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Infections in patients with rheumatoid arthritis receiving tofacitinib versus tumour necrosis factor inhibitors: results from the open-label, randomised controlled ORAL Surveillance trial

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ABSTRACT

Objectives To characterise infections in patients with rheumatoid arthritis (RA) in ORAL Surveillance.

Methods In this open-label, randomised controlled trial, patients with RA aged≥50 years with ≥1 additional cardiovascular risk factor received tofacitinib 5 or 10 mg two times per day or a tumour necrosis factor inhibitor (TNFi). Incidence rates (IRs; patients with first events/100 patient-years) and hazard ratios (HRs) were calculated for infections, overall and by age (50–<65 years; ≥65 years). Probabilities of infections were obtained (Kaplan-Meier estimates). Cox modelling identified infection risk factors.

Results IRs/HRs for all infections, serious infection events (SIEs) and non-serious infections (NSIs) were higher with tofacitinib (10>5 mg two times per day) versus TNFi. For SIEs, HR (95% CI) for tofacitinib 5 and 10 mg two times per day versus TNFi, respectively, were 1.17 (0.92 to 1.50) and 1.48 (1.17 to 1.87). Increased IRs/HRs for all infections and SIEs with tofacitinib 10 mg two times per day versus TNFi were more pronounced in patients aged≥65 vs 50–<65 years. SIE probability increased from month 18 and before month 6 with tofacitinib 5 and 10 mg two times per day versus TNFi, respectively. NSI probability increased before month 6 with both tofacitinib doses versus TNFi. Across treatments, the most predictive risk factors for SIEs were increasing age, baseline opioid use, history of chronic lung disease and time-dependent oral corticosteroid use, and, for NSIs, female sex, history of chronic lung disease/infections, past smoking and time-dependent Disease Activity Score in 28 joints, C-reactive protein.

Conclusions Infections were higher with tofacitinib versus TNFi. Findings may inform future treatment decisions.

Trial registration number NCT02092467.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with rheumatoid arthritis (RA) have an increased susceptibility to infections due to multiple factors, including age, disease activity, comorbidities and RA treatments.

WHAT THIS STUDY ADDS

⇒ In patients with RA aged≥50 years and with ≥1 additional cardiovascular risk factor, dose-dependent increases in the incidence and risk of all infections, serious infection events (SIEs) and non-serious infections (NSIs) were observed with tofacitinib (5 mg two times per day (recommended dosage for RA) and 10 mg two times per day) versus tumour necrosis factor inhibitors (TNFi).

⇒ Across treatment groups, the incidence of all infections and SIEs were increased in patients aged≥65 versus 50–<65 years, with increased risks more pronounced with tofacitinib 10 mg two times per day versus TNFi in older patients.

⇒ Across treatment groups, the most predictive risk factors for SIEs were increasing age, baseline opioid use, history of chronic lung disease and time-dependent oral corticosteroid use; while those for NSIs were female sex, history of chronic lung disease/infections, past smoking and time-dependent higher Disease Activity Score in 28 joints, C-reactive protein score.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings from ORAL Surveillance may inform treatment decisions for patients with RA; the higher risk of infections with tofacitinib versus TNFi, and risk factors identified for infections, should be considered as part of the shared decision-making between physicians and patients.

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory autoimmune disorder.[1] Compared with the general population, patients with RA are at a greater risk of infections, including serious infections requiring hospitalisation.[2 3] In patients with RA, infections contribute to morbidity and mortality[4 5] and may cause treatment discontinuation.[6]

The increased susceptibility to infections in patients with RA has been attributed to disease pathophysiology, comorbidities, lifestyle factors and use of immunomodulatory drugs.[3] Analyses of real-world and clinical trial data from patients

with RA have shown that the risk of serious and non-serious infections (NSIs) is increased in those receiving biologic disease-modifying antirheumatic drugs (bDMARDs) versus conventional synthetic DMARDs (csDMARDs),[7 8] and the risk of infections varies across treatments. For example, the tumour necrosis factor inhibitor (TNFi), etanercept, has been associated with reduced risk of infections versus other TNFi agents[9–11] and the Janus kinase (JAK) inhibitor, tofacitinib.[12]

ORAL Surveillance was a postauthorisation study that assessed the safety of tofacitinib versus TNFi in patients with RA aged≥50 years with ≥1 additional cardiovascular (CV) risk factor.[13] An ad hoc safety analysis of ORAL Surveillance reported the incidence of non-fatal and fatal serious infection events (SIEs) to be greater with tofacitinib versus TNFi.[14] Risk of SIEs (non-fatal/fatal) with tofacitinib was further increased in patients aged>65 years versus younger patients[14]; therefore, the European Medicines Agency recommended that patients aged>65 years should be treated with tofacitinib only when there is no suitable alternative treatment.[15] Along with increasing age, a safety analysis of randomised controlled trials/long-term extension (LTE) studies (excluding ORAL Surveillance) identified tofacitinib dose, male sex, geographical region (Asia and Australia/New Zealand/rest of the world (ROW) versus the USA/Canada), increasing Health Assessment Questionnaire-Disability Index Score, postbaseline lymphopenia, corticosteroid use, increasing body mass index (BMI) and history of diabetes and chronic lung disease as significant risk factors for SIEs in tofacitinib-treated patients.[16]

Using the final dataset from ORAL Surveillance, we sought to compare infections in patients with RA receiving tofacitinib versus TNFi, and to identify risk factors for infections in these patients.

METHODS

Study design and patients

ORAL Surveillance was a phase IIIb/IV randomised, open-label, safety endpoint study conducted from March 2014 to July 2020 in patients with active RA despite methotrexate treatment who were aged≥50 years with ≥1 additional CV risk factor.[13]

Patients with infections requiring treatment≤2 weeks prior to study start or infections requiring hospitalisation or parenteral antimicrobial therapy≤6 months prior to study start were excluded. Patients had to screen negative for active tuberculosis (TB) or inadequately treated TB (active or latent) at study entry and annually for the full study duration. Patients newly testing positive for latent TB had to receive isoniazid or other TB prophylaxis to continue in the study. Complete inclusion and exclusion criteria are published elsewhere.[13]

Patients were randomised 1:1:1 to receive oral tofacitinib 5 or 10 mg two times per day, or subcutaneous TNFi (adalimumab 40 mg once every 2 weeks (North America: the United States, Puerto Rico and Canada) or etanercept 50 mg once weekly (ROW)). Patients continued their prestudy stable dose of methotrexate unless modification was clinically indicated.

In February 2019, following a study amendment, the tofacitinib 10 mg two times per day dose was reduced to 5 mg two times per day after the Data Safety Monitory Board noted an increased frequency of pulmonary embolism in patients receiving tofacitinib 10 mg two times per day versus TNFi and an increase in overall mortality with tofacitinib 10 vs 5 mg two times per day and TNFi.

If a patient experienced an SIE, they may have had their study drug temporarily discontinued until they recovered, but they were not excluded from the study.

ORAL Surveillance was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council on Harmonisation, and was approved by the Institutional Review Board and/or Independent Ethics Committee at each centre. Patients provided written informed consent.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Outcomes

Treatment-emergent adverse events (AEs) assessed in this analysis included: all infections, SIEs (non-fatal/fatal), NSIs, herpes zoster (HZ) and adjudicated opportunistic infections (including HZ and TB). These events are defined in online supplemental material.

Statistical analysis

Safety outcomes were analysed using the safety analysis set, which included all randomised patients receiving ≥1 dose of study drug. For patients randomised to tofacitinib 10 mg two times per day who had their dose reduced to 5 mg two times per day in February 2019, the data collected after the dose switch were counted in the tofacitinib 10 mg two times per day group.

Infection events were counted within the predefined risk period, based on the 28-day on-treatment time, defined as time from the first study dose to the last study dose +28 days or to the last contact date, whichever was earliest. The last contact date was defined as the maximum of AE start date, AE stop date, last visit date, withdrawal date or telephone contact date; if a patient died, the last contact date was the death date. Patients without events were censored at the end of the risk period. For patients with multiple SIEs, NSIs and HZ, these were reported as separate events if the event start dates were different.

