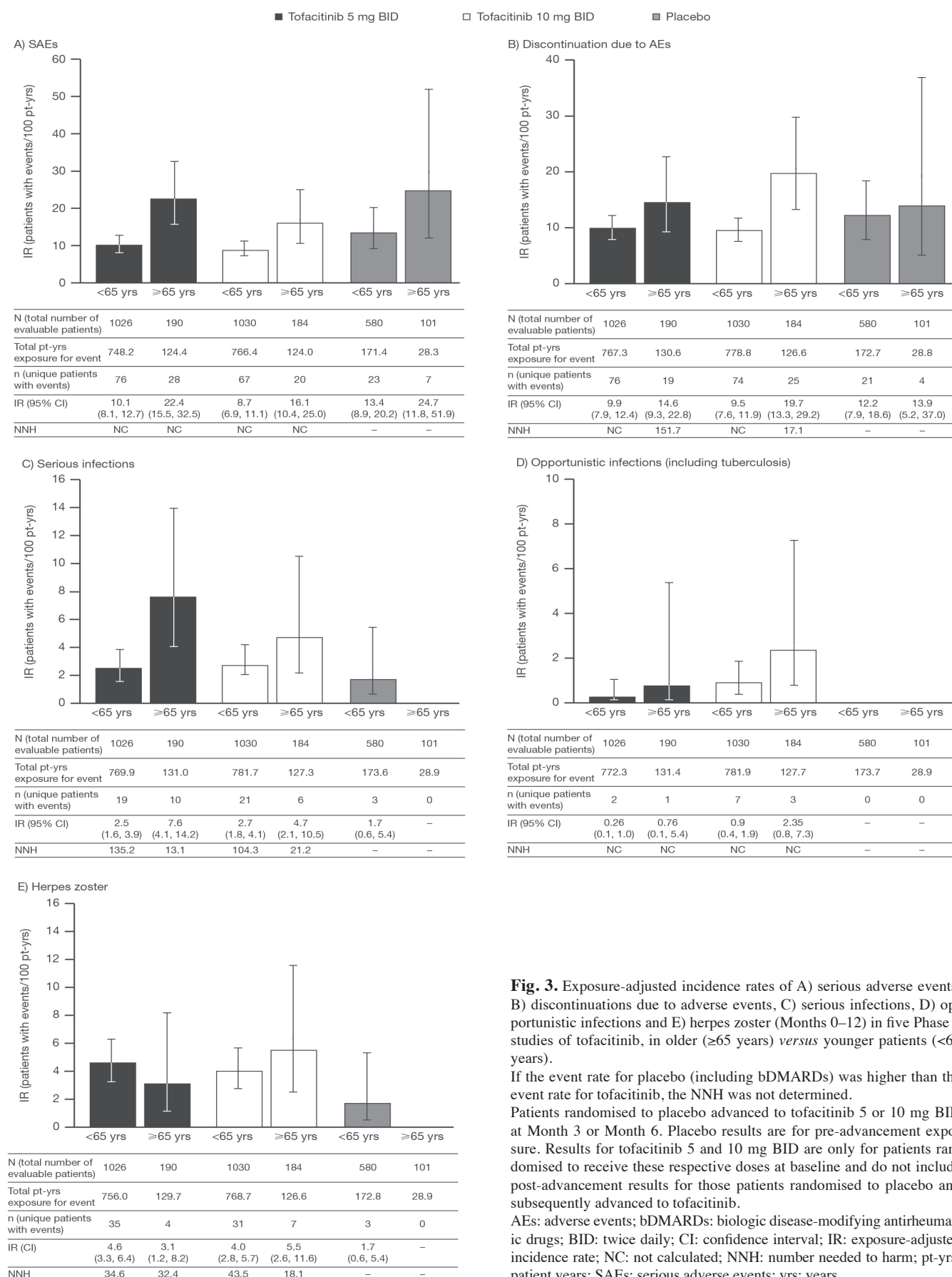


Fig. 3. Exposure-adjusted incidence rates of A) serious adverse events, B) discontinuations due to adverse events, C) serious infections, D) opportunistic infections and E) herpes zoster (Months 0–12) in five Phase 3 studies of tofacitinib, in older (≥65 years) versus younger patients (<65 years).

If the event rate for placebo (including bDMARDs) was higher than the event rate for tofacitinib, the NNH was not determined.

