OPEN

Incidence Rates of Interstitial Lung Disease Events in Tofacitinib-Treated Rheumatoid Arthritis Patients

Post Hoc Analysis From 21 Clinical Trials

Gustavo Citera, MD, Eduardo Mysler, MD,† Hugo Madariaga, MD,‡ Mario H. Cardiel, MD, MSc,§ Oswaldo Castañeda, MD,|| Aryeh Fischer, MD,¶ Pascal Richette, MD, PhD,# Sandra Chartrand, MD, FRCPC,** Jin Kyun Park, MD,†† Sander Strengholt, MD,‡‡ Jose L. Rivas, MD,§§ Amit V. Thorat, MD,|||| Tanya Girard, PhD,¶¶ Kenneth Kwok, MSc,## Lisy Wang, MD,*** and Dario Ponce de Leon, MD†††*

Background/Objective: Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). Interstitial lung disease (ILD) is an extra-articular manifestation of RA. We investigated incidence rates of ILD in patients with RA, receiving tofacitinib 5 or 10 mg twice daily, and identified potential risk factors for ILD.

Methods: This post hoc analysis comprised a pooled analysis of patients receiving tofacitinib 5 or 10 mg twice daily or placebo from 2 phase (P)1, 10 P2, 6 P3, 1 P3b/4, and 2 long-term extension studies. Interstitial lung disease events were adjudicated as "probable" (supportive clinical evidence) or "possible" (no supportive clinical evidence) compatible adverse events. Incidence rates (patients with events per 100 patient-years) were calculated for ILD events.

Results: Of 7061 patients (patient-years of exposure = 23,393.7), 42 (0.6%) had an ILD event; median time to ILD event was 1144 days. Incidence rates for ILD with both tofacitinib doses were 0.18 per 100 patient-years. Incidence rates generally remained stable over time. There were 17 of 42 serious adverse events (40.5%) of ILD; for all ILD events (serious and nonserious), 35 of 42 events (83.3%) were mild to moderate in severity. A multivariable Cox regression analysis identified age 65 years or older (hazard ratio 2.43 [95% confidence interval, 1.13–5.21]), current smokers (2.89 [1.33–6.26]), and Disease Activity Score in 28 joints–erythrocyte sedimentation rate score (1.30 [1.04–1.61]) as significant risk factors for ILD events.

Conclusions: Across P1/2/3/4/long-term extension studies, incidence rates for ILD events were 0.18 following tofacitinib treatment, and ILD events were associated with known risk factors for ILD in RA.

Key Words: clinical trials, interstitial lung disease, pulmonary fibrosis, rheumatoid arthritis, risk factors

(*J Clin Rheumatol* 2021;27: e482–e490)

From the *Instituto de Rehabilitación Psicofísica; and †Organización Médica de Investigación, Buenos Aires, Argentina; ‡Clínica del Sur, Arequipa, Peru; §Centro de Investigación Clínica de Morelia, Morelia, Mexico; ||Clínica Anglo Americana, Lima, Peru; ¶Department of Medicine, University of Colorado, Denver, CO; #Department of Rheumatology, Hôpital Lariboisière, Assistance Publique-Hôpitaux de Paris, Paris, France; **Department of Medicine, Hôpital Maisonneuve-Rosemont Affiliated to Université de Montréal, Montreal, Quebec, Canada; ††Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea; ‡‡Pfizer Inc., Capelle aan den IJssel, the Netherlands; §§Pfizer SLU, Madrid, Spain; ||||Pfizer Australia, Sydney, New South Wales, Australia; ¶¶Pfizer Inc., Montreal, Quebec, Canada; ##Pfizer Inc., New York, NY; ***Pfizer Inc., Groton, CT; and †††Pfizer Inc., Lima, Peru.

A.F. is a former employee of University of Colorado, Denver, CO.

This study was sponsored by Pfizer Inc. G.C. has received research grants from Novartis and Pfizer Inc. and is a speaker, advisor and/or consultant to AbbVie, Bristol-Myers Squibb, Eli Lilly, Genzyme, Janssen, Novartis, Pfizer Inc., and Roche. E.M. has received research grants from Eli Lilly, Pfizer Inc., and Roche and is a member of the speakers' bureaus for AbbVie, Bristol-Myers Squibb, Eli Lilly, Pfizer Inc., Roche, and Sanofi. M.H.C. has received research grants from Gilead, Pfizer Inc., and Roche; and is a consultant and member of the speakers' bureaus for Eli Lilly and Pfizer Inc. A.F. has received research grants from Boehringer Ingelheim and Corbus and is a consultant to Boehringer Ingelheim and Roche. A.F. is a former employee of the University of Colorado and is currently employed by Bristol-Myers Squibb. P.R. is a consultant to Pfizer Inc. S.C. is a consultant to AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Novartis, and Pfizer Inc. J.L.R., A.V.T., T.G., K.K., L.W., and D.P.L., are employees and shareholders of Pfizer Inc. S.S. is a former employee of Pfizer Inc., Capelle aan den IJssel, the Netherlands. J.K.P., H.M., and O.C. declare no conflict of interest.

Medical writing support, under the guidance of the authors, was provided by Jennifer Stewart, PhD, MBA, and Jennifer Arnold, PhD, CMC Connect, McCann Health Medical Communications and was funded by Pfizer Inc., New York, NY, in accordance with Good Publication Practice (GPP3) guidelines (*Ann Intern Med* 2015;163:461–464).

The data reported in this manuscript have been previously presented at the American College of Rheumatology Annual Scientific Meeting, Chicago, IL, October 19 to 24, 2018, Citera G, Mysler E, Madariaga H, et al. Low interstitial lung disease event rate in patients with rheumatoid arthritis: pooled post hoc analysis of data from the tofacitinib clinical development program [abstract]. *Arthritis Rheumatol* 2018; 70(suppl 10). These data were also previously presented at the Mexican Congress of Rheumatology, Mazatlán, México, February 14 to 19, 2019; the Pan-American Congress of Rheumatology, Quito, Ecuador, April 27 to 30, 2019; and the Laurentian Conference of Rheumatology, Estérel, Québec, Canada, May 9 to 11, 2019.

Author Contributions: G.C., E.M., H.M., M.H.C., O.C., A.F., J.K.P., and T.G. were involved in the conception and design of the study/analyses. G.C., E.M., M.H.C., A.F., J.K.P., S.S., J.L.R., A.V.T., T.G., K.K., L.W., and D.P. performed the data and statistical analyses. M.H.C., J.K.P., A.V.T., S.S., J.L.R., T.G., K.K., L.W., and D.P. were involved in subject recruitment, study monitoring, and/or data acquisition (conducted the experiment). All authors were involved in data interpretation and manuscript drafting, reviewing, and development. The views and opinions expressed within this manuscript are those of all authors and do not necessarily represent those of the sponsor.