Crude incidence rates (IRs; for all infections, SIEs, NSIs and HZ) were expressed as the number of patients with first events per 100 patient-years, along with two-sided 95% CIs derived by exact Poisson method.[17] HR (for all infections, SIEs, NSIs and HZ) and 95% CIs for pairwise treatment comparisons (tofacitinib 5 or 10 mg two times per day versus TNFi; tofacitinib 10 vs 5 mg two times per day) were estimated using Cox proportional hazard regression models.[18]

For SIEs, the number needed to harm (NNH; number of patient-years of tofacitinib exposure needed to have one additional AE relative to TNFi) was calculated post hoc for tofacitinib 5 or 10 mg two times per day versus TNFi. The NNH for patients exposed for 5 years was calculated by dividing the number of patient-years needed to harm by 5.

The cumulative probabilities of patients experiencing a first event (SIE, NSI and HZ) at specific time intervals after initiation of each treatment were measured post hoc using Kaplan-Meier estimates of the survivor function.

Potential baseline and time-dependent risk factors (online supplemental table 1) for first SIEs, NSIs and all HZ (non-serious and serious) were evaluated post hoc, overall and for each individual treatment group; a model selection process was conducted using Cox proportional hazards (simple and multivariable) regression models (additional details are in online supplemental material).

Across all analyses, no adjustments for multiple comparisons were applied.

Table 1 Selected demographics and baseline disease characteristics in ORAL Surveillance

	Tofacitinib 5 mg two times per day (N=1455)	Tofacitinib 10 mg two times per day (N=1456)	TNFi (N=1451)
Age (years), mean (SD)	60.8 (6.8)	61.4 (7.1)	61.3 (7.5)
≥65 years, n (%)	413 (28.4)	478 (32.8)	462 (31.8)
Male sex, n (%)	286 (19.7)	332 (22.8)	334 (23.0)
RA disease duration (years), mean (SD)	10.4 (8.8)	10.2 (9.0)	10.6 (9.3)
Smoking status, n (%)			
Current smoker	411 (28.2)	402 (27.6)	353 (24.3)
Past smoker	309 (21.2)	302 (20.7)	326 (22.5)
Never smoked	735 (50.5)	752 (51.6)	772 (53.2)
Geographical region, n (%)*			
North America	402 (27.6)	409 (28.1)	432 (29.8)
ROW	1053 (72.4)	1047 (71.9)	1019 (70.2)
BMI (kg/m^2), mean (SD) (number of patients with missing values)	29.7 (6.5) (7)	29.7 (6.3) (3)	29.8 (6.6)(7)
≥30 kg/m^2, n (%)	606 (41.6)	594 (40.8)	617 (42.5)
≥35 kg/m^2, n (%)	256 (17.6)	261 (17.9)	267 (18.4)
Concomitant medication use at baseline (day 1)			
Opioids, n (%)	293 (20.1)	283 (19.4)	288 (19.8)
Oral corticosteroids, n (%)	776 (53.3)	773 (53.1)	774 (53.3)
Oral corticosteroid dose (mg/day), mean (range)†	6.0‡ (0.7–20.0)	6.1§ (0.6–20.0)	6.1¶ (0.3–20.0)
Medical history, n (%)			
Diabetes	243 (16.7)	261 (17.9)	255 (17.6)
Chronic lung disease (COPD or ILD)	178 (12.2)	173 (11.9)	172 (11.9)
Extra-articular disease	532 (36.6)	521 (35.8)	552 (38.0)
Nodules	301 (20.7)	268 (18.4)	287 (19.8)
Coronary artery disease	161 (11.1)	172 (11.8)	164 (11.3)
Heart failure	18 (1.2)	23 (1.6)	18 (1.2)
Infection	574 (39.5)	549 (37.7)	556 (38.3)
Positive for anticitrullinated protein antibodies, n (%)	1093 (75.1)	1129 (77.5)	1119 (77.1)
HAQ-DI, mean (SD) (number of patients with missing values)	1.6 (0.6) (11)	1.6 (0.6) (18)	1.6 (0.6) (25)
DAS28-4(CRP), mean (SD) (number of patients with missing values)	5.8 (0.9) (11)	5.8 (0.9) (17)	5.8 (0.9) (26)

For patients randomised to the tofacitinib 10 mg two times per day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two times per day group.
*In North America (the USA, Puerto Rico and Canada), patients randomised to TNFi received adalimumab 40 mg once every 2 weeks; in the ROW, patients randomised to TNFi received etanercept 50 mg once weekly.
†In patients taking oral corticosteroids at baseline with known dosing information.
‡n=769.
§n=771.
¶n=773.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; HAQ-DI, Health Assessment Questionnaire-Disability Index; ILD, interstitial lung disease; n, number of patients meeting baseline criteria; N, number of evaluable patients; RA, rheumatoid arthritis; ROW, rest of the world; SD, standard deviation; TNFi, tumour necrosis factor inhibitor.

RESULTS

Patients

Overall, 4362 patients were randomised and treated (tofacitinib 5 mg two times per day: N=1455; tofacitinib 10 mg two times per day: N=1456; TNFi: N=1451); median follow-up was 4.0 years. Total exposure was 5073.5, 4773.4 and 4940.7 patient-years for tofacitinib 5 or 10 mg two times per day, or TNFi, respectively.[13] For the tofacitinib 10 mg two times per day group, approximately 79% of exposure occurred prior to the study amendment (ie, before patients randomised to tofacitinib 10 mg two times per day had their dose reduced to 5 mg two times per day); approximately 21% of exposure occurred after patients had switched to tofacitinib 5 mg two times per day. Table 1 shows selected patient demographics/baseline disease characteristics; full details are published elsewhere.[13]

Across treatments, 4.7%–5.2% of patients were reported to have received HZ vaccination (Zostavax or Shingrix) prior to study start, and 0.3%–0.8% of patients received HZ vaccination on/after study day 1. At screening, 11.5%–12.3% of patients had latent TB with a positive QuantiFERON Gold or tuberculin skin test and negative chest radiograph, and received isoniazid or other TB prophylaxis prior to the first dose of study drug. Overall, 16.8%–20.2% of patients received isoniazid or other TB prophylaxis on/after the first dose of study drug.

Incidence and risk of infections in ORAL Surveillance

Incidence and risk of all infections

Across treatments, the most frequent treatment-emergent AEs by Medical Dictionary for Regulatory Activities' System Organ Class were infections and infestations.[13] The most frequently reported infections were upper respiratory tract infections, bronchitis and urinary tract infections (table 2).

For all infections, and infections excluding HZ, IRs were higher and risk was increased for both tofacitinib doses versus TNFi and for tofacitinib 10 vs 5 mg two times per day (figure 1).