Patients randomised to placebo advanced to tofacitinib 5 or 10 mg BID at Month 3 or Month 6. Placebo results are for pre-advancement exposure. Results for tofacitinib 5 and 10 mg BID are only for patients randomised to receive these respective doses at baseline and do not include post-advancement results for those patients randomised to placebo and subsequently advanced to tofacitinib.

AEs: adverse events; bDMARDs: biologic disease-modifying antirheumatic drugs; BID: twice daily; CI: confidence interval; IR: exposure-adjusted incidence rate; NC: not calculated; NNH: number needed to harm; pt-yrs: patient years; SAEs: serious adverse events; yrs: years.

Table III. Exposure-adjusted incidence rates for safety events of special interest in LTE studies of tofacitinib, by age group (<65 years vs. ≥65 years).

	Tofacitinib 5 mg BID <65 years (n=1189)	Tofacitinib 5 mg BID ≥65 years (n=232)	Tofacitinib 10 mg BID <65 years (n=2252)	Tofacitinib 10 mg BID ≥65 years (n=429)
Total exposure (pt-yrs)	2721	522	2351	440
SAEs				
Patients with events (n)	216	79	241	93
IR (95% CI)	8.44 (7.39, 9.64)	17.56 (14.08, 21.89)	10.75 (9.48, 12.20)	22.73 (18.55, 27.85)
Discontinuations due to AEs				
Patients with events (n)	163	48	160	66
IR (95% CI)	6.03 (5.17, 7.03)	9.24 (6.97, 12.26)	6.84 (5.86, 7.99)	15.18 (11.93, 19.32)
Serious infections				
Patients with events (n)	64	20	65	35
IR (95% CI)	2.38 (1.86, 3.03)	3.89 (2.51, 6.02)	2.78 (2.18, 3.54)	8.06 (5.79, 11.22)
Herpes zoster*				
Patients with events (n)	97	31	96	26
IR (95% CI)	3.76 (3.08, 4.59)	6.40 (4.50, 9.10)	4.20 (3.44, 5.13)	6.12 (4.17, 8.98)
Opportunistic infections†				
Patients with events (n)	11	2	11	3
IR (95% CI)	0.41 (0.22, 0.73)	0.39 (0.10, 1.54)	0.47 (0.26, 0.85)	0.68 (0.22, 2.12)
MACE				
Patients with events (n)	5	3	7	1
Total exposure (pt-yrs)	2309	439	2350	439
IR (95% CI)	0.22 (0.09, 0.52)	0.69 (0.22, 2.14)	0.30 (0.14, 0.63)	0.23 (0.03, 1.62)
Malignancies‡				
Patients with events (n)	25	8	14	13
IR (95% CI)	0.92 (0.62, 1.36)	1.53 (0.77, 3.07)	0.60 (0.35, 1.01)	2.96 (1.72, 5.10)

*Herpes zoster (serious and non-serious). †Including tuberculosis. ‡Excluding non-melanoma skin cancer. AEs: adverse events; BID: twice daily; CI: confidence interval; IR: exposure-adjusted incidence rate; LTE: long-term extension; MACE: major adverse cardiovascular events; pt-yrs: patient-years; SAEs: serious adverse events.

• LTE studies

IRs for AEs of interest in the LTE population can be found in Table III. Similar to the pooled Phase 3 studies, significant differences in IR were in favour of younger patients compared with older patients for SAEs and discontinuations due to AEs (both tofacitinib doses), herpes zoster (tofacitinib 5 mg BID), and serious infections (tofacitinib 10 mg BID).

MACE, OIs and malignancies occurred infrequently in patients who received tofacitinib in LTE studies (16, 27 and 60 out of 4102 patients, respectively) and, therefore, no conclusions can be made about differences between age groups for these infrequent outcomes. Although the patient numbers in some geographic regions were low, IRs for discontinuations due to AEs and SAEs

were numerically higher in the older group compared with the younger group, when evaluating across regions (data not shown).

• Analyses of serious adverse events by age group and selected baseline characteristics

PRs for SAEs in older and younger patients according to selected baseline demographics and characteristics are presented in Supplementary Figure 2. CIs generally included 1.0 with few exceptions. Trends in PRs generally suggested a trend towards a lower probability of SAEs in older males versus females, and in patients without COPD/asthma versus those with COPD/asthma (Supplementary Fig. 2), although 95% CIs included 1.0. Similar trends were observed in patients with-

out diabetes at baseline (Supplementary Fig. 2). The probability of SAEs was lower (not significantly) in patients who had never smoked. For all observations, 95% CIs for PRs overlapped for older and younger patients, indicating no significant differences according to age group (Supplementary Fig. 2).

