Analysis of Infections and All-Cause Mortality in Phase II, Phase III, and Long-Term Extension Studies of Tofacitinib in Patients With Rheumatoid Arthritis

Stanley Cohen, Sebastián C. Radominski, Juan J. Gomez-Reino, Lisy Wang, Sriram Krishnaswami, Susan P. Wood, Koshika Soma, Chudi I. Nduaka, Kenneth Kwok, Hernan Valdez, Birgitta Benda, and Richard Riese

Objective. To determine the rate of infection and all-cause mortality across tofacitinib phase II, phase III, and long-term extension (LTE) studies in patients with moderately to severely active rheumatoid arthritis (RA).

Methods. Pooled data from studies of tofacitinib were analyzed. In these studies, tofacitinib was administered as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs. The cutoff date for inclusion of data was April 19, 2012.

Results. Across phase II, phase III, and LTE studies, 4,789 patients received tofacitinib (8,460 patient-years of exposure). The overall rate of serious infection was 3.09 events per 100 patient-years (95% confidence interval [95% CI] 2.73–3.49), and rates were stable over time. A Cox proportional hazards model showed that age, corticosteroid dose, diabetes, and tofacitinib dose were independently linked to the risk of serious infection. Lymphocyte counts of <0.5 × 10⁹/mm³ were rare but were associated with an increased risk of treated and/or serious infection. Overall, all-cause mortality rates were 0.30 events per 100 patient-years (95% CI 0.20–0.44).

Conclusion. The overall risk of infection (including serious infection) and mortality rates in RA patients treated with tofacitinib appear to be similar to those observed in RA patients treated with biologic agents. The rates of serious infection were stable over time.

Tofacitinib (CP-690,550) is an oral JAK inhibitor used for the treatment of rheumatoid arthritis (RA) and has a novel mechanism of action. The JAK family of tyrosine kinases includes JAK-1, JAK-2, JAK-3, and Tyk-2. Tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK-3 and/or JAK-1, with functional selectivity over receptors that signal in pairs of JAK-2 (1). Common γ-chain–containing receptors using JAK-1 and JAK-3 include
infections, including serious infections, and mortality with DMARDs (4,5). Here, we describe pooled data on the risk of infection is further increased in patients treated with DMARDs (4,5). Patients with RA already have a higher risk of death (2) and infection (3) compared with the general population, and the risk of infection is further increased in patients treated with DMARDs (4,5). Here, we describe pooled data on infections, including serious infections, and mortality across this tofacitinib RA clinical development program.

**PATIENTS AND METHODS**

Three collections of pooled safety data were used for the analyses (see Supplementary Appendix 2, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38779/abstract).

**Pooled phase II, phase III, and LTE studies in tofacitinib-treated patients (P2P3LTE).** This data set includes any patient in the phase II or phase III studies described in Table 1 or in LTE studies (patients entering from the phase II/III studies shown in Table 1) who received tofacitinib at any time (all doses combined).

**Pooled phase III studies (P3All).** This data set consists of pooled data from 5 phase III studies in patients with moderate-to-severe RA and an inadequate response to nonbiologic or biologic DMARDs (Table 1). Patients received tofacitinib (5 mg twice daily or 10 mg twice daily) or placebo as monotherapy or in combination with nonbiologic DMARDs (mainly MTX). Patients randomized to receive placebo were advanced in a double-blind manner to receive tofacitinib at a dosage of 5 mg twice daily or 10 mg twice daily, at 3 months or 6 months. Data from patients receiving placebo were classified within the placebo group until the patients advanced to the tofacitinib group and then were classified within the tofacitinib group. One phase III study included an active-treatment control group (40 mg of adalimumab, administered subcutaneously every 2 weeks, in patients receiving background MTX).

**Pooled LTE studies.** This data set consists of pooled data from 2 ongoing, open-label LTE studies (Table 1). RA patients from qualifying index studies were allowed to enroll in LTE studies (Table 1). In LTE studies, patients from phase II studies (Table 1) initiated treatment with tofacitinib at a dosage of 5 mg twice daily. In patients from phase III studies (Table 1) and additional ongoing phase I, phase II, and phase III studies (see Supplementary Appendix 2, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38779/abstract), treatment with tofacitinib was initiated at a dosage of 10 mg twice daily, with the exception of patients in phase III studies from China and Japan, in whom treatment was initiated at a dosage of 5 mg twice daily, as required by the protocols.