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

Correspondence: Dario Ponce de Leon, MD, Pfizer Inc., Jr Gonzalo Martin de Trujillo, 250 Dpt: 301, Lima, 33 Santiago de Surco, Peru.
E-mail: Dario.PoncedeLeon@pfizer.com.

ISSN: 1076-1608
DOI: 10.1097/RHU.0000000000001552

Interstitial lung disease (ILD) comprises a collection of lung disorders that affect the tissue and space around the alveoli,[1] with an estimated prevalence of 67 to 98 per 100,000 and incidence of 19 to 32 per 100,000 per year in the general population.[2,3] Interstitial lung disease is a common, chronic, and progressive extra-articular manifestation of rheumatoid arthritis (RA),[1–4] occurring in 4% to 58% of patients with RA,[5–7] with estimates varying due to different diagnosis methods used.[8] Rheumatoid arthritis–associated ILD (RA-ILD) causes significant morbidity and is one of the most significant causes of death in patients with RA, together with cardiovascular complications, accounting for at least 13% of excess mortality associated with RA.[5,6,9]

Previous studies have identified advancing age (≥65 years), male gender, and Asian ancestry (i.e., Japanese patients[10]) as risk factors for RA-ILD.[1,2,5,11,12] Furthermore, patients with RA who have a history of smoking, the MUC5B promoter variant rs35705950, a high Disease Activity Score in 28 joints–erythrocyte sedimentation rate (DAS28–4[ESR]) score, rheumatoid nodules, high levels of circulating rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP), and longer time from onset of the first RA symptoms to secondary care intervention also have an increased risk of developing RA-ILD.[5,11–15] The association between RA-ILD and the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), tumor necrosis factor inhibitors (TNFi), and non-TNFi biologics remains unclear.[5,16–18] These limited and conflicting data create challenges for clinicians managing patients with RA-ILD.[17] Consequently, there is a need to monitor the incidence of RA-ILD in patients receiving immunotherapies.

Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. The efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) administered as monotherapy or in combination with csDMARDs, mainly methotrexate (MTX), in patients with moderately to severely active RA, have been demonstrated in phase (P)2,[19–23] P3,[24–30] and P3b/4[31] studies of up to 24 months' duration and long-term extension (LTE) studies with up to 114 months' observation.[32–34]

This post hoc analysis pooled data from P1, P2, P3, P3b/4, and LTE studies to investigate the incidence rates (IRs) of ILD events in patients with active RA receiving tofacitinib 5 or 10 mg BID and to identify potential risk factors for ILD events.

METHODS

Study Design and Patients

This post hoc analysis of pooled data included 2 cohorts. The overall cohort comprised a pooled analysis of patients receiving tofacitinib 5 or 10 mg BID (based on average dose), including patients who switched from placebo to tofacitinib 5 or 10 mg BID, in the following 21 studies: 2 P1 studies (A3921130 [NCT01262118], A3921152 [NCT01484561]); 10 P2 studies (A3921019 [NCT00147498], A3921025 [NCT00413660], A3921035 [NCT00550446], A3921039 [NCT00603512, Japan study], A3921040 [NCT00687193, Japan study], A3921068 [NCT01164579], A3921073 [NCT00976599], A3921109 [NCT01059864], A3921129 [NCT01359150], A3921237 [NCT02147587]); 6 P3 studies (A3921032 [NCT00960440], A3921044 [NCT00847613, 2-year data], A3921045 [NCT00814307], A3921046 [NCT00856544], A3921064 [NCT00853385], A3921069 [NCT01039688, 2-year data]); 1 P3b/4 study (A3921187 [NCT02187055]); and 2 LTE studies (A3921024 [NCT00413699, main study database locked: March 2017], A3921041 [NCT00661661, Japan LTE study, 2-year data]).

The randomized controlled cohort comprised a pooled analysis of patients receiving tofacitinib 5 or 10 mg BID or placebo in the following randomized controlled studies: 9 P2 studies (A3921019 [NCT00147498], A3921025 [NCT00413660], A3921035 [NCT00550446], A3921039 [NCT00603512, Japan study], A3921040 [NCT00687193, Japan study], A3921068 [NCT01164579]), A3921073 [NCT00976599], A3921129 [NCT01359150], A3921237 [NCT02147587]); 6 P3 studies (A3921032 [NCT00960440], A3921044 [NCT00847613, 2-year data], A3921045 [NCT00814307], A3921046 [NCT00856544], A3921064 [NCT00853385], A3921069 [NCT01039688, 2-year data]); and 1 P3b/4 study (A3921187 [NCT02187055]).

Study designs and patient inclusion/exclusion criteria have been reported.[19–29,31–42] In studies with a placebo group, total exposure to placebo was 4 to 52 weeks, and in some studies, patients were re-randomized to tofacitinib treatment after the placebo-controlled period. Concomitant therapy with stable doses of nonsteroidal anti-inflammatory drugs and low-dose oral corticosteroids was permitted in P2 and P3 studies, with adjustment of dose permitted at the investigator's discretion in LTE studies. Concomitant therapy with csDMARDs was largely permitted; however, use of biologic DMARDs (bDMARDs) was prohibited except for studies wherein adalimumab was an active comparator.

Although patients with ILD were not specifically excluded from trial participation, patients with current or recent history of uncontrolled pulmonary disease were excluded. At screening, ILD-related assessments were based on physician's judgment, and no specific diagnostic criteria were mandated. In most studies, a chest radiograph taken ≤3 months before screening was required to rule out *Mycobacterium tuberculosis* infection; however, chest radiographs were not reviewed for ILD at baseline. Therefore, subclinical disease at the time of enrollment cannot be ruled out.

All 21 clinical trials were conducted in compliance with the Declaration of Helsinki, International Council for Harmonization Guidelines for Good Clinical Practice, and local country regulations, and all study protocols were approved by the institutional review board or independent ethics committee at each center. Patients provided written informed consent. Ethics approval and patient consent were not applicable for this post hoc analysis as the data presented herein are an amalgam of these studies.

ILD Event Adjudication

To be considered for review by the adjudication committee, potential ILD events must have onset following the first dose of tofacitinib and were identified from adverse events (AEs) coded to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) "Interstitial Lung Disease SMQ (20000042)." Potential ILD events were adjudicated by 3 independent pulmonologists as "probable" (compatible AE with supportive clinical evidence) or "possible" (compatible AE with no supportive clinical evidence) based on available data (e.g., availability of clinical evaluations, pulmonary function tests, chest radiographs, and/or chest computed tomography scans among patients with potential ILD events).