Table 2 Summary of infection AEs in ORAL Surveillance

Patients with events, n (%)	Tofacitinib 5 mg two times per day (N=1455)	Tofacitinib 10 mg two times per day (N=1456)	TNFi (N=1451)
Infections and Infestations (MedDRA System Organ Class)*	1036 (71.2)	1055 (72.5)	930 (64.1)
Most frequently reported, by MedDRA Preferred Term (≥3% of patients with events in any treatment group)*			
Upper respiratory tract infection	308 (21.2)	312 (21.4)	255 (17.6)
Bronchitis	222 (15.3)	237 (16.3)	163 (11.2)
Urinary tract infection	186 (12.8)	221 (15.2)	184 (12.7)
HZ (non-serious/serious)†	176 (12.1)	167 (11.5)	55 (3.8)
Nasopharyngitis	164 (11.3)	165 (11.3)	158 (10.9)
Pneumonia	95 (6.5)	101 (6.9)	78 (5.4)
Sinusitis	92 (6.3)	79 (5.4)	91 (6.3)
Pharyngitis	86 (5.9)	79 (5.4)	75 (5.2)
Influenza	90 (6.2)	91 (6.3)	71 (4.9)
Latent TB	87 (6.0)	67 (4.6)	91 (6.3)
Gastroenteritis	64 (4.4)	79 (5.4)	53 (3.7)
Respiratory tract infection	43 (3.0)	43 (3.0)	31 (2.1)
Cellulitis	36 (2.5)	32 (2.2)	50 (3.4)
SIEs	141 (9.7)	169 (11.6)	119 (8.2)
Non-fatal	135 (9.3)	156 (10.7)	115 (7.9)
Fatal	6 (0.4)	13 (0.9)	4 (0.3)
Patients with 1 SIE	110 (7.6)	140 (9.6)	95 (6.6)
Patients with 2 SIEs‡	22 (1.5)	23 (1.6)	18 (1.2)
Patients with 3 SIEs‡	7 (0.5)	2 (0.1)	5 (0.3)
Patients with ≥4 SIEs‡	2 (0.1)	4 (0.3)	1 (0.1)
NSIs	983 (67.6)	1003 (68.9)	882 (60.8)
Patients with 1 NSI event	307 (21.1)	326 (22.4)	334 (23.0)
Patients with 2 NSI events‡	226 (15.5)	228 (15.7)	200 (13.8)
Patients with 3 NSI events‡	160 (11.0)	135 (9.3)	117 (8.1)
Patients with ≥4 NSI events‡	290 (19.9)	314 (21.6)	231 (15.9)
NSIs excluding all HZ	954 (65.6)	968 (66.5)	870 (60.0)
All HZ (non-serious/serious)§	180 (12.4)	178 (12.2)	58 (4.0)
Seriousness			
Non-serious¶	170 (94.4)	161 (90.4)	56 (96.6)
Serious¶	10 (5.6)	17 (9.6)	2 (3.4)
Severity			
Mild¶	61 (33.9)	49 (27.5)	16 (27.6)
Moderate¶	110 (61.1)	116 (65.2)	40 (69.0)
Severe¶	9 (5.0)	13 (7.3)	2 (3.4)
All HZ (non-serious/serious)§			
Patients with 1 HZ event	138 (9.5)	137 (9.4)	46 (3.2)
Patients with 2 HZ events‡	33 (2.3)	35 (2.4)	11 (0.8)
Patients with 3 HZ events‡	9 (0.6)	5 (0.3)	1 (0.1)
Patients with ≥4 HZ events‡	0 (0.0)	1 (0.1)	0 (0.0)
Adjudicated multidermatomal HZ**	29 (2.0)	24 (1.7)	12 (0.8)
Adjudicated special interest HZ††	17 (1.2)	17 (1.2)	4 (0.3)
Discontinuation from study drug due to HZ	6 (0.4)	12 (0.8)	2 (0.1)
Adjudicated opportunistic infections*	39 (2.7)	44 (3.0)	21 (1.5)
HZ adjudicated as an opportunistic infection*,‡‡	34 (2.3)	32 (2.2)	13 (0.9)
TB adjudicated as an opportunistic infection*	1 (0.1)	5 (0.3)	5 (0.3)
Adjudicated opportunistic infections excluding HZ and TB	4 (0.3)	7 (0.5)	3 (0.2)

For patients randomised to the tofacitinib 10 mg two times per day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two times per day group.
*Reported elsewhere.[13]
†Includes the Preferred Term HZ from the clinical database recorded on the AE case report forms.
‡Events were counted as separate events if the event start dates were different.
§Includes HZ adjudicated as opportunistic infections and non-adjudicated HZ events, which included preferred terms of genital HZ, HZ, HZ cutaneous disseminated, HZ disseminated, HZ infection neurological, HZ meningitis, HZ meningoencephalitis, HZ necrotising retinopathy, HZ oticus, HZ pharyngitis, ophthalmic HZ, HZ ophthalmic and HZ multidermatomal, from the clinical database recorded on the AE case report forms.
¶Percentages calculated based on number of patients with HZ adjudicated as opportunistic infections and non-adjudicated HZ events from the clinical database.
**Cases of HZ involving non-adjacent dermatomes or >2 adjacent dermatomes.
††Cases of HZ involving two adjacent dermatomes.
‡‡Cases of multidermatomal HZ and disseminated HZ (diffuse rash (>6 dermatomes)), encephalitis, pneumonia and other organ involvement) were adjudicated as opportunistic infections.
AE, adverse event; HZ, herpes zoster; MedDRA, Medical Dictionary for Regulatory Activities; n, number of patients with events; N, number of evaluable patients; NSI, non-serious infection; SIE, serious infection event; TB, tuberculosis; TNFi, tumour necrosis factor inhibitors.

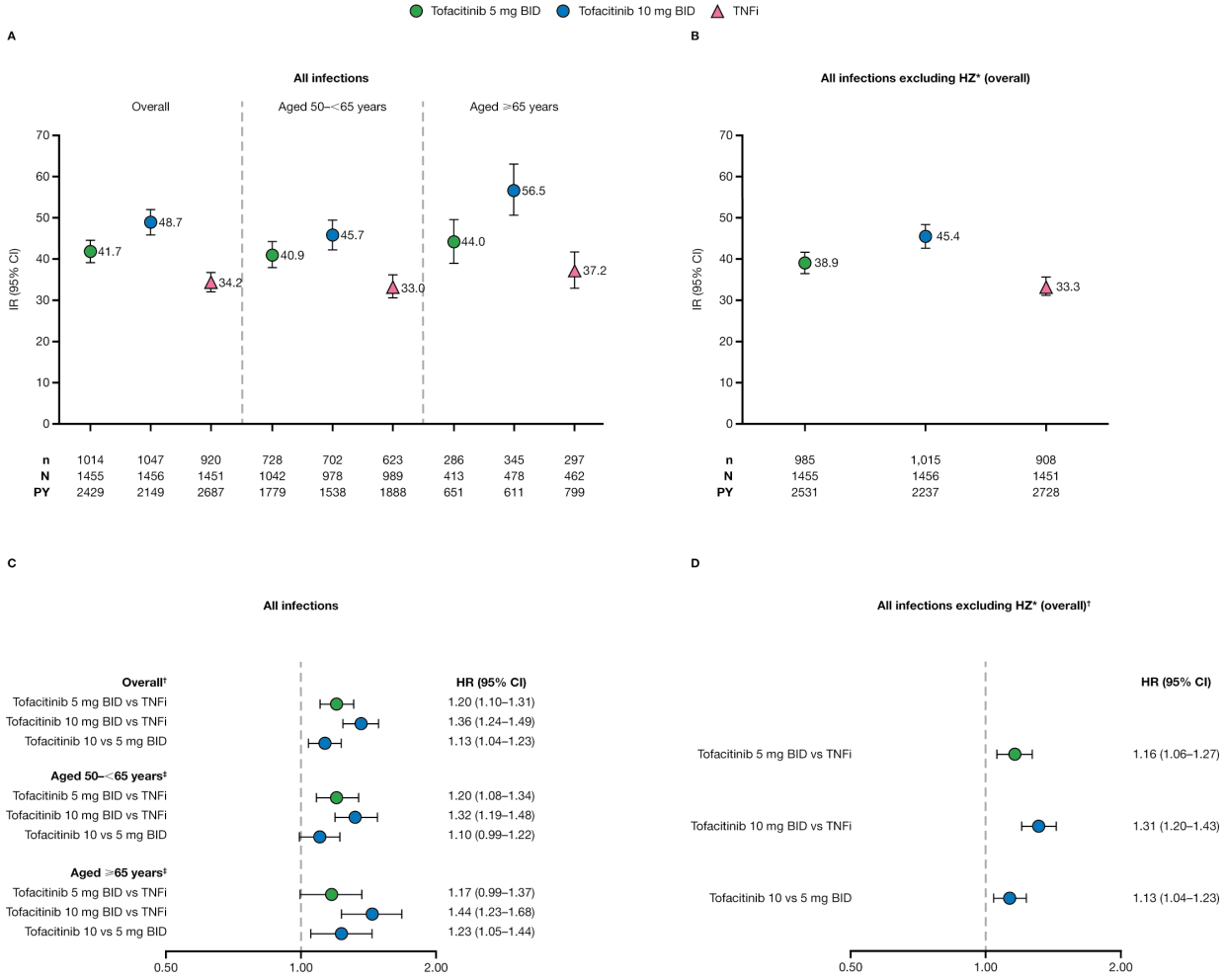

Figure 1 IRs (patients with first events/100 PY; 95% CIs) for (A) all infections, overall and stratified by age, and (B) all infections excluding HZ; and HRs (95% CIs) for (C) all infections, overall and stratified by age, and (D) all infections excluding HZ, in ORAL Surveillance. HRs are shown on a logarithmic scale. For patients randomised to the tofacitinib 10 mg two times per day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two times per day group. *Excludes HZ adjudicated as opportunistic infections and non-adjudicated HZ events from the clinical database. †HRs (95% CIs) based on a simple Cox proportional hazard model for pairwise treatment comparisons, with treatment as covariate. ‡HRs (95% CIs) based on a multivariable Cox proportional hazard model for pairwise treatment comparisons with treatment, sex, region and smoking as covariates.
BID, two times per day; HR, hazard ratio; HZ, herpes zoster; IR, incidence rate; N, number of evaluable patients; n, number of patients with events; PY, patient-years; TNFi, tumour necrosis factor inhibitors.