In LTE studies, the dosage of tofacitinib could be reduced from 10 mg twice daily to 5 mg twice daily, tofacitinib could be temporarily discontinued for up to 28 days, or the dosage of tofacitinib could be increased from 5 mg twice daily to 10 mg twice daily at the discretion of the investigator. Dosage adjustment or discontinuation of permitted concomitant RA medications (including MTX, leflunomide, sulfasalazine, antimalarials, auranofin, injectable gold preparations, nonsteroidal antiinflammatory drugs, and/or glucocorticoids [up to 10 mg prednisone/day or equivalent]) was allowed. Patients were classified according to a dosage of 5 mg twice daily or 10 mg twice daily, based on the highest tofacitinib dosage administered during the first 135 days of treatment in LTE studies.

In some studies, data collection and analyses were still ongoing at the time of this analysis (i.e., the databases are not locked; some values may change for the final, locked databases) (see Supplementary Appendix 2, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38779/abstract). All protocols were approved by Institutional Review Boards and/or Independent Ethics Committees and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines established by the International Conference on Harmonisation.

In general, phase III and LTE studies excluded patients with a significant infection within the past 6 months; white blood cell counts of <3.0 × 10^9/mm³; absolute neutrophil counts of <1.2 × 10^9/mm³; untreated or inadequately treated Mycobacterium tuberculosis (TB) infection (as determined by chest radiography and QuantiFeron testing or, if QuantiFeron tests were unavailable, by purified protein derivative skin testing); recurrent herpes zoster infection or disseminated (single episode) herpes simplex virus infection; or infection with human immunodeficiency virus, hepatitis B virus (HBV), or hepatitis C virus (HCV). Study treatment was discontinued and patients were withdrawn from the studies if a serious infection developed or if they had 2 sequential absolute neutrophil counts of <0.5 × 10^9/mm³.

**Safety evaluations.** Safety monitoring included the collection of all adverse events (AEs) and serious AEs (SAEs), regardless of the presumed causality, graded in terms of severity and relationship to study treatment and coded using Medical Dictionary for Regulatory Activities version 13.1 (for phase II and phase III studies) and version 14.1 (for LTE studies). The severity of neutropenia and lymphopenia was defined according to the Outcome Measures in Rheumatology (OMERACT) criteria (6).

SAEs were defined as follows: fatal or life-threatening, requiring hospitalization or extension of existing hospitalization, resulting in persistent or significant disability/incapacity or congenital abnormality/birth defect, or considered to be an important medical event. Serious infections were defined as...
those requiring hospitalization for treatment or parenteral antimicrobial therapy or otherwise meeting the SAE criteria.

The investigators assessed cause of death and its relationship to the study medication. Deaths occurring in phase III and LTE studies after February 25, 2009 were also adjudicated by an independent external cardiovascular safety end point adjudication committee whose members were blinded with regard to the treatment assignments.

**Statistical analysis.** Overall mortality and infection data pooled from the P2P3LTE population (cutoff date: April 19, 2012) are reported. Exposure-estimated incidence rates and exposure-adjusted event rates were calculated as the

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### Table 1. Phase II, phase III, and LTE studies of tofacitinib in RA included in the pooled analysis*