Data Analysis

Incidence rates (patients with events per 100 patient-years) and 95% confidence intervals (CIs; calculated via the Exact Poisson method adjusted for exposure) were calculated for ILD events. Incidence rates were based on the number of patients with events between the first and last tofacitinib dose plus 28 days, divided by the time accruing during the risk period (i.e., between the first and last tofacitinib dose plus 28 days, or the time accruing to

the first event, whichever occurred first). Incidence rates at 6-month intervals and by patient age, region, and background therapy were described for the overall cohort. Background therapy groups were assigned based on the patient's exposure to tofacitinib 5 or 10 mg BID monotherapy or combination therapy with background MTX for ≥80% of the patient's tofacitinib exposure. Patients who were not on monotherapy or combination therapy for ≥80% of the time were assigned to the mixed group. Because of the limited patient-years for placebo exposure in the placebo group, direct comparisons of ILD event IRs were not considered.

A descriptive case-matched control analysis was used to identify potential ILD risk factors. Patients in the overall cohort who received tofacitinib 5 or 10 mg BID and had an ILD event (cases) were matched to patients who did not have an ILD event (controls) by age and gender, at a ratio of 1:5.

The following ILD event risk factors were screened for patients in the overall cohort using a backward selection Cox regression model: age (<65 and ≥65 years), body mass index (BMI; <25, 25 to <30, and ≥30 kg/m^2), disease duration (early [<1 year], late [≥1 year]), gender (female, male), race (White, Black, Asian, other), smoking history (nonsmoker, previous smoker, current smoker), baseline anti-CCP positive (anti-CCP+; yes/no), C-reactive protein (CRP; mg/L), DAS28–4(ESR) score, DAS28–4(ESR) disease severity (defined as DAS28–4[ESR] >2.6 to ≤3.2 [low]; >3.2 to ≤5.1 [moderate]; >5.1 [high]), Health Assessment Questionnaire–Disability Index, RF positive (RF+; yes/no), and baseline corticosteroid use (yes/no); prior use of TNFi (yes/no), MTX (yes/no), and csDMARDs other than MTX (yes/no); baseline diabetes (yes/no), history of ILD (defined by the MedDRA PT "Interstitial Lung Disease SMQ [20000042]"; [yes/no]), and background DMARD use at time of first ILD event (yes/no). Factors with less than 50% missing observations and identified as significant at $p = 0.15$ in the backward selection model were analyzed using a multivariable Cox regression model to identify significant risk factors at $p < 0.05$. Weight (in kilograms), baseline MTX dose (in milligrams per week), corticosteroid daily dose (in milligrams), use of prior non-TNFi bDMARDs (yes/no), region (Europe, Latin America, United States/Canada, rest of the world, Asia), and whether patients were using tofacitinib as monotherapy or in combination with csDMARDs 14 days before the event (yes/no) were not included in the backward selection Cox regression model because they were highly correlated with other risk factors. The time-varying tofacitinib dose (in milligrams) and the latest postbaseline DAS28–4(ESR) assessment were then added to the selected model. The time-varying tofacitinib dose variable captured the randomization dose in the index studies or the average dose in the LTE studies for each patient, depending on the time of the event or censoring date. Postbaseline DAS28–4(ESR) assessment was defined as a continuous variable (DAS28–4[ESR] score) and a categorical variable (disease severity, defined as DAS28–4[ESR] >2.6 to ≤3.2 [low]; >3.2 to ≤5.1 [moderate]; >5.1 [high]) in separate models, and the latest assessment during the tofacitinib exposure period and within 180 days prior to the ILD event or censoring date was used in the model.

Adverse events were analyzed for the overall cohort only. Data from patients who received at least 1 dose of tofacitinib were included. Severity of ILD events was adjudicated using the 1 to 5 whole-integer scale of the Common Terminology Criteria for Adverse Events v3.0 for pulmonary/upper respiratory AEs (1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, disabling, 5 = associated with death). Incidence rates of serious infections were determined for patients with and without ILD events in the overall cohort. Mortality is reported in the overall cohort for patients with and without an ILD event based on deaths that occurred at any time after the last dose of tofacitinib (not limited to the 28-day risk window).

RESULTS

Overall Cohort

Patients

In total, 7061 patients (patient-years of exposure 23,393.7) who received tofacitinib (5 mg BID average dose, n = 3066 [patient-years of exposure 8397.0]; 10 mg BID average dose, n = 3995 [patient-years of exposure 14,996.7]) in P1, P2, P3, P3b/4, and LTE studies were included in the overall cohort analysis. The data included up to 9.5 years of exposure to tofacitinib.

Baseline Demographics and Disease Characteristics

Most patients in this cohort were female (82.6%), aged 18 to 86 years, with a mean age of 52.1 years. Mean duration of RA since diagnosis was 8.0 years. In this cohort, 81.5% and 59.6% of patients were previously treated with MTX or corticosteroids, respectively, 17.0% of patients were current smokers at baseline, and 76.3% and 23.7% of patients were from non-Asian (United States/Canada, Europe, Latin America, and rest of the world) and Asian countries, respectively. For patients with ILD events, no patients had a known history of ILD at baseline (defined by the MedDRA PT "Interstitial Lung Disease SMQ [20000042]").

ILD Event IRs

In this cohort, 42 of 7061 patients (0.6%) had an ILD event, with a median time from first dose of treatment to ILD event of 1144 days. Of 81 potential cases reviewed by the adjudication committee, 34 (42.0%) were not considered to be ILD. Of the 47 cases (58.0%) considered to be ILD, 5 were not related to this analysis: 2 occurred outside the risk period, and 3 occurred in patients not treated with tofacitinib. This committee confirmed 34 cases as probable ILD and 8 cases as possible ILD within the risk period of tofacitinib exposure. The IR for an ILD event was 0.18 for both tofacitinib 5 mg BID (95% CI, 0.10–0.29) and 10 mg BID (0.12–0.26) (Fig. 1A; Table 1). Incidence rates for the all-tofacitinib group generally remained stable over time, although the number of events in each interval was small (Fig. 2).

Descriptive differences in IRs were observed for age, race, and resident country (Table 1). Incidence rates were numerically higher in patients 65 years or older versus younger than 65 years. Incidence rates were highest among Black patients; however, the number of patients with events and the patient-years of exposure were too low to support further analysis. Incidence rates were also numerically higher for the population of patients residing in Asian versus non-Asian countries. The higher IR observed for Asian countries was influenced by an IR of 0.89 for ILD events in patients from Thailand, Malaysia, and the Philippines.