• Analyses of potential correlation between patient age, probability of ACR20 response and probability of SAEs

Correlations between the probabilities of ACR20 response and SAEs at Month 3 were similar for older and younger patients in the pooled Phase 3 population, both in the tofacitinib 5 mg BID group (-0.53 and -0.40, respectively; both $p < 0.0001$) and tofacitinib 10 mg BID group (-0.47 and -0.47, respectively; both $p < 0.0001$). The estimated probability of an SAE at Month 3 ranged from approximately 1.0% to 12.5%, and no trends in probabilities of SAEs were evident based on patient age or dose of tofacitinib received (Fig. 4).

Discussion

Response to tofacitinib in older patients with RA

In the present analysis, the probability of an ACR20 or ACR50 response, or improvement ≥ 0.22 from baseline in HAQ-DI at Month 3, was similar in older and younger patients who received tofacitinib. Additionally, no clear trend in the probability of ACR20 and HAQ-DI responses between older and younger patients were observed across geographic regions, however, these findings should be interpreted with caution due to the small patient numbers involved, particularly in the older patient groups. Only the probability of an ACR70 response appeared to be somewhat lower in older patients than in younger patients; however, limited numbers of patients in either group achieved this endpoint. Previous studies have suggested the potential for reduced therapeutic response to bDMARDs in older patients with RA (29-31).

Safety and tolerability profile of tofacitinib in older patients

Across all treatment groups (including

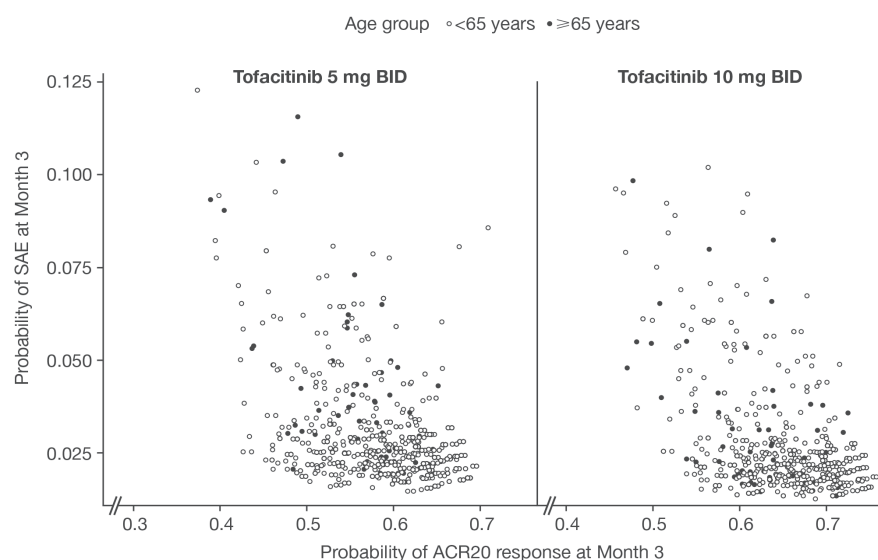


Fig. 4. Estimated probability of ACR20 response *versus* probability of SAE (Month 3) in older (≥ 65 years) *versus* younger patients (< 65 years) participating in Phase 3 randomised clinical studies. ACR: American College of Rheumatology; BID: twice daily; SAE: serious adverse event.

placebo), older patients generally had an increased risk of SAEs, and of discontinuation due to AEs, compared with younger patients, as shown by IR differences. This finding is consistent with observations from studies of csDMARDs and bDMARDs, including TNFi, in patients with RA (32–35). Limited patient numbers in some geographic regions precluded definitive statistical analysis comparing discontinuations due to AEs and SAEs across geographic areas. However, a trend for numerically higher IRs for discontinuations due to AEs and SAEs across regions was observed in older patients *versus* younger patients in the LTE studies. Data by geographic region (US *vs.* non-US populations) have been reported previously for tofacitinib in a pooled analysis of Phase 2 and Phase 3 studies. Although data in this pooled analysis were not stratified by age, IRs for discontinuations due to AEs and SAEs were similar for US and non-US populations (36). Additionally, increasing age has been identified as an independent risk factor for serious infection in patients receiving bDMARDs and csDMARDs (37). The results of our analysis suggest an increased risk of serious infection events in older *versus* younger patients who receive tofacitinib 5 mg BID. This observation is supported by the findings of a recent pooled analysis of in-