| Clinicaltrials.gov identifier† | Sponsor ID | Tofacitinib dosages and patient populations | Control group | Treatment duration |
|-----------------------------|------------|---------------------------------------------|---------------|--------------------|
| **Phase II randomized, double-blind studies** | | | | |
| NCT00413660 | A3921025 | 1, 3, 5, 10, or 15 mg bid or 20 mg qd in patients receiving background MTX | Placebo | 24 weeks |
| NCT00603512 | A3921039 | 1, 3, 5, or 10 mg bid in Japanese patients receiving background MTX | Placebo | 12 weeks |
| NCT00147498 | A3921019 | 5, 15, or 30 mg (monotherapy) in patients with an inadequate response to MTX, etanercept, infliximab, or adalimumab | Placebo | 6 weeks |
| NCT00550446 | A3921035 | 1, 3, 5, 10, or 15 mg bid (monotherapy) in patients with an inadequate response to MTX | Placebo or adalimumab | 24 weeks |
| NCT00687193 | A3921040 | 1, 3, 5, 10, or 15 mg bid (monotherapy) in Japanese patients | Placebo | 12 weeks |
| NCT01059864 | A3921109 | Patients receiving tofacitinib 10 mg bid (monotherapy) for 6 weeks, randomized to placebo or atorvastatin for a further 6 weeks | Tofacitinib plus placebo versus tofacitinib plus atorvastatin | 6 weeks plus 6 weeks |
| **Phase III randomized, double-blind studies** | | | | |
| NCT00853385 | A3921064, ORAL Standard | 5 or 10 mg bid in patients receiving background MTX following an inadequate response to MTX | Placebo or adalimumab | 12 months |
| NCT00847613 | A3921044, ORAL Scan | 5 or 10 mg bid in patients receiving background MTX following an inadequate response to MTX | Placebo | 24 months (12-month data available at data cutoff) |
| NCT00960440 | A3921032, ORAL Step | 5 or 10 mg bid in patients receiving background MTX following an inadequate response to ≥1 TNF inhibitor | Placebo | 6 months |
| NCT00856544 | A3921046, ORAL Sync | 5 or 10 mg bid in patients receiving background nonbiologic DMARD(s) following an inadequate response to ≥1 biologic or nonbiologic DMARD | Placebo | 12 months |
| NCT00814307 | A3921045, ORAL Solo | 5 or 10 mg bid (monotherapy) in patients with an inadequate response to ≥1 biologic or nonbiologic DMARD | Placebo | 6 months |
| **LTE open-label studies** | | | | |
| NCT00413699 | A3921024, ORAL Sequel | 5 or 10 mg bid in patients from phase II and phase III studies, as monotherapy or with background nonbiologic DMARDs | – | As required |
| NCT00661661 | A3921041 | 5 or 10 mg bid in Japanese patients from phase II and phase III, as monotherapy or with background nonbiologic DMARDs | – | As required |

* In addition to the phase II and phase III qualifying index studies, the long-term extension (LTE) data set includes patients enrolled from an ongoing (at the time of the April 2012 data cut) phase I study in 33 patients with rheumatoid arthritis (RA) (NCT01262118), 3 ongoing phase II studies (NCT01164579, NCT00976599, and NCT01359150), and 1 ongoing phase III study in methotrexate (MTX)-naive patients (NCT01039688).

† See Supplementary Appendix 1 (available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38779/abstract) for the references associated with the listed studies.
number of unique patients with an event (for that time period), divided by the total exposure in that treatment group in the pooled cohort, multiplied by 100. The incidence rate calculations censor patient exposure at the time of event, while exposure-adjusted event rate calculations do not.

The relationship between potential risk factors (age, race, diabetes, glucocorticoid use, baseline disease activity [based on the Disease Activity Score in 28 joints (7)], disease duration, lymphopenia, prior therapy, concomitant background therapy, prior treated infection, geography) and the occurrence of serious infections was investigated using a Cox proportional hazards model. Following the initial screening, selected relevant clinical factors were assessed in more detail (see Supplementary Appendix 2, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38779/abstract).

RESULTS

Patient disposition and duration of exposure. In the P2P3LTE population, 4,789 patients (at baseline, ages 18–86 years; ~80% female; concomitant glucocorticoid use in 50–60%) received tofacitinib, with 8,460 patient-years of exposure as of April 19, 2012. In the P3All population, exposure to placebo (202.6 patient-
Table 2. Common infection AEs and rates of infection and serious infection in phase III and LTE studies of tofacitinib in rheumatoid arthritis*  