Incidence rates were numerically similar for tofacitinib monotherapy (0.16 [95% CI, 0.09–0.28]), combination therapy (0.18 [0.12–0.27]), and mixed groups (0.22 [0.08–0.48]; Fig. 3).

Randomized Controlled Cohort

Patients

Of the 7319 patients enrolled in P2, P3, and P3b/4 studies, 5824 patients who received tofacitinib (5 mg BID, n = 2664; 10 mg BID, n = 2024) or placebo (n = 1136) were included in the randomized controlled cohort.

ILD Event IRs

Interstitial lung disease event IRs were 0.12 (95% CI, 0.02–0.34) with tofacitinib 5 mg BID, 0.10 (0.01–0.36) with 10 mg BID, and 0.32 (0.01–1.79) with placebo (Fig. 1B).

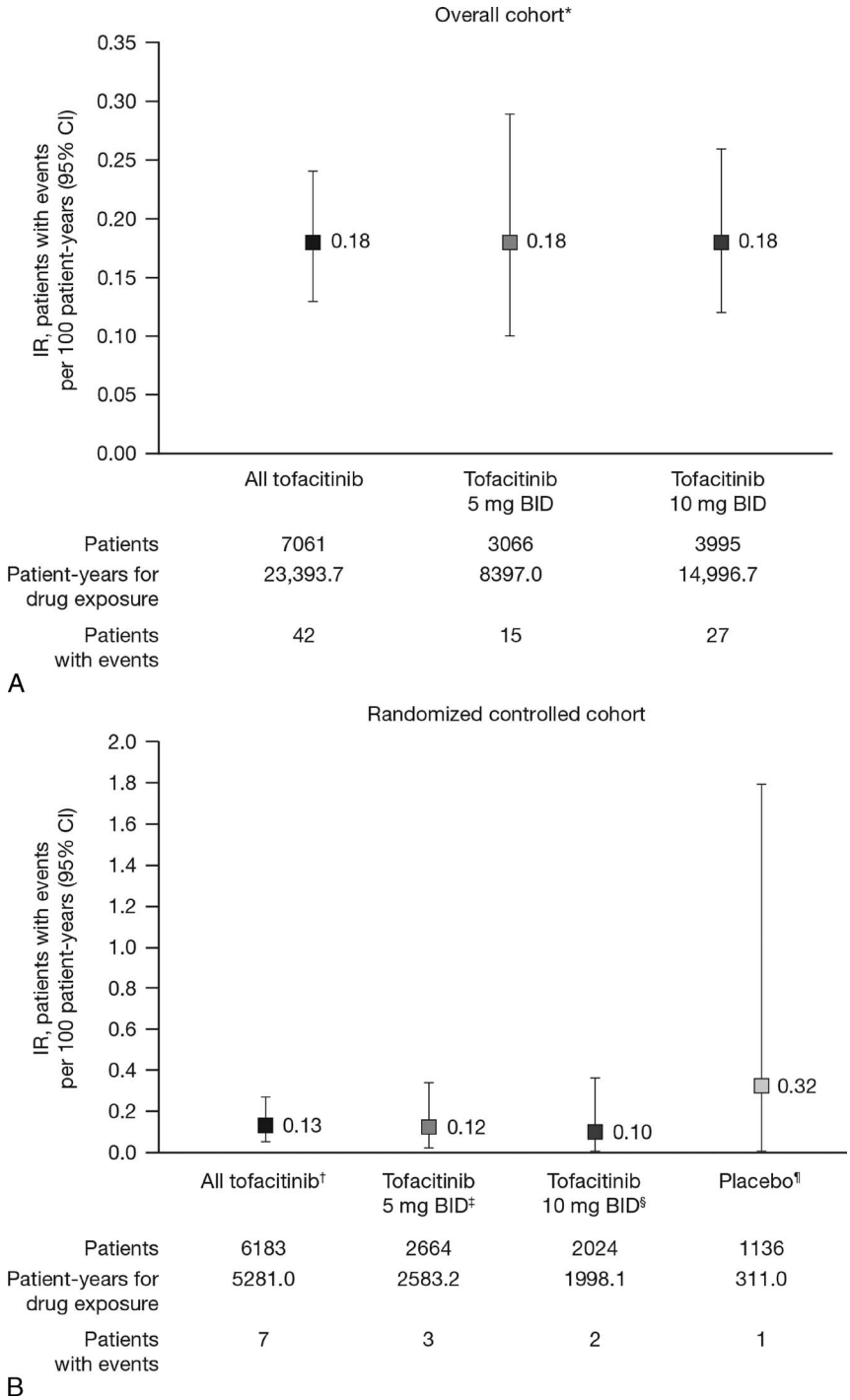

FIGURE 1. Incidence rates for ILD events in patients receiving (A) all tofacitinib doses or tofacitinib 5 or 10 mg BID in the overall cohort, and (B) all tofacitinib doses, tofacitinib 5 or 10 mg BID, or placebo in the randomized controlled cohort. *Data for the overall cohort are derived based on the average dose of tofacitinib received. †The all-tofacitinib group in the randomized controlled cohort comprised all patients who had ever received tofacitinib, including patients who switched from placebo or adalimumab to tofacitinib. ‡Includes patients randomized to receive tofacitinib 5 mg BID. §Includes patients randomized to receive tofacitinib 10 mg BID. ¶Includes patients randomized to receive placebo.

Case-Matched Control Analysis

In the descriptive case-matched control analysis (cases, n = 42; controls, n = 210) of the overall cohort, the ILD events group had a numerically higher proportion of patients who were Asian and previous or current smokers, were RF+ and anti-CCP + at baseline, had higher baseline mean ESR and CRP, and had received prior MTX, non-MTX csDMARDs, TNFi, and concomitant corticosteroids versus controls (Table 2).