Across treatments, IRs for all infections were greater in patients aged≥65 vs 50–<65 years (figure 1A). In both age groups, risk for all infections increased with tofacitinib (10>5 mg two times per day) versus TNFi (figure 1C).

HRs for the combined tofacitinib doses versus TNFi for all infections and all infections excluding HZ (as well as SIEs, NSIs, NSIs excluding HZ and all HZ) are shown in online supplemental table 2).

Incidence and risk of SIEs

Across treatments, IRs of SIEs (non-fatal/fatal) were greater in patients aged≥65 vs 50–<65 years (figure 2A). Overall, IRs of SIEs were higher with tofacitinib (10>5 mg two times per day) versus TNFi. NNH was 238 and 83 patient-years, respectively, for tofacitinib 5 and 10 mg two times per day (figure 2A), corresponding to 48 and 17 patients who would need to be treated with tofacitinib 5 and 10 mg two times per day, respectively, versus TNFi, over 5 years to have one additional event. Similar trends for IRs were observed across age groups. Risk increased with both tofacitinib doses versus TNFi and tofacitinib 10 vs 5 mg two times per day, although 95% CIs for HRs included 1 for tofacitinib 5 mg two times per day versus TNFi, overall and across age groups, and for tofacitinib 10 vs 5 mg two times per day for patients aged≥50–<65 years (figure 2B). The increased risk for SIEs with tofacitinib 10 mg two times per day versus TNFi (and tofacitinib 10 vs 5 mg two times per day) was more pronounced in patients aged≥65 vs 50–<65 years (figure 2B). Cumulative probability of a first SIE with tofacitinib 5 and 10 mg two times per day versus TNFi increased from month 18 and before month 6, respectively (figure 2C).

A total of 31 (2.1%) patients in the tofacitinib 5 mg two times per day group, 29 (2.0%) patients in the tofacitinib 10 mg two times per day group and 24 (1.7%) patients in the TNFi group experienced multiple SIEs (table 2).

Risk of fatal SIEs was greater with tofacitinib 10 mg two times per day versus TNFi (HR (95% CI), 3.34 (1.09 to 10.25)); HRs were 1.47 (0.41 to 5.21) for tofacitinib 5 mg two times per day

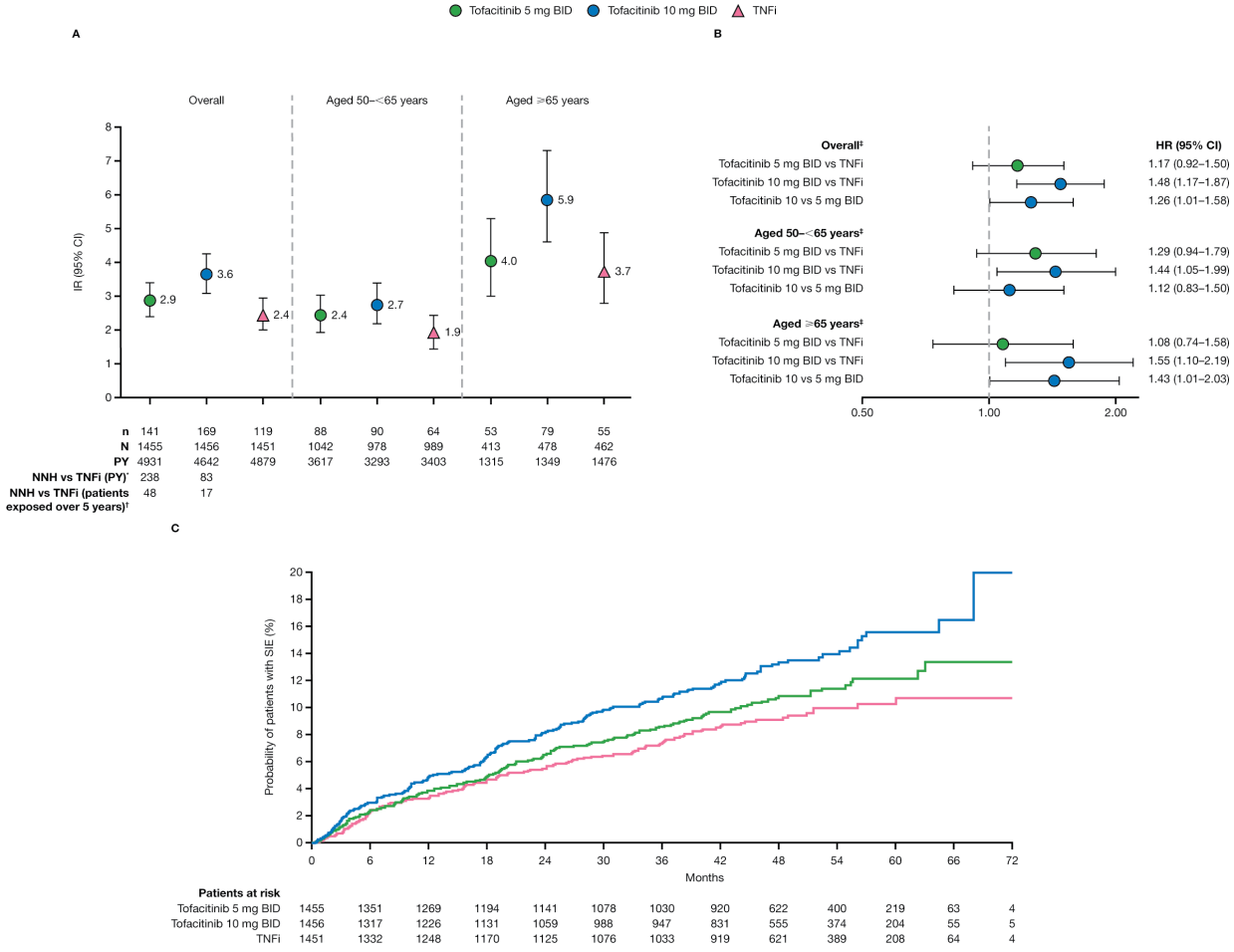

Figure 2 (A) IRs (patients with first events/100 PY; 95% CIs) and (B) HRs (95% CIs) for SIEs, overall and stratified by age; and (C) cumulative probabilities of experiencing a first SIE (Kaplan-Meier method), in ORAL Surveillance. HRs are shown on a logarithmic scale. For patients randomised to the tofacitinib 10 mg two times per day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two times per day group. IRs and HRs for SIEs overall have been reported previously.[13] *Number of PY of exposure to tofacitinib required to have one additional event, relative to a TNFi †Number of patients who would need to be treated over 5 years with tofacitinib rather than a TNFi to result in one additional event. ‡HRs (95% CIs) based on a simple Cox proportional hazard model for pairwise treatment comparisons, with treatment as covariate.
BID, two times per day; HR, hazard ratio; IR, incidence rate; N, number of evaluable patients; n, number of patients with events; PY, patient-years; SIE, serious infection event; TNFi, tumour necrosis factor inhibitors.

versus TNFi and 2.27 (0.86 to 5.98) for tofacitinib 10 vs 5 mg two times per day.

Incidence and risk of NSIs

For NSIs, and NSIs excluding HZ, IRs were higher and risk was increased with tofacitinib (10>5 mg two times per day) versus TNFi and tofacitinib 10 vs 5 mg two times per day (figure 3). The cumulative probability of a first NSI with tofacitinib 5 and 10 mg two times per day versus TNFi increased before month 6 (figure 3E).