| Patients with infections and infestations | Phase III studies | LTE studies |
|------------------------------------------|------------------|-------------|
| Unique patients with event, no.          | Tofacitinib, 5 mg bid (n = 1,216) | Tofacitinib, 5 mg bid (n = 1,421) | |
| Exposure, patient-years                  | 243              | 846         | |
| EAER, events per 100 patient-years (95% CI) | 2.67–8.18        | 3.215       | |
| Common infection AEs, no. (EAER, events per 100 patient-years) (95% CI)† | 14 (4.87) [2.67–8.18] | 127 (3.95) [3.29–4.70] | |
| Bronchitis                               | 13 (4.50) [2.40–7.72] | 13 (4.50) [2.40–7.72] | |
| Herpes zoster                            | 16 (5.54) [3.09–6.83] | 127 (3.95) [3.29–4.70] | |
| Influenza                                | 8 (2.78) [3.18–9.02] | 4 (8.53) [2.32–21.79] | |
| Nasopharyngitis                          | 14 (4.87) [2.66–8.16] | 127 (3.95) [3.29–4.70] | |
| Upper respiratory tract infection        | 51 (16.86) [2.26–5.58] | 4 (8.53) [2.32–21.79] | |
| Urinary tract infection                  | 27 (4.69) [0.54–11.64] | 127 (3.95) [3.29–4.70] | |
| Patients ages >65 years with infections and infestations | 100 (n = 3,209.91) | 84 (n = 2,775.84) | |
| Unique patients with event, no.          | 29               | 84          | |
| Exposure, patient-years                  | 900.87           | 3.22 (2.24–4.63) | |
| IR, patients with events per 100 patient-years (95% CI) | 909.08 | 2.97 (2.04–4.33) | |
| Patients ages >65 years with serious infections and infestations | 1,796.50 | 781.74 | |
| Unique patients with event, no.          | 19               | 769.89      | |
| Exposure, patient-years                  | 1,796.50         | 769.89      | |
| IR, patients with events per 100 patient-years (95% CI) | 1,796.50 | 769.89 | |
| Patients ages >65 years with serious infections and infestations | 361 | 22 | |
| Unique patients with event, no.          | 10              | 10          | |
| Exposure, patient-years                  | 521              | 10          | |
| IR, patients with events per 100 patient-years (95% CI) | 521 | 10 | |

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Serious infections and infestations with tofacitinib and in combination with background DMARD therapy  

| Unique patients with event, no. | 28 | 23 | 55 | 3 | 3 | 48 | 63 | 111 |
|---------------------------------|----|----|----|---|---|----|----|-----|
| Exposure, patient-years         | 784.34 | 795.29 | 1,836.01 | 174.53 | 178.66 | 3,215.4 | 2,781.9 | 5,997.3 |
| IR, patients with events per 100 patient-years (95% CI) | 3.57 (2.47–5.17) | 2.89 (1.92–4.35) | 3.00 (2.30–3.90) | 1.72 (0.55–5.33) | 1.68 (0.54–5.21) | 1.49 (1.13–1.98) | 2.27 (1.77–2.90) | 1.85 (1.54–2.23) |

Serious infections and infestations with tofacitinib monotherapy  

| Unique patients with event, no. | 1 | 4 | 6 | 0 | N/A | 36 | 37 | 73 |
|---------------------------------|---|---|---|---|-----|----|----|-----|
| Exposure, patient-years         | 117.21 | 113.79 | 256.90 | 2793 | N/A | 3,237.6 | 2,784.6 | 6,022.2 |
| IR, patients with events per 100 patient-years (95% CI) | 0.85 (0.12–6.06) | 3.52 (1.32–9.37) | 2.34 (1.05–5.20) | N/A | 1.11 (0.80–1.54) | 1.33 (0.96–1.83) | 1.21 (0.96–1.53) |

Serious infections and infestations in patients receiving concomitant glucocorticoids at baseline  

| Unique patients with event, no. | 25 | 14 | 43 | 3 | 2 | 51 | 61 | 112 |
|---------------------------------|----|----|----|---|---|----|----|-----|
| Exposure, patient-years         | 503.44 | 508.92 | 1,167.32 | 113.23 | 102.12 | 1,728.1 | 1,446.9 | 3,175.1 |
| IR, patients with events per 100 patient-years (95% CI) | 4.96 (3.35–7.34) | 2.75 (1.63–4.65) | 3.68 (2.73–4.96) | 2.65 (0.85–8.22) | 1.96 (0.49–7.83) | 2.95 (2.24–3.88) | 4.22 (3.28–5.42) | 3.53 (2.93–4.25) |