Multivariable Cox Regression Model

Age, BMI, race, smoking history, baseline CRP, and baseline corticosteroid use were analyzed in the overall cohort using a final

TABLE 1. Incidence Rates[a] for ILD Events in the Overall Cohort According to Tofacitinib Dose, Patient Age, Patient Race, and Region

Phase 1, 2, 3, 3b/4, and LTE Studies (Pooled Analysis Set)	All Tofacitinib (N = 7061)		
	n/N1 (%)	Patient-Years	IR (95% CI)
Overall (all tofacitinib doses)	42/7061 (0.6)	23,393.7	0.18 (0.13–0.24)
Dose			
5 mg BID	15/3066 (0.5)	8397.0	0.18 (0.10–0.29)
10 mg BID	27/3995 (0.7)	14,996.7	0.18 (0.12–0.26)
Age			
<65 y	32/6042 (0.5)	20,454.1	0.16 (0.11–0.22)
≥65 y	10/1019 (1.0)	2939.6	0.34 (0.16–0.63)
Race			
White	23/4576 (0.5)	15,433.5	0.15 (0.09–0.22)
Black	2/219 (0.9)	608.1	0.33 (0.04–1.19)[b]
Asian[c]	13/1566 (0.8)	5095.3	0.26 (0.14–0.44)
Other	4/700 (0.6)	2256.8	0.18 (0.05–0.45)
Region			
Asia	14/1673 (0.8)	5525.2	0.25 (0.14–0.43)
Korea	2/316 (0.6)	1048.8	0.19 (0.02–0.69)
India	1/197 (0.5)	577.1	0.17 (0.00–0.97)
Thailand/Malaysia/ Philippines	6/208 (2.9)	677.1	0.89 (0.33–1.93)
China/Taiwan	0/260 (0.0)	968.5	0.00 (0.00–0.38)
Japan	4/556 (0.7)	1743.7	0.23 (0.06–0.59)
Australia/New Zealand	1/136 (0.7)	510.1	0.20 (0.00–1.09)
Non-Asian	28/5388 (0.5)	17,868.5	0.16 (0.10–0.23)
USA/Canada	9/1745 (0.5)	5092.4	0.18 (0.08–0.34)
Europe	10/2382 (0.4)	8756.9	0.11 (0.05–0.21)
Latin America	9/1221 (0.7)	3980.1	0.23 (0.10–0.43)
Rest of the world	0/40 (0.0)	39.1	0.00 (0.00–9.43)

[a]Patients with events per 100 patient-years.

[b]Incidence rate for ILD events was highest among Black patients compared with other races; however, the low number of patients with events and patient-years of exposure precluded further evaluation.

[c]Asian race included patients from either Asian or non-Asian countries.

N, number of patients evaluated; N1, number of patients evaluated in subgroup; n, number of patients with ILD event in subgroup.

multivariable Cox regression model, with time-varying tofacitinib dose and the latest postbaseline DAS28–4(ESR) assessment subsequently added. Because of missing data for some patients, data for 6384 patients (including 39 patients with ILD events) were included in the final model. This model identified older patients (≥65 years; hazard ratio [HR] 2.43 [95% CI, 1.13–5.21], $p = 0.023$) and current smokers (2.89 [1.33–6.26], $p = 0.007$) as 2.4 and 2.9 times more likely to have an ILD event versus younger patients (<65 years) and patients who had never smoked, respectively. Furthermore, for every 1-unit increase in DAS28–4(ESR) score (assessed during the tofacitinib exposure period and within 180 days prior to the ILD event), patients were 1.3 times more likely to have an ILD event (HR, 1.30 [1.04–1.61], $p = 0.019$). In a separate model using DAS28–4(ESR) as a categorical variable, patients with high disease activity (DAS28–4[ESR] >5.1) were numerically more likely to have an ILD event versus patients with low disease activity (DAS28–4 [ESR] <2.6) (2.60 [0.92–7.29], $p = 0.070$, not statistically significant). Patients of Asian race were numerically more likely to have an ILD event versus White patients (2.16 [0.92–5.08], $p = 0.078$, not statistically significant).

AE Analysis in the Overall Cohort

Of the 42 AEs of ILD, 17 (40.5%) were considered serious AEs. For all ILD events (serious and nonserious), 35 of 42 events (83.3%) were mild to moderate in severity.

Rates of serious infections were numerically higher for patients with ILD events versus those without ILD events (Table 3). Among 7019 patients without ILD events, the frequency of all-cause mortality was 1.6% (115 deaths; including those that occurred any time after the last dose of tofacitinib). The frequency of all-cause mortality in patients with ILD events was 7.1% (3 deaths/42 cases). For the 3 patients with an ILD event who died, ILD was present at the time of death; however, there was no direct relationship observed between ILD and cause of death. One of these deaths was attributed to septic shock and thromboangiitis obliterans (male, 47, race = other, Brazil), 1 was attributed to multiorgan failure and thrombotic thrombocytopenic purpura (female, 58, Asian, Japan; patient had a positive sputum culture for gram-positive and cytomegalovirus-positive antigenemia), and 1 was attributed to septic shock and pneumonia (female, 52, White, Brazil).

DISCUSSION

Interstitial lung disease significantly impacts patients with RA, contributing to decreased quality of life, progression of disability, and mortality,[12,43] yet strategies for optimal management of ILD are ambiguous and consist of smoking cessation, chronic glucocorticoids, and immunosuppressive agents.[8] Treatment is further complicated by the association between first-line csDMARDs and the onset of drug-induced pneumonitis.[44,45]

The use of bDMARDs raises similar concerns regarding pulmonary toxicity, yet conflicting evidence exists for their involvement in the onset or exacerbation of RA-ILD.[46–49] Data suggesting an association between the use of TNFi and non-TNFi biologics and risk of RA-ILD have largely been limited to case reports on ILD.[46–49] Conversely, some case reports have associated TNFi therapies with improvement of RA-ILD.[47,48] Results from animal models suggest that tofacitinib could potentially suppress ILD progression by increasing myeloid-derived suppressor cells and suppressing the proinflammatory T helper 17 cells, which may be involved in the pathogenesis of RA-ILD.[50] Data regarding the use of DMARDs in patients with RA-ILD are limited, and conflicting evidence exists for some therapies.[46–49] Consequently, there is a need for data evaluating ILD risk with DMARDs to allow clinicians and patients to make more informed treatment decisions.