Incidence and risk of HZ

IRs of all HZ (non-serious/serious) were greater in patients aged≥65 vs 50–<65 years (all treatments; figure 4A). IRs and risk for all HZ were greater with both doses of tofacitinib versus TNFi overall and across age groups (figure 4 A,B). The cumulative probability of a first HZ event with tofacitinib 5 and 10 mg two times per day versus TNFi increased before month 6 (figure 4C).

IRs (95% CIs) of adjudicated multidermatomal HZ were higher for tofacitinib 5 (0.6 (0.4 to 0.8)) and 10 mg two times per day (0.5 (0.3 to 0.7)) versus TNFi (0.2 (0.1 to 0.4)). IRs of adjudicated special interest HZ were also higher for tofacitinib 5 (0.3 (0.2 to 0.5) and 10 mg two times per day (0.4 (0.2 to 0.6)) versus TNFi (0.1 (0.0 to 0.2)).

A total of 42 (2.9%), 41 (2.8%) and 12 (0.8%) patients in the tofacitinib 5 mg two times per day, tofacitinib 10 mg two times per day and TNFi groups, respectively, reported multiple HZ events (table 2).

Risk factors for infections in ORAL Surveillance

Baseline and time-dependent risk factors across all treatments

Risk factors for infections ($p<0.10$) identified via simple analyses across all treatments are shown in online supplemental table 3. Figure 5 shows risk factors for infections ($p<0.10$) identified via multivariable analyses across all treatments. The most predictive risk factors for SIEs were increasing age, opioid use, history of chronic lung disease at baseline and time-dependent oral corticosteroid use ($p<0.001$; figure 5A). Patients in North America had a 22% lower risk of SIEs versus patients in the ROW ($p<0.05$; figure 5A). The most predictive risk factors for NSIs were female

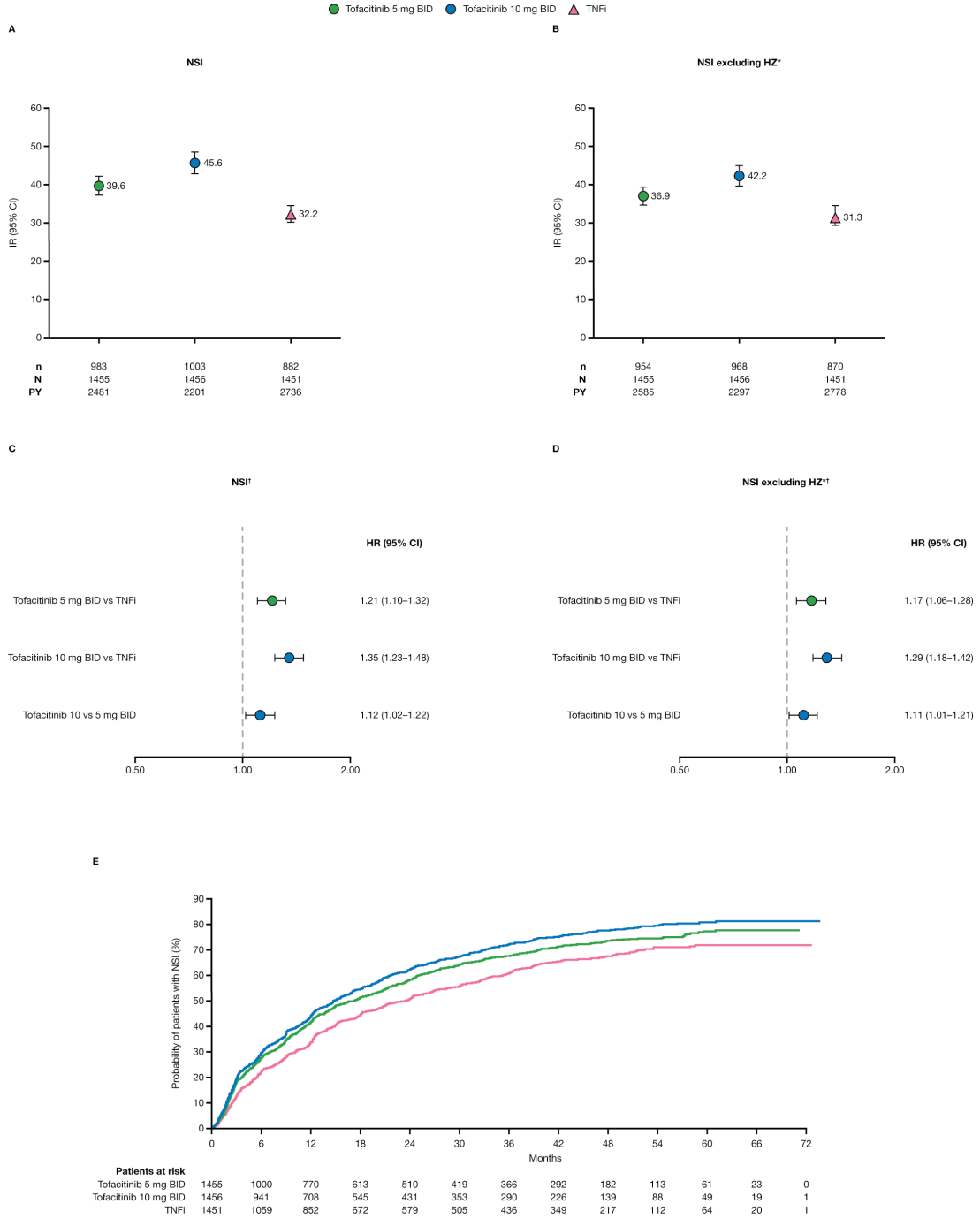

Figure 3 IRs (patients with first events/100 PY; 95% CIs) for (A) NSIs and (B) NSIs excluding HZ; HRs (95% CIs) for (C) NSIs and (D) NSIs excluding HZ; and (E) cumulative probabilities of experiencing a first NSI (Kaplan-Meier method), in ORAL Surveillance. HRs are shown on a logarithmic scale. For patients randomised to the tofacitinib 10 mg two times per day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two times per day group. *Excludes HZ adjudicated as opportunistic infections and non-adjudicated HZ events from the clinical database. †HRs (95% CIs) based on a simple Cox proportional hazard model for pairwise treatment comparisons, with treatment as covariate.
BID, two times per day; HR, hazard ratio; HZ, herpes zoster; IR, incidence rate; N, number of evaluable patients; n, number of patients with events; NSI, non-serious infection; PY, patient-years; TNFi, tumour necrosis factor inhibitors.

sex, history of chronic lung disease/infections, past smoking at baseline and time-dependent higher Disease Activity Score in 28 joints, C-reactive protein score ($p<0.001$; figure 5B). The most predictive risk factors for all HZ (non-serious/serious) were increasing age, history of chronic renal disease, female sex and history of coronary artery disease at baseline ($p<0.05$; figure 5C).

Baseline risk factors for individual treatments

Baseline risk factors for infections ($p<0.10$) identified using simple analyses for individual treatments are shown in online supplemental table 4. Table 3 summarises baseline risk factors for infections ($p<0.10$) identified using multivariable analyses for individual treatments. The most predictive baseline risk factors for SIEs included: increasing age and history of chronic lung disease for tofacitinib