Serious infections and infestations in patients without concomitant glucocorticoids at baseline  

| Unique patients with event, no. | 4 | 13 | 18 | 0 | 1 | 33 | 39 | 72 |
|---------------------------------|---|----|----|---|---|----|----|-----|
| Exposure, patient-years         | 397.44 | 400.16 | 926.48 | 89.23 | 76.54 | 1,481.8 | 1,328.9 | 2,810.7 |
| IR, patients with events per 100 patient-years (95% CI) | 1.01 (0.38–2.68) | 3.25 (1.89–5.60) | 19.4 (1.22–30.8) | 0 | 1.31 (0.18–9.28) | 2.23 (1.58–3.13) | 2.94 (2.14–4.02) | 2.56 (2.03–3.23) |

* In the phase III studies, patients who advanced from placebo to tofacitinib are counted in the placebo group until advancement and in the tofacitinib group (all doses) after advancement. AEs = all-cause adverse events according to Medical Dictionary for Regulatory Activities preferred terms; bid = twice daily; EAER = exposure-adjusted event rate; 95% CI = 95% confidence interval; IR = incidence rate; DMARD = disease-modifying antirheumatic drug; N/A = not applicable.

† Infection adverse events occurring in ≥2% of any treatment group in phase III studies (up to 3 months of treatment, with control groups) or in ≥5% of any treatment group in long-term extension (LTE) studies.
years) and adalimumab (178.9 patient-years) was substantially lower than the exposure to tofacitinib (2,098.2 patient-years). As of April 19, 2012, data were available from 4,102 patients in the LTE studies, which had a longer mean treatment duration, longer maximum treatment duration, and greater exposure to tofacitinib at a dosage of 5 mg twice daily (826 days, 1,844 days, and 3,243 patient-years, respectively) compared with a dosage of 10 mg twice daily (374 days, 1,353 days, and 2,791 patient-years, respectively).

**Infections and serious infections.** In the P3All population, at month 3, the proportions of patients with treated infections (i.e., those requiring antimicrobial therapy or surgical intervention) were 4.5% in the group receiving tofacitinib 5 mg twice daily (95% confidence interval [95% CI] 3.43–5.85), 5.7% in the group receiving tofacitinib 10 mg twice daily (95% CI 4.45–7.14), 3.4% in the adalimumab group (95% CI 1.39–6.94), and 3.8% in the placebo group (95% CI 2.51–5.54). At month 6, the proportions were 5.4% (95% CI 4.27–6.66), 4.9% (95% CI 3.87–6.18), 7.4% (95% CI 4.17–11.84), and 2.7% (95% CI 1.00–5.82), respectively. Most treated infections were mild or moderate in severity, and, in the majority of patients requiring temporary discontinuation, the duration of therapy cessation was ≤2 weeks. In total, 3.7% of patients in the group receiving tofacitinib 5 mg twice daily (95% CI 2.06–6.20), 3.3% of patients in the group receiving tofacitinib 10 mg twice daily (95% CI 1.82–5.49), 0.0% of the patients in the adalimumab group (95% CI 0.00–6.16), and 1.2% of patients in the placebo group (95% CI 0.03–6.31) were permanently withdrawn from the P3All population due to infection AEs. There was no difference in the length of time until permanent discontinuation due to serious infection between patients receiving tofacitinib at a dosage of 5 mg twice daily and those receiving a dosage of 10 mg twice daily, in the P3All or the LTE population (data not shown).

In the P3All population, the exposure-adjusted event rates for infection of any severity were similar among patients who received tofacitinib 5 mg twice daily, patients who received tofacitinib 10 mg twice daily, and those who received placebo (84.7 [95% CI 74.36–96.01], 89.1 [95% CI 78.66–100.84], and 79.3 [95% CI 65.85–94.26] events per 100 patient-years, respectively) during the first 3 months. The rate in the group treated with adalimumab was 70.4 events per 100 patient-years (95% CI 48.33–98.60). In the LTE study population, the rates of infection were 26.3 events per 100 patient-years in the group treated with tofacitinib 5 mg twice daily (95% CI 24.57–28.15) and 45.0 events per 100 patient-years in the group treated with tofacitinib 10 mg twice daily (95% CI 42.54–47.59). The rates were similar in patients receiving background DMARDs and those who received tofacitinib as monotherapy.