fection and mortality data across Phase 2, Phase 3 and LTE studies of tofacitinib in patients with RA (38). In addition, there appeared to be an increased risk of serious infection events in older patients who received tofacitinib compared with those who received placebo, which is in agreement with reports from multiple RA patient databases of bDMARDs, and with both the general and RA population (39). The small differences between IRs (with overlapping CIs) obtained for patients receiving placebo and for younger tofacitinib-treated patients suggests that there was no incremental increase in risk of serious infection from an interaction between advancing age and exposure to tofacitinib.

In pooled Phase 3 studies, differences in IRs for OIs and HZ in older *versus* younger patients, suggests there were no significant differences between age groups. In the LTE population, differences in IRs for HZ were numerically higher in older *versus* younger tofacitinib-treated patients (tofacitinib 10 mg BID group) and significantly higher in the tofacitinib 5 mg BID group. This increase in risk of HZ with advancing age observed in tofacitinib-treated patients is consistent with the magnitude of age-related increase that is described in the literature (40, 41) suggesting that there is no incremental risk from an

interaction between advancing age and exposure to tofacitinib.

Influence of baseline characteristics on treatment response and safety profile

Certain comorbid conditions occur at higher frequency in patients with RA and other rheumatic conditions (42). In addition, female gender and cigarette smoking are known to be predictive of worse clinical outcomes in RA (4). In the present analysis, a higher BMI appeared to reduce the probability of an ACR20 response, irrespective of age. This is consistent with results from observational and interventional studies in patients receiving bDMARDs (29, 43). Furthermore, a separate study of 495 patients, most of whom (86% [426/495]) received methotrexate, identified a dose-response relationship between BMI and change in the Disease Activity Score in 28 joints (DAS28) (44). We also observed non-significant trends towards an increased probability of SAEs in patients with COPD/asthma, and patients with diabetes, showed trends towards an increased probability of SAEs, irrespective of treatment. These trends were clearer in younger patients than in older patients, possibly owing to the comparatively smaller data set for the older patient group.

Analyses of potential correlation between patient age, probability of ACR20 response and probability of SAEs

Overall, the correlations between probability of ACR20 response and probability of SAEs (both at Month 3) were negative in older and younger patients who received tofacitinib 5 and 10 mg BID in Phase 3 studies. This may suggest that SAEs observed in the first three months of tofacitinib therapy were mostly related to RA, and that greater treatment efficacy is associated with a lower proportion of risk of SAEs.

After imputation was applied, missing values for patients who discontinued for any reason (*e.g.* due to an AE) were handled by setting the ACR value to nonresponsive from that visit onward. Thus, if a patient discontinued at a

visit but had responsive ACR values at that visit, the ACR value was still set to nonresponsive. It must be noted that not all SAEs in this study resulted in discontinuation (and hence ACR20 imputation to non-response).

Potential limitations of the present analysis

For both Phase 3 and LTE analyses of safety data, the comparative exposure to tofacitinib was limited in older patients compared with younger patients, although the mean duration of exposure was similar in older and younger patients. Similarly, exposure to placebo, from which response PRs were calculated, was limited due to study design and randomisation. Therefore, it would be useful to seek validation of the above results in a larger population of older patients receiving tofacitinib (or comparator therapies) for RA. Additionally, the effect of age on patient-reported outcomes (PROs) was not investigated in this study. Although the effect of tofacitinib dose on PROs has previously been reported (45), further investigation into the possible impact of patient age would be informative.

Conclusions

In totality, the efficacy of tofacitinib appears similar for patients aged 65 years and over compared with younger patients. While the overall risk of SAEs and discontinuations due to AEs was higher in older *versus* younger patients, irrespective of treatment (including placebo), there was no evidence of an incremental risk of these outcomes that might suggest an interaction between older age and exposure to tofacitinib. There was an increase in the risk of serious infection events in older *versus* younger tofacitinib-treated patients. The corresponding evaluation in patients treated with placebo also showed a numerical increase in SIEs in older *versus* younger patients. Increased rates for these adverse events in patients aged ≥ 65 years are consistent with published reports in RA patients treated with cs- and/or bDMARDs. These factors should be taken into consideration when tofacitinib treatment is considered for older patients with RA.

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