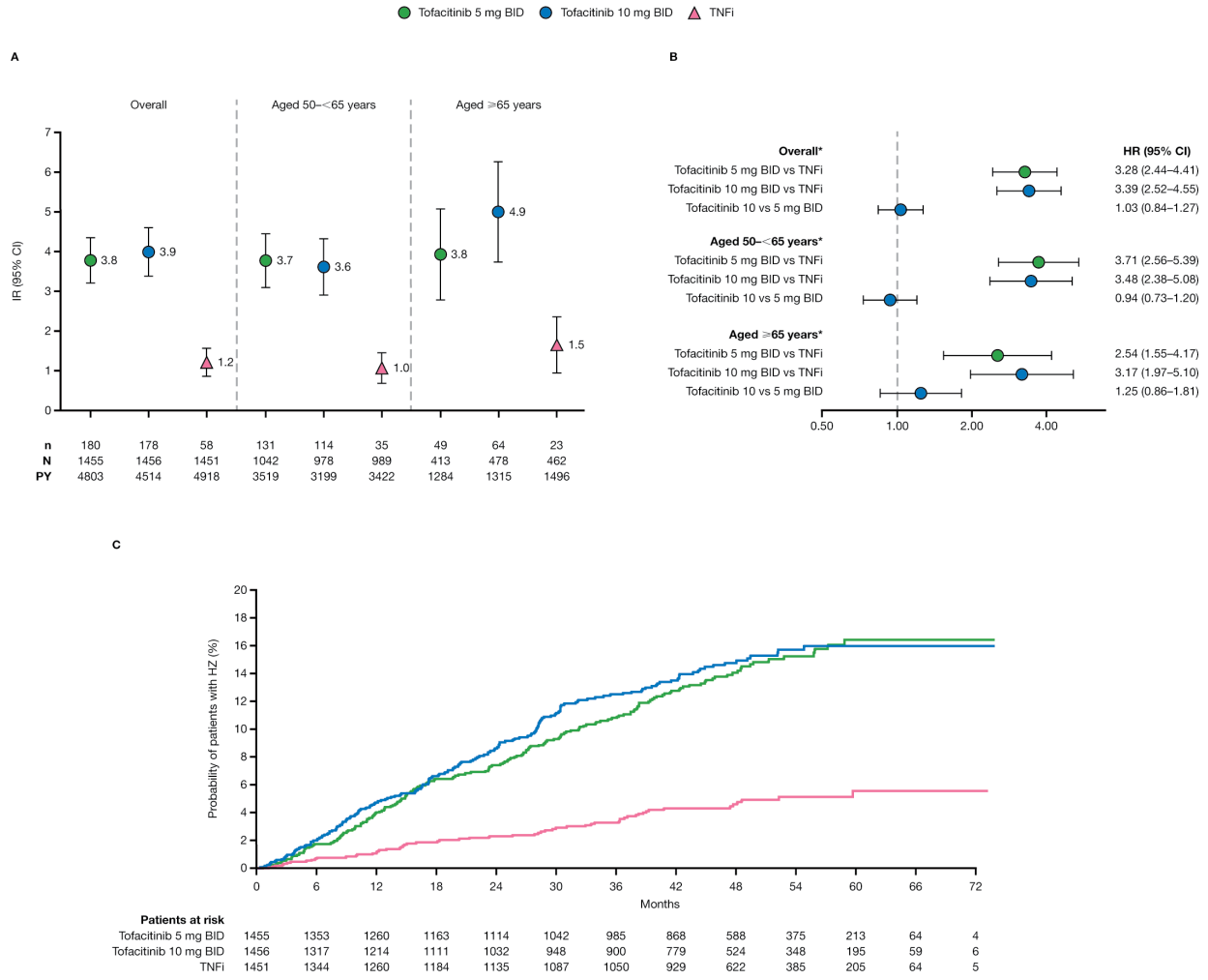

Figure 4 (A) IRs (patients with first events/100 PY; 95% CIs) and (B) HRs (95% CIs) for all HZ (non-serious/serious), overall and stratified by age; and (C) cumulative probabilities of experiencing a first HZ (non-serious/serious) event (Kaplan-Meier method), in ORAL Surveillance. HRs are shown on a logarithmic scale. For patients randomised to the tofacitinib 10 mg two times per day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two times per day group. All HZ events (non-serious/serious) include HZ adjudicated as opportunistic infections and non-adjudicated HZ events from the clinical database. *HRs based on a multivariable Cox proportional hazard model for pairwise treatment comparisons with treatment, age, region, smoking and baseline corticosteroid use as covariates.
BID, two times per day; HR, hazard ratio; HZ, herpes zoster; IR, incidence rate; N, number of evaluable patients; n, number of patients with events; PY, patient-years; TNFi, tumour necrosis factor inhibitors.

5 mg two times per day (p<0.001); increasing age (p<0.001) and opioid use (p<0.01) for tofacitinib 10 mg two times per day; and increasing age (p<0.001), opioid use and history of chronic lung disease for TNFi (p<0.01; table 2). The most predictive baseline risk factors for NSIs included: female sex, past smoking and history of chronic lung disease for tofacitinib 5 mg two times per day (p<0.001); female sex and history of infection for tofacitinib 10 mg two times per day; and history of infection (p<0.001) and female sex (p<0.01) for TNFi (table 3).

The HRs for SIEs and NSIs comparing tofacitinib and TNFi were consistent when based on the simple Cox models (with treatment group as the only covariate; figures 2 and 3), multivariable Cox models via backward selection (figure 5) and multivariable Cox models with each of the time-dependent covariates included (data not shown).

DISCUSSION

In ORAL Surveillance, there were dose-dependent increases in the IRs/HRs for all infections, SIEs and NSIs with tofacitinib versus TNFi. For SIEs, 95% CIs for HRs included 1 for tofacitinib 5 mg two times per day versus TNFi, overall and across age groups. Kaplan-Meier plots suggested that patients were more likely to experience a first SIE with tofacitinib 5 and 10 mg two times per day versus TNFi from month 18 onwards and before month 6, respectively; and patients were more likely to experience a first NSI or HZ event with both tofacitinib doses versus TNFi before month 6. The increases in all infections and SIEs with tofacitinib 10 mg two times per day vs TNFi (and tofacitinib 10 vs 5 mg two times per day) were more pronounced in patients aged≥65 vs 50–<65 years. While the number of patients with repeated SIEs was generally balanced across treatment groups, a greater proportion of patients had 2, 3 and ≥4 NSIs with tofacitinib (both doses) versus TNFi. Across age groups, the incidence and risk of HZ was greater with both doses of tofacitinib versus TNFi. IRs of adjudicated opportunistic infections were <1 for all treatment groups and are published elsewhere.[13]

IRs of SIEs were higher in ORAL Surveillance relative to those previously reported in a pooled analysis of data from the Phase I–IIIb/IV and LTE tofacitinib clinical trials. In ORAL Surveillance, IRs (95% CI) were 2.9 (2.4 to 3.4) and 3.6 (3.1 to