In the P2P3LTE population, 259 patients had serious infections (overall incidence rate 3.09 events per 100 patient-years; 95% CI 2.73–3.49). The most common serious infection was pneumonia; other commonly reported serious infections included skin and soft tissue infection. The incidence rates of serious infection were stable over time, with a decrease in the point estimates during the 2 latest time intervals (36–42 months and >42 months) (Figure 1A).

In the LTE population but not the P3All population, the incidence rates of serious infection were numerically higher in the group receiving tofacitinib at a dosage of 10 mg twice daily compared with the group receiving tofacitinib at a dosage of 5 mg twice daily, but the 95% CIs overlapped (3.6 events per 100 patient-years [95% CI 2.96–4.38] and 2.62 events per 100 patient-years [95% CI 2.11–3.24], respectively) (Table 2). In the P3All and LTE populations, the incidence rates were numerically higher in patients receiving background DMARDs (compared with those receiving tofacitinib monotherapy) and in patients receiving glucocorticoids, although the 95% CIs overlapped (Table 2).

In a Cox proportional hazards model in the P2P3LTE population, age (≥65 years), corticosteroid dose ≥7.5 mg, diabetes, and tofacitinib dose were independent factors associated with an increased risk of serious infection, because the lower limits of the 95% CIs were >1 (Figure 1B). The risk (hazard ratios [95% CI]) of serious infection was increased in the following populations: ≥65 years versus <65 years of age (2.17 [95% CI 1.64–2.88]), patients with diabetes versus those without diabetes (1.99 [95% CI 1.39–2.85]), patients receiving glucocorticoid doses of ≥7.5 mg versus <7.5 mg (1.4 [95% CI 1.05–1.88]), and patients receiving tofacitinib at a dosage of 10 mg twice daily versus a dosage of 5 mg twice daily (1.4 [95% CI 1.13–1.83]). The estimated increased risk of serious infection with the 10 mg twice daily dosage compared with the 5 mg twice daily dosage reflected a net effect in the P3All population (no difference) and LTE population (2-fold) between the 2 doses.

Relative to patients with an inadequate response to nonbiologic DMARDs, those with an inadequate response to biologic DMARDs showed a hazard ratio of 1.15, with CIs including the value 1. Results of the tests of interaction between tofacitinib dose and age (estimate 1.00 [95% CI 0.91–1.11]), corticosteroid dose (0.85 [95%
CI 0.77–0.95]), and diabetes (1.03 [95% CI 0.90–1.17]) did not show an increased risk attributable to tofacitinib in these subgroups of patients. The likelihood of serious infection did not appear to be increased in patients who previously experienced a treated infection within the first 6 months of tofacitinib therapy, and the duration of RA was not associated with an increased risk of serious infection.

**Herpes zoster and hepatitis virus infection.** Non-serious or serious herpes zoster infections were reported in 346 patients in the P2P3LTE population (incidence rate 4.27 events per 100 patient-years [95% CI 3.85–4.75]). In the P3All population, the incidence rates of herpes zoster infection were 2.81 events per 100 patient-years in patients treated with adalimumab (95% CI 1.17–6.76) and 1.49 events per 100 patient-years in the placebo group (95% CI 0.48–4.61). Rates of herpes zoster infection were similar in patients treated with tofacitinib at a dosage of 5 mg twice daily and those treated with tofacitinib at a dosage of 10 mg twice daily (for P3All, 4.39 events per 100 patient-years [95% CI 3.21–6.01] and 4.23 per 100 patient-years [95% CI 3.08–5.82], respectively; for LTE, 4.18 events per 100 patient-years [95% CI 3.51–4.97] and 4.50 per 100 patient-years [95% CI 3.77–5.38]).