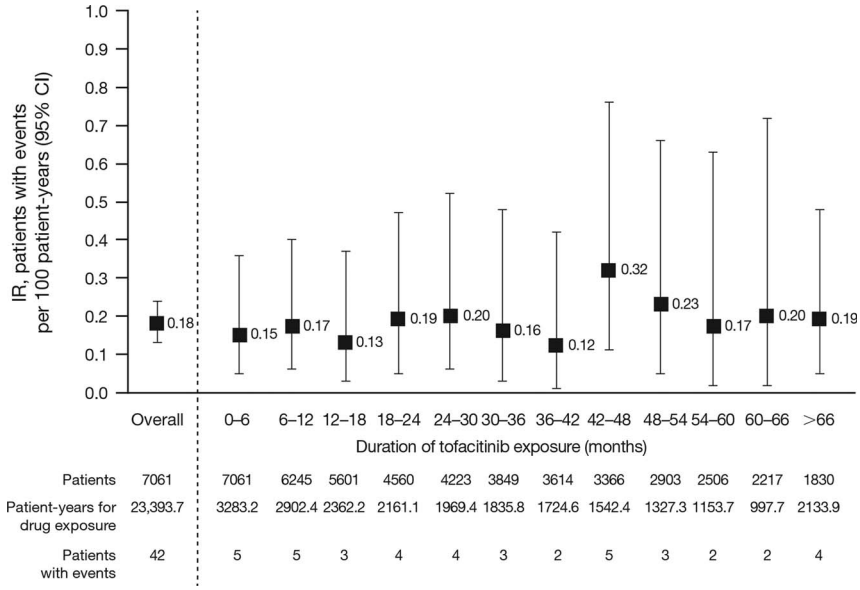

FIGURE 2. Incidence rates for ILD events in the overall cohort (all tofacitinib doses) by 6-month time interval.

Data regarding IR for ILD events in patients with RA are limited to data from cohort studies of healthcare insurance claims databases. A US-based retrospective cohort study among patients with autoimmune disease who were members of Kaiser Permanente Northern California (1998–2007) reported that the age- and gender-standardized IR for ILD events for patients with RA was 0.21 (per 100 patient-years; 95% CI, 0–0.43) for patients exposed to TNFi therapies, with no significant difference associated with exposure to any TNFi versus nonbiologic therapies (HR, 1.03 [95% CI, 0.00–1.12]).[51] A retrospective cohort study of patients with RA selected from the MarketScan database (2010–2012) found the ILD event IR was 0.16 (0.08–0.31) for patients exposed to TNFi therapies.[1] Interstitial lung disease event IRs were also reported for tocilizumab (0.10 [0.0–0.55]), abatacept (0.11 [0.01–0.41]), and rituximab (0.47 [0.13–1.21]).[1] In a follow-up study, data from the MarketScan database (2010–2015) showed the ILD event IR for tofacitinib was 0.26 (95% CI, 0.10–0.69) with an adjusted HR of 1.68 (0.47–5.99) versus abatacept.[52] Analysis of the 2006–2014 Medicare database (n = 104,870) showed that the crude IR and adjusted HR for ILD events (versus abatacept) were lowest for tofacitinib users (IR, 0.31 [0.12–0.81]; HR, 0.82 [0.30–2.22]) versus users of other csDMARDs and bDMARDs.[52]

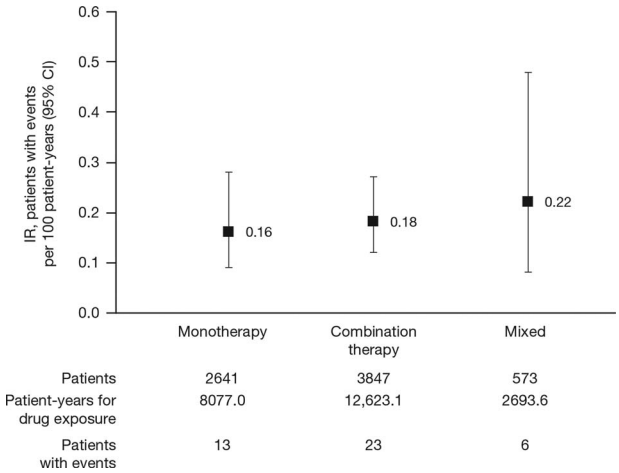

FIGURE 3. Incidence rates for ILD events in patients receiving monotherapy, combination therapy, or mixed therapy in the overall cohort. Background therapy groups were assigned based on the patient's exposure to monotherapy or combination therapy for ≥80% of the patient's tofacitinib exposure. If a patient was not on either monotherapy or combination therapy for ≥80% of the time, the patient was assigned to the mixed group.

In this analysis, IRs for ILD events were 0.18 for both doses of tofacitinib and associated with known risk factors for ILD. No dose relationship was observed for ILD events in the overall cohort, and results were similar for patients receiving tofacitinib as monotherapy and combination therapy.

In a descriptive case-matched control analysis (by age and gender), ILD events were numerically higher in patients with known risk factors for ILD, including Asian ancestry, previous or current smokers, serum markers for RA and inflammation, and prior treatment with csDMARDs and TNFi. The observation that Asian patients had higher IRs for ILD events than White patients corresponds with studies that have shown an association between genetic factors and susceptibility to ILD in Japanese patients.[10] A multivariable Cox regression model identified older age (≥65 years), current smokers, and DAS28–4(ESR) score as risk factors for RA-ILD, consistent with previous reports.[1,2,5,12,14,15] In this analysis, Asian ancestry was not a significant (at the 5% level) risk factor for ILD, but patients of Asian ancesry were numerically more likely to have an ILD event versus White patients.

In this analysis, AEs of ILD were reported by 42 patients in the overall cohort; 40.5% of ILD events were serious, and most (83.3%) AEs of ILD (serious and nonserious) were mild to moderate in severity. Rates of serious infections were numerically higher for patients with ILD events versus those without ILD events. Furthermore, for patients with ILD events, the frequency of all-cause mortality was 7.1% (3 deaths/42 cases). Although ILD was present at the time of death for all 3 patients, there was no direct relationship observed between ILD and cause of death.

This analysis had several limitations. First, subclinical ILD at the time of enrolment cannot be ruled out, and baseline ILD may have contributed to the IR of ILD events. Interstitial lung

disease–related assessments were based on each physician's clinical judgment with no specific diagnostic criteria required, resulting in variability in the data available to the adjudication committee. These factors account for the variability in incidence and prevalence rates observed across study populations, making comparisons difficult. This was a post hoc analysis of studies that were neither designed nor powered to detect differences in ILD event rates between tofacitinib and placebo; thus, direct comparisons of ILD event IRs were not considered. Most studies were of tofacitinib in combination with csDMARDs; a controlled comparison of tofacitinib monotherapy versus combination therapy was not performed. Furthermore, results from this study are limited to patients with RA who had been included in clinical trials, which may differ from patients with RA in routine clinical practice. Additionally, the case-matched control analysis was exploratory in nature. Conclusions regarding potential risk factors for ILD events are limited by the relatively small numbers of patients who experienced an ILD event in this analysis.

In all, in this post hoc analysis across P1, P2, P3, P3b/4, and LTE studies, the IR for ILD events was 0.18 for both doses of tofacitinib, and ILD events appeared to be associated with known risk factors. These results highlight the importance of accounting for known risk factors of RA-ILD in clinical practice.