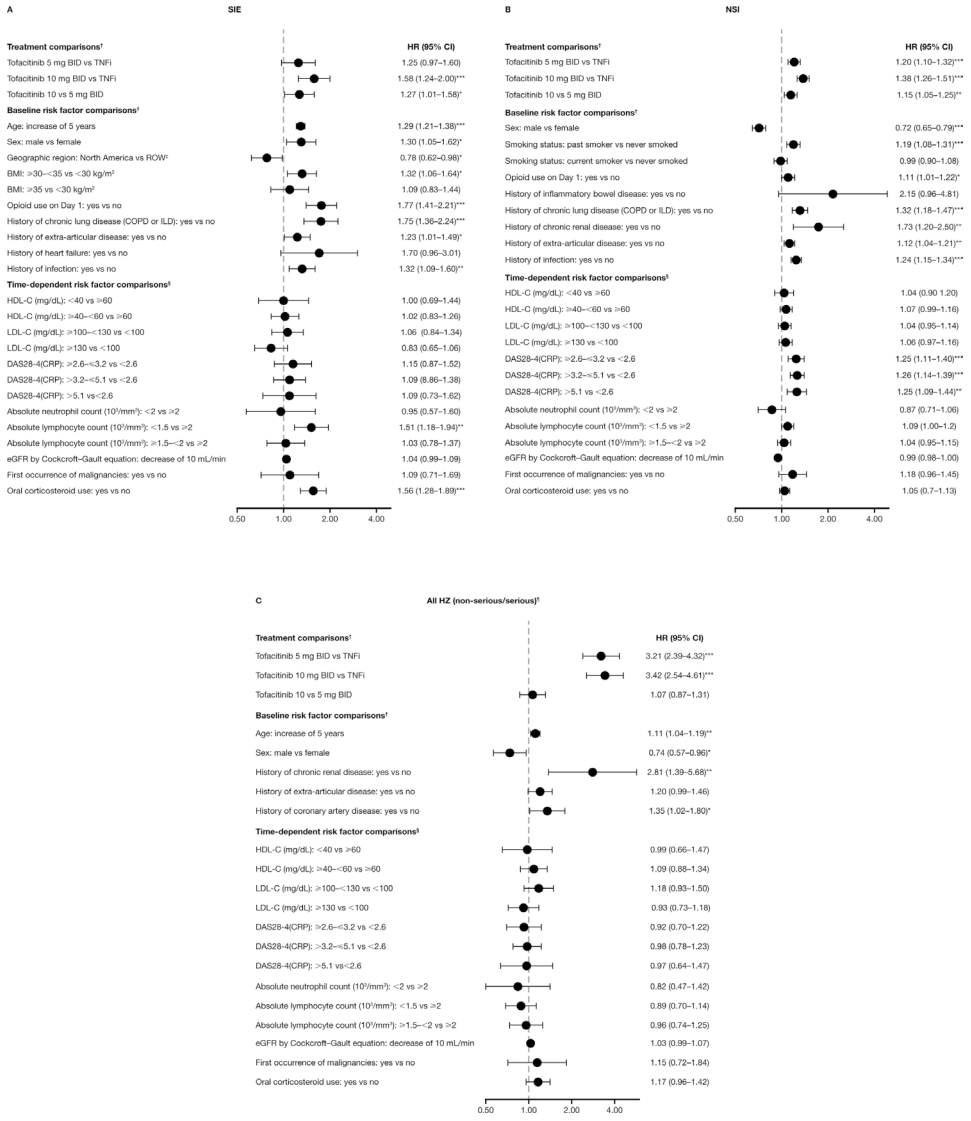

Figure 5 HRs (95% CIs) of potential baseline and time-dependent risk factors for (A) SIEs, (B) NSIs and (C) all HZ (non-serious/serious) in ORAL Surveillance (multivariable Cox analyses across treatments). For patients randomised to the tofacitinib 10 mg two times per day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two times per day group. *p<0.05, **p<0.01; ***p<0.001. HRs are shown on a logarithmic scale. †HRs were based on a backward model selection algorithm on a multivariable Cox model, including effects of treatment group (tofacitinib 5 mg two times per day, 10 mg two times per day and TNFi) and a set of candidate baseline risk factors previously selected via a simple Cox model; risk factors with p<0.10 in the simple model (see online supplemental table 3) were entered into the multivariable model, and the risk factors with p<0.10 were retained in the multivariable model, with p<0.05 interpreted as predictive. ‡In North America (the USA, Puerto Rico and Canada), patients randomised to TNFi received adalimumab 40 mg once every 2 weeks; in the ROW, patients randomised to TNFi received etanercept 50 mg once weekly. §HRs were based on a multivariable Cox time-dependent model including the fixed effects of treatment group (tofacitinib 5 mg two times per day, tofacitinib 10 mg two times per day and TNFi), the final set of baseline covariates selected from the previous multivariable Cox model, using a backward selection algorithm and a time-dependent covariate (a separate model was generated for each individual time-dependent risk factor). ¶All HZ events (non-serious/serious) include HZ adjudicated as opportunistic infections and non-adjudicated HZ events from the clinical database.
BID, two times per day; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DAS28-4(CRP), Disease Activity Score in 28 joints, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; HZ, herpes zoster; ILD, interstitial lung disease; LDL-C, low-density lipoprotein cholesterol; NSI, non-serious infection; ROW, rest of the world; SIE, serious infection event; TNFi, tumour necrosis factor inhibitors.

4.2) for tofacitinib 5 and 10 mg two times per day, respectively, while in the wider tofacitinib clinical programme, IRs were 2.8 (2.5 to 3.2) and 2.3 (2.1 to 2.6) for average total daily doses of tofacitinib 5 and 10 mg two times per day, respectively.[16] When inclusion criteria mimicking ORAL Surveillance (aged≥50 years with ≥1 additional CV risk factor (current smoker, hypertension, high-density lipoprotein cholesterol<40 mg/dL, diabetes mellitus, history of myocardial infarction or coronary heart disease at baseline)) were applied to the pooled Phase I–IIIb/IV and LTE data, IRs for SIEs increased to 3.7 (3.1 to 4.4) and 3.3 (2.8 to 3.8) for average tofacitinib 5 and 10 mg two times per day, respectively (data on file). Overall, this is in line with previous studies showing that traditional CV risk factors may contribute to an increased risk of SIEs in patients with RA.[3 19]

Table 3 HRs (95% CIs) of potential baseline risk factors for SIEs and NSIs in ORAL Surveillance (multivariable Cox analyses performed for individual treatments)

Baseline risk factor comparisons, HR (95% CI)	Tofacitinib 5 mg two times per day (N=1455)	Tofacitinib 10 mg two times per day (N=1456)	TNFi (N=1451)
SIEs			
Age: increase of 5 years	1.28 (1.14 to 1.44)***	1.32 (1.19 to 1.47)***	1.26 (1.13 to 1.41)***
Positive for anticitrullinated protein antibodies: yes versus no	2.08 (1.29 to 3.36)**		
BMI: ≥30–<35 versus <30 kg/m^2	1.72 (1.18 to 2.52)**	1.37 (0.97 to 1.92)	
BMI: ≥35 versus <30 kg/m^2	1.51 (0.96 to 2.38)	0.77 (0.49 to 1.21)	
Opioid use on day 1: yes versus no	1.63 (1.13 to 2.36)**	1.67 (1.19 to 2.35)**	1.91 (1.30 to 2.81)**
History of chronic lung disease (COPD or ILD): yes versus no	2.13 (1.42 to 3.20)***	1.47 (0.98 to 2.23)	1.85 (1.18 to 2.89)**
History of extra-articular disease: yes versus no	1.36 (0.97 to 1.91)		
History of heart failure: yes versus no		2.17 (0.94 to 5.01)*	2.82 (1.03 to 7.75)*
History of infection: yes versus no		1.34 (0.98 to 1.81)	1.51 (1.05 to 2.17)*
NSIs			
Sex: male versus female	0.73 (0.62 to 0.87)***	0.69 (0.59 to 0.81)***	0.77 (0.65 to 0.91)**
Race: non-white versus white	1.19 (1.03 to 1.38)*		
Smoking status: past smoker versus never smoked	1.34 (1.14 to 1.58)***		
Smoking status: current smoker versus never smoked	1.01 (0.87 to 1.18)		
Opioid use day 1: yes versus no		1.19 (1.02 to 1.39)*	1.21 (1.03 to 1.43)*
History of chronic lung disease (COPD or ILD): yes versus no	1.38 (1.15 to 1.66)***	1.32 (1.09 to 1.59)**	1.30 (1.06 to 1.59)*
History of chronic renal disease: yes versus no	2.52 (1.39 to 4.59)**	2.16 (1.19 to 3.93)*	
History of extra-articular disease: yes versus no		1.21 (1.06 to 1.37)**	
History of infection: yes versus no	1.21 (1.06 to 1.37)**	1.31 (1.15 to 1.49)***	1.27 (1.11 to 1.45)***

For patients randomised to the tofacitinib 10 mg two times per day group who had their dose of tofacitinib reduced to 5 mg two times per day, the data collected after patients were switched to tofacitinib 5 mg two times per day were counted in the tofacitinib 10 mg two times per day group. HRs (95% CIs) were based on a backward selection algorithm used on a multivariable Cox model including candidate baseline risk factors previously selected via a simple Cox model; risk factors with p<0.10 in the simple model (see online supplemental table 4) were entered into the multivariable model, and the risk factors with p<0.10 were retained in the multivariable model, with p<0.05 interpreted as predictive. Blank cells indicate risk factors that were not included but retained in the final multivariable Cox model for that particular treatment (ie, risk factors with p≥0.10 in the final multivariable model).

*p<0.05; **p<0.01; ***p<0.001.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; NSI, non-serious infection; SIE, serious infection event; TNFi, tumour necrosis factor inhibitors.

Increasing age is a known risk factor for infections in patients with RA and in the general population.[20 21] In ORAL Surveillance, across all treatments, the incidence of infections, including SIEs, was generally greater in patients aged≥65 vs 50–<65 years; this finding aligns with previous analyses of pooled phase III and LTE studies of tofacitinib-treated patients with RA[22] and pooled phase II–IIIb/IV studies from the tofacitinib clinical programme.[23] The SIE risk was similar between age groups for tofacitinib 5 mg two times per day and adalimumab, but greater in older versus younger patients with tofacitinib 10 mg two times per day.[23] In ORAL Surveillance, an elevated risk of SIEs with tofacitinib 10 mg two times per day versus the other treatment groups was present in both age groups, but was most pronounced among those aged≥65 years. These findings could guide shared decision-making in older patients with RA.