In the LTE population, the rate of herpes zoster infection was higher in patients ages ≥65 years compared with those ages <65 years (6.27 events per 100 patient-years [95% CI 4.84–8.13] and 3.97 events per 100 patient-years [95% CI 3.45–4.57], respectively), and concomitant glucocorticoid treatment at baseline appeared to modestly increase the risk (4.77 events per 100 patient-years [95% CI 3.67–6.22]) versus 3.83 events per 100 patient-years [95% CI 2.75–5.33] in the P3All population and 4.90 events per 100 patient-years [95% CI 4.18–5.76] versus 3.69 events per 100 patient-years [95% CI 3.04–4.49] in the LTE population). The incidence rate of herpes zoster infection was higher in Asian patients (in LTE studies, 6.75 events per 100 patient-years [95% CI 5.56–8.22] versus 3.54 events per 100 patient-years [95% CI 2.98–4.21] in white patients and 2.21 events per 100 patient-years [95% CI 0.71–6.85] in black patients). The overall incidence rates for herpes zoster infection in patients with tofacitinib were stable over time (data not shown).

Serious herpes zoster infections requiring hospitalization or parenteral antiviral therapy were infrequent, with 3 cases in phase II studies (1 each in patients receiving tofacitinib at dosages of 5, 10, and 15 mg twice daily), 5 cases in phase III studies (4 in patients receiving tofacitinib 5 mg twice daily and 1 in a patient receiving tofacitinib at a dosage of 10 mg twice daily), and 13 cases in LTE studies (11 in patients receiving tofacitinib 5 mg twice daily and 2 in patients receiving tofacitinib 10 mg twice daily). The 3 cases in phase II studies, 3 of 5 cases in phase III studies, and 9 of 13 cases in LTE studies occurred in Asian patients. Overall, 4 patients had herpes zoster ophthalmicus, and 2 patients had multidermatomal herpes zoster. More details regarding herpes zoster infection in this clinical development program for tofacitinib in RA have been reported elsewhere (8).

The number of reports of positive test results for HBV infection or HCV infection was small. There were 3 cases of HBV infection in Asian patients: 1 possible reactivation of HBV with an elevated transaminase level, 1 possible false-positive result of a hepatitis surface antigen test (or transient reactivation of HBV without an elevation in the transaminase level and with a negative HBV DNA test result), and 1 case of new HBV infection, which was mild in severity with a transaminase level 2–3 times the upper limit of normal. Antiviral agents were not given in 2 cases (it is unknown whether antiviral agents were given in the third case), and at the time of this report, 1 case of hepatitis was resolved (2 were ongoing).

**TB and opportunistic infections.** In the P2P3LTE population, TB was reported in 16 patients (4 from the Philippines, 3 from Korea, 2 each from India and China, and 1 each from Japan, Thailand, Mexico, the US, and Spain). There were no cases of TB in phase II studies. In the P3All population, 6 cases of TB (all in patients treated with tofacitinib at a dosage of 10 mg twice daily) were reported; there were no cases in the placebo group or the adalimumab group. In the LTE population, TB was reported in 10 patients (5 in the group receiving tofacitinib at a dosage of 5 mg twice daily and 5 in the group receiving tofacitinib at a dosage of 10 mg twice daily).

Excluding cases of TB, 25 patients within the P2P3LTE population experienced an opportunistic infection (0.30 events per 100 patient-years [95% CI 0.20–0.44]). In addition to the 2 cases of multidermatomal herpes zoster described above, 5 patients had esophageal candidiasis (several cases represented incidental findings on endoscopies performed for other reasons), 6 patients had cytomegalovirus infection/viremia, 3 patients had cryptococcal infection (2 cases of pneumonia and 1 case of meningitis), 3 patients had *Pneumocystis jiroveci* pneumonia, 2 patients had nontuberculous mycobacteria in the lung, and 1 patient had BK virus–
associated encephalitis, which improved with discontinuation of study drug and appropriate medical therapy. Among patients with opportunistic infections, 1 death occurred (due to P jiroveci pneumonia).

Baseline glucocorticoid treatment did not appear to be associated with an increased risk of opportunistic infection, including TB, in the P3All and LTE study populations. In the P3All cohort but not the LTE cohort, male patients and patients ages ≥65 years were at slightly increased risk compared with female patients and those ages <65 years (the 95% CIs overlapped).

**Neutrophil and lymphocyte levels.** In the P3All population, dose-dependent decreases in neutrophil counts in the tofacitinib and adalimumab groups were of a similar magnitude. Neutrophil counts remained largely within reference ranges, and the