TABLE 2. Case-Matched Control Analysis[a] of Demographic and Baseline Disease Characteristics of Patients With and Without an ILD Event Who Received Tofacitinib 5 or 10 mg BID in the Overall Cohort

	Cases[b] (N = 42)	Controls[c] (N = 210)
Average dose, n (%)		
5 mg BID	15 (35.7)	82 (39.0)
10 mg BID	27 (64.3)	128 (61.0)
Age, mean (SD), y	57.6 (10.1)	57.8 (10.1)
Female (%)	33 (78.6)	165 (78.6)
BMI, mean (SD), kg/m^2	26.9 (5.5)	27.5 (6.1)
Race, n (%)		
White	23 (54.8)	154 (73.3)
Black	2 (4.8)	2 (<1.0)
Asian	13 (31.0)	37 (17.6)
Other	4 (9.5)	17 (8.1)
Smoking status, n (%)		
Never smoked	20 (47.6)	126 (60.0)
Previous or current smoker	21 (50.0)	83 (39.5)
Concomitant medications, n (%)		
MTX	26 (61.9)	103 (49.0)
MTX weekly dose, mean (SD), mg	16.1 (4.4)	16.0 (4.7)
Corticosteroids[d]	30 (71.4)	111 (52.9)
Corticosteroid daily dose, mean (SD), mg	6.7 (3.8)	6.0 (2.7)
Prior medications, n (%)		
MTX	38 (90.5)	167 (79.5)
Other csDMARD (non-MTX)	26 (61.9)	116 (55.2)
TNFi	11 (26.2)	39 (18.6)
Other bDMARD (non-TNFi)	1 (2.4)	14 (6.7)
Baseline HAQ-DI, mean (SD)	1.6 (0.8)	1.4 (0.7)
Baseline DAS28–4(ESR), mean (SD)	6.6 (1.0)	6.3 (0.9)
Disease duration, mean (SD), y[e]	8.5 (7.3)	8.7 (8.9)
ESR, mean (SD), mm/h	57.0 (35.0)	46.9 (25.1)
CRP, mean (SD), mg/L	25.4 (27.9)	15.4 (19.5)
RF+, n (%)	33 (89.2)	132 (71.0)
Anti-CCP+, n (%)	23 (54.8)	98 (46.7)

[a]Patients with an ILD event (cases) were matched to patients without an ILD event (controls) by age and gender, at a ratio of 1 case to 5 controls.

[b]Patients in the overall cohort who received tofacitinib 5 or 10 mg BID and had an ILD event.

[c]Patients in the overall cohort who received tofacitinib 5 or 10 mg BID but did not have an ILD event.

[d]Refers to prednisone or equivalent.

[e]Disease duration is defined from first diagnosis to day 1 of the qualifying study.

HAQ-DI, Health Assessment Questionnaire–Disability Index; N, number of patients evaluated; n, number of patients in subgroup.

TABLE 3. Proportion and IRs[a] for All Serious Infections for Patients With and Without an ILD Event Who Received Tofacitinib 5 or 10 mg BID in the Overall Cohort

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	All Tofacitinib Doses
Patients with ILD events, N	15	27	42
Serious infections			
n (%)	2 (13.3)	3 (11.1)	5 (11.9)
IR (95% CI)	2.89 (0.35–10.44)	3.01 (0.62–8.80)	2.96 (0.96–6.91)
Patients without ILD events, N	3051	3968	7019
Serious infections			
n (%)	231 (7.6)	340 (8.6)	571 (8.1)
IR (95% CI)	2.81 (2.46–3.19)	2.30 (2.06–2.56)	2.48 (2.28–2.69)

[a]Patients with events per 100 patient-years.

N, number of patients evaluated in subgroup; n, number of patients with serious infections.

KEY POINTS

1. In this post hoc analysis of data pooled across 21 clinical trials from the tofacitinib clinical trial program, the IR for ILD events was 0.18 per 100 patient-years following treatment with either tofacitinib 5 or 10 mg BID.
2. The incidence of ILD events appeared to be associated with known risk factors of established RA-ILD, including age (≥65 years), current smokers, and DAS28–4(ESR) score.
3. These results highlight the importance of identifying known risk factors of RA-ILD in clinical practice.

REFERENCES

1. Curtis JR, Sarsour K, Napalkov P, et al. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti–tumor necrosis factor alpha agents, a retrospective cohort study. *Arthritis Res Ther*. 2015;17:319.
2. Coultas DB, Zumwalt RE, Black WC, et al. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med*. 1994;150:967–972.

3. Duchemann B, Annesi-Maesano I, Jacobe de Naurois C, et al. Prevalence and incidence of interstitial lung diseases in a multi-ethnic county of greater Paris. *Eur Respir J*. 2017;50:1602419.
4. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis–associated interstitial lung disease. *Eur Respir J*. 2010; 35:1322–1328.
5. Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum*. 2010;62:1583–1591.
6. Olson AL, Swigris JJ, Sprunger DB, et al. Rheumatoid arthritis–interstitial lung disease–associated mortality. *Am J Respir Crit Care Med*. 2011;183: 372–378.
7. Gabbay E, Tarala R, Will R, et al. Interstitial lung disease in recent onset rheumatoid arthritis. *Am J Respir Crit Care Med*. 1997;156:528–535.
8. Iqbal K, Kelly C. Treatment of rheumatoid arthritis–associated interstitial lung disease: a perspective review. *Ther Adv Musculoskelet Dis*. 2015;7: 247–267.
9. van den Hoek J, Boshuizen HC, Roorda LD, et al. Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. *Rheumatol Int*. 2017;37:487–493.
10. Furukawa H, Oka S, Shimada K, et al. Genetics of interstitial lung disease: vol de nuit (night flight). *Clin Med Insights Circ Respir Pulm Med*. 2015;9:1–7.
11. Kiely P, Busby AD, Nikiphorou E, et al. Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. *BMJ Open*. 2019;9:e028466.
12. Kelly CA, Saravanan V, Nisar M, et al. Rheumatoid arthritis–related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study. *Rheumatology (Oxford)*. 2014;53:1676–1682.
13. Juge PA, Lee JS, Ebstein E, et al. MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. *N Engl J Med*. 2018;379:2209–2219.
14. Saag KG, Kolluri S, Koehnke RK, et al. Rheumatoid arthritis lung disease. Determinants of radiographic and physiologic abnormalities. *Arthritis Rheum*. 1996;39:1711–1719.
15. Sparks JA, He X, Huang J, et al. Rheumatoid arthritis disease activity predicting incident clinically apparent rheumatoid arthritis–associated interstitial lung disease: a prospective cohort study. *Arthritis Rheumatol*. 2019;71:1472–1482.
16. Dixon WG, Hyrich KL, Watson KD, BSRBR Control Centre Consortium, et al. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis–associated interstitial lung disease: results from the British Society for Rheumatology biologics register. *Ann Rheum Dis*. 2010; 69:1086–1091.
17. Druce KL, Iqbal K, Watson KD, et al. Mortality in patients with interstitial lung disease treated with rituximab or TNFi as a first biologic. *RMD Open*. 2017;3:e000473.
18. Sawada T, Inokuma S, Sato T, et al. Leflunomide-induced interstitial lung disease: prevalence and risk factors in Japanese patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2009;48:1069–1072.
19. Fleischmann R, Cutolo M, Genovese MC, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum*. 2012;64:617–629.
20. Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum*. 2009;60:1895–1905.
21. Kremer JM, Cohen S, Wilkinson BE, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum*. 2012;64:970–981.
22. Tanaka Y, Suzuki M, Nakamura H, et al, Tofacitinib Study Investigators. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res (Hoboken)*. 2011;63:1150–1158.
23. Tanaka Y, Takeuchi T, Yamanaka H, et al. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. *Mod Rheumatol*. 2015;25:514–521.
24. Fleischmann R, Kremer J, Cush J, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med*. 2012;367: 495–507.
25. van der Heijde D, Tanaka Y, Fleischmann R, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum*. 2013;65:559–570.
26. Lee EB, Fleischmann R, Hall S, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. *N Engl J Med*. 2014;370:2377–2386.
27. van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med*. 2012; 367:508–519.
28. Burmester GR, Blanco R, Charles-Schoeman C, et al. Tofacitinib (CP-690 ,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet*. 2013;381:451–460.
29. Kremer J, Li Z-G, Hall S, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann Intern Med*. 2013;159:253–261.
30. van der Heijde D, Strand V, Tanaka Y, et al. Tofacitinib in combination with methotrexate in patients with rheumatoid arthritis: clinical efficacy, radiographic, and safety outcomes from a twenty-four-month, phase III study. *Arthritis Rheumatol*. 2019;71:878–891.
31. Fleischmann R, Mysler E, Hall S, et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. *Lancet*. 2017;390:457–468.
32. Wollenhaupt J, Silverfield J, Lee EB, et al. Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. *J Rheumatol*. 2014;41: 837–852.
33. Yamanaka H, Tanaka Y, Takeuchi T, et al. Tofacitinib, an oral Janus kinase inhibitor, as monotherapy or with background methotrexate, in Japanese patients with rheumatoid arthritis: an open-label, long-term extension study. *Arthritis Res Ther*. 2016;18:34.
34. Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. *Arthritis Res Ther*. 2019; 21:89.
35. Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis*. 2013;72:517–524.
36. Turner SM, Beysen C, Charles-Schoeman C, et al. Increased selective clearance of cholesteryl-ester in patients with rheumatoid arthritis is reversed by treatment with tofacitinib. *Arterioscler Thromb Vasc Biol*. 2013;33: abstract 124.
37. Kremer JM, Kivitz AJ, Simon-Campos JA, et al. Evaluation of the effect of tofacitinib on measured glomerular filtration rate in patients with active rheumatoid arthritis. *Arthritis Rheumatol*. 2014;66: abstract 459.
38. Conaghan PG, Østergaard M, Bowes MA, et al. Comparing the effects of tofacitinib, methotrexate and the combination, on bone marrow oedema,

synovitis and bone erosion in methotrexate-naive, early active rheumatoid arthritis: results of an exploratory randomised MRI study incorporating semiquantitative and quantitative techniques. *Ann Rheum Dis*. 2016;75: 1024–1033.

39. McInnes IB, Kim HY, Lee SH, et al. Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study. *Ann Rheum Dis*. 2014;73:124–131.
40. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Ann Rheum Dis*. 2016;75:687–695.
41. Charles-Schoeman C, Fleischmann R, Davignon J, et al. Potential mechanisms leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. *Arthritis Rheumatol*. 2015;67:616–625.
42. Winthrop KL, Wouters AG, Choy EH, et al. The safety and immunogenicity of live zoster vaccination in patients with rheumatoid arthritis before starting tofacitinib: a randomized phase II trial. *Arthritis Rheumatol*. 2017;69:1969–1977.
43. Natalini JG, Swigris JJ, Morisset J, et al. Understanding the determinants of health-related quality of life in rheumatoid arthritis–associated interstitial lung disease. *Respir Med*. 2017;127:1–6.
44. Conway R, Low C, Coughlan RJ, et al. Methotrexate and lung disease in rheumatoid arthritis: a meta-analysis of randomized controlled trials. *Arthritis Rheumatol*. 2014;66:803–812.
45. Martin N, Innes JA, Lambert CM, et al. Hypersensitivity pneumonitis associated with leflunomide therapy. *J Rheumatol*. 2007;34:1934–1937.
46. Lindsay K, Melsom R, Jacob BK, et al. Acute progression of interstitial lung disease: a complication of etanercept particularly in the presence of rheumatoid lung and methotrexate treatment. *Rheumatology (Oxford)*. 2006;45:1048–1049.
47. Bargagli E, Galeazzi M, Rottoli P. Infliximab treatment in a patient with rheumatoid arthritis and pulmonary fibrosis. *Eur Respir J*. 2004; 24:708.
48. Wang Y, Xu SQ, Xu JH, et al. Treatment with etanercept in a patient with rheumatoid arthritis–associated interstitial lung disease. *Clin Med Insights Case Rep*. 2011;4:49–52.
49. Hadjinicolaou AV, Nisar MK, Bhagat S, et al. Non-infectious pulmonary complications of newer biological agents for rheumatic diseases—a systematic literature review. *Rheumatology (Oxford)*. 2011;50: 2297–2305.
50. Sendo S, Saegusa J, Ichise Y, et al. Tofacitinib facilitates the expansion of myeloid-derived suppressor cells and ameliorates interstitial lung disease in SKG mice. *Arthritis Rheumatol*. 2018;70(suppl 10): abstract 49.
51. Herrinton LJ, Harrold LR, Liu L, et al. Association between anti–TNF-α therapy and interstitial lung disease. *Pharmacoepidemiol Drug Saf*. 2013; 22:394–402.
52. Xie F, Annapureddy N, Chen L, et al. Rheumatoid arthritis and the risk for interstitial lung disease: a comparison of risk associated with biologic and conventional DMARDs. *Arthritis Rheumatol*. 2018;69: abstract 137.