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

Post Hoc Analysis From 21 Clinical Trials

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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 (P1, 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 events were 0.18 following tofacitinib treatment, and ILD 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

(Ann Rheum Dis 2021;70: e482–e490)
**METHODS**

**Study Design and Patients**

This post hoc analysis 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 (A3921109 [NCT00147498], A3921025 [NCT00041360], A3921035 [NCT00550446], A3921039 [NCT00603512, Japan study], A3921040 [NCT00687193, Japan study], A3921068 [NCT01164579]), 10 P2 studies (A3921019 [NCT00147498], A3921025 [NCT00041360], A3921035 [NCT00550446], A3921039 [NCT00603512, Japan study], A3921040 [NCT00687193, Japan study], A3921068 [NCT01164579], A3921073 [NCT00976599], A3921129 [NCT01359159], A3921237 [NCT02145758]); 6 P3 studies (A3921032 [NCT00960440], A3921044 [NCT00847613, 2-year data], A3921045 [NCT0084307], A3921046 [NCT00856544], A3921064 [NCT01039385], A3921109 [NCT01039688, 2-year data]); and 1 P3b study (A3921187 [NCT01262118], A3921032 [NCT00147498], A3921025 [NCT00041360], A3921035 [NCT00550446], A3921039 [NCT00603512, Japan study], A3921040 [NCT00687193, Japan study], A3921068 [NCT01164579], A3921073 [NCT00976599], A3921129 [NCT01359159], A3921237 [NCT02145758]).

**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/m²), disease duration (early [<1 year], late [≥21 year]), gender (female, male), race (White, Black, Asian, other), smoking history (non-smoker, 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 ≥32 [low]; >32 to ≤51.1 [moderate]; >51.1 [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).
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) | 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)   |             |
| 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; \(N_1\), 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) ≤3.6) (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,\(^{12,44}\) yet strategies for optimal management of ILD are ambiguous and consist of smoking cessation, chronic glucocorticoids, and immunosuppressive agents.\(^{3}\) Treatment is further complicated by the association between first-line csDMARDs and the onset of drug-induced pneumonitis.\(^{34,45}\) 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 biologies 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.\(^{34,49}\) Consequently, there is a need for data evaluating ILD risk with DMARDs to allow clinicians and patients to make more informed treatment decisions.
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, 0.00–0.43) 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]).

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. 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]). In a follow-up study, data from the MarketScan database (2010–2015) showed the ILD event IR for tocilizumab was 0.26 (95% CI, 0.10–0.69) with an adjusted HR of 1.68 (0.47–5.99) versus abatacept. 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 tocilizumab users (HR, 0.31 [0.12–0.81]; HR, 0.82 [0.30–2.22]) versus users of other csDMARDs and bDMARDs.

In this analysis, IRs for ILD events were 0.18 for both doses of tocilizumab 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 tocilizumab 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. 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. Asian ancestry was not a significant (at the 5% level) risk factor for ILD, but patients of Asian ancestry 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 event IRs for patients receiving tocilizumab and associated with known risk factors for ILD.
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

| TABLE 2. Case-Matched Control Analysis 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** (N = 42) | **Controls** (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/m² | 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) | 18 (8.6) |
| 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 | 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 | 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 (78.6) | 132 (63.0) |
| Anti-CCP+, n (%) | 23 (54.8) | 98 (46.7) |

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 identifying known risk factors of RA-ILD in clinical practice.

**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.

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