In ORAL Surveillance, incidence of SIEs was greater with both tofacitinib doses (10>5 mg two times per day) versus TNFi. Analyses of real-world data from a 5-year postauthorisation safety study using the US CorEvitas registry reported no significant differences in SIE risk with tofacitinib versus bDMARDs (including both TNFi and non-TNFi agents).[24] Similarly, a real-world US claims database study observed no significant differences in risk of hospital admission for SIE between tofacitinib and a variety of bDMARDs, except for an increased risk with tofacitinib versus etanercept.[12] It is likely that the real-world studies mainly included patients receiving tofacitinib 5 mg two times per day (the approved dose for RA in the USA at the time), which may be why no significant differences in risk of SIEs were observed between tofacitinib and TNFi; this is similar to the results of ORAL Surveillance for tofacitinib 5 mg two times per day versus TNFi. However, ORAL Surveillance differs from these real-world studies with regard to patient selection, study design and the RA treatments compared.

Previous studies have reported variation in the risk of SIEs between individual RA treatments.[9–11] In the current multivariable analysis, patients in North America who received adalimumab had a lower risk of SIEs versus patients in the ROW who received etanercept. It is worth noting, however, that, in simple analyses, a higher crude risk of SIEs was observed for North America versus the ROW for the TNFi group but not for either tofacitinib dose (data not shown). Treatment comparisons across geographical regions are inherently biased; for example, IRs of comorbidities were generally higher in North America versus the ROW.[13]

Risk factors identified for SIEs in ORAL Surveillance were generally similar to those previously reported in an integrated safety analysis of patients with RA receiving tofacitinib[16]; common risk factors included tofacitinib dose, increasing age, male sex, geographical region (Asia and Australia/New Zealand/ROW vs the USA/Canada), corticosteroid use, increasing BMI, chronic lung disease and lymphopenia. The tofacitinib prescribing information requires the monitoring of lymphocyte counts at baseline and every 3 months.[25] Previous analysis also identified history of diabetes as a predictive risk factor for SIEs with tofacitinib in patients with RA.[16] In ORAL Surveillance, history of diabetes was identified as a predictive risk factor for SIEs in the simple but not the multivariable Cox regression

analyses; it is possible that history of diabetes was strongly associated with other, more predictive baseline risk factors that were included within the final multivariable model. It should be noted that only increasing age and baseline opioid use were identified as predictive risk factors for SIEs for both tofacitinib doses when treatment groups were analysed individually. Baseline opioid use was also a risk factor for NSIs across all treatments combined and has previously been reported to increase the risk of infections in patients with RA.[26 27] Other risk factors for NSIs, which have been previously reported in registry data analyses of patients with RA receiving bDMARDs, include female sex and comorbidities.[8]

In agreement with the current findings, real-world studies of patients with RA have consistently reported a greater risk of HZ (non-serious/serious) with JAK inhibitors versus bDMARDs.[12 24 28] For example, real-world US registry and claims database studies of patients with RA reported that HZ risk was twofold higher with tofacitinib versus bDMARDs.[12 24] Previously characterised risk factors for HZ with tofacitinib include increasing age, geographical region (Asia (particularly Japan and Korea) vs the USA/Canada), being a past smoker versus having never smoked, and corticosteroid use.[16] It is noteworthy that geographical region, smoking status and corticosteroid use were not predictive risk factors for HZ in the current study.

A post hoc analysis of phase III studies of patients with RA evaluated the safety of tofacitinib administered as monotherapy or combined with csDMARDs, with or without corticosteroids at baseline.[29] IRs of SIEs and HZ were the greatest in patients receiving tofacitinib combined with csDMARDs along with corticosteroid use at baseline. In ORAL Surveillance, oral corticosteroid use was a predictive risk factor for SIEs but not HZ. The impact of concomitant csDMARDs on IRs of infections was not evaluated in ORAL Surveillance, but it should be noted that all patients received methotrexate at the start of the trial.

A limitation of the current analyses is that ORAL Surveillance was designed to assess non-inferiority of tofacitinib versus TNFi across the primary safety endpoints of adjudicated major adverse CV events and malignancies excluding NMSC; it was not powered to compare infection events across treatment groups. Multiple SIE, NSI and HZ events were reported as separate events if the event start dates differed; it is possible that some subsequent events may have overlapped with the initial event. The Cox regression analyses of risk factors for infections were exploratory in nature; interaction terms among risk factors and between risk factors and treatments were not included in the models, and associations identified between risk factors and events do not imply causality. Backward selection, while commonly used in analysing clinical trial data,[30] may yield a biased relationship between selected covariates and the outcome, and CIs and p values may be underestimated.[31] Further, the stability of the backward selection may be affected by a small number of events in some cases.[30] Some risk factors evaluated in the Cox regression analyses, such as history of inflammatory bowel disease, chronic renal disease and heart failure, were associated with low N values; these results should be interpreted with caution. P values were reported with no adjustment for multiple comparisons, which may have increased the likelihood of false positive findings. Smoking status (eg, years smoked or years since quitting smoking) was not fully characterised. The IRs and risk of infections observed with tofacitinib and TNFi were not compared with that of placebo, csDMARDs or other bDMARDs. The tofacitinib 10 mg two times per day group included data from patients who had their dose reduced from 10 to 5 mg two times per day. Additionally, since TNFi drug (adalimumab or etanercept; not randomly assigned) was confounded by geographical region (North America or ROW), definitive conclusions cannot be made regarding risk of SIEs with tofacitinib versus etanercept or adalimumab, or for etanercept versus adalimumab.

CONCLUSIONS

Results of ORAL Surveillance showed dose-dependent increases in all infections, SIEs and NSIs with tofacitinib versus TNFi in patients aged≥50 years with ≥1 additional CV risk factor. The risk for all infections and SIEs increased with both tofacitinib doses versus TNFi, regardless of age, although an elevated risk with tofacitinib 10 mg two times per day versus 5 mg two times per day and TNFi was most pronounced in patients aged≥65 vs 50–<65 years. The NNH for tofacitinib 5 mg two times per day (recommended dosage for RA) versus TNFi for SIEs was 238 patient-years, meaning that over 5 years of treatment, 48 patients would need to be treated with tofacitinib 5 mg two times per day rather than TNFi to result in one additional SIE. ORAL Surveillance showed higher rates of MACE, malignancies (excluding NMSC) and venous thromboembolic events with tofacitinib versus TNFi (NNH (patient-years) for tofacitinib 5 mg two times per day versus TNFi: 567, 276 and 763 for MACE, malignancies and venous thromboembolic events, respectively, meaning over 5 years of treatment, 113, 55 and 153 patients, respectively, would need to be treated to have one additional event with tofacitinib 5 mg two times per day versus a TNFi).[13 32] The current post hoc analysis revealed a higher risk of NSI and HZ with tofacitinib versus TNFi, and higher risk of SIE with tofacitinib 10 mg two times per day versus TNFi, particularly in patients aged≥65 years. These results should be carefully considered as part of shared decision-making between physicians and patients.

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Correction notice This article has been corrected since it published. In Table 3, there was a typographical error in the upper confidence interval of the hazard ratio for 'history of extra-articular disease: yes versus no' as a risk factor for serious infectionevents with tofacitinib 5 mg two times per day. The incorrect value was 1.19, this has now been corrected to 1.91 in the online version only.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by ORAL Surveillance was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Council on Harmonisation, and was approved by the Institutional Review Board and/or Independent Ethics Committee at each centre. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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Correction: *Infections in patients with rheumatoid arthritis receiving tofacitinib versus tumour necrosis factor inhibitors: results from the open-label randomised controlled ORAL Surveillance trial*

Balanescu AR, Citera G, Pascual-Ramos V, *et al*. Infections in patients with rheumatoid arthritis receiving tofacitinib versus tumour necrosis factor inhibitors: results from the open-label randomised controlled ORAL Surveillance trial. *Ann Rheum Dis* 2022;81:1491–503. doi:10.1136/ard-2022-222405.

In Table 3, there was a typographical error in the upper confidence interval of the hazard ratio for 'history of extra-articular disease: yes versus no' as a risk factor for serious infection events with tofacitinib 5 mg two times per day. The incorrect value was 1.19, this has now been corrected to 1.91.

The value has now been corrected in the online publication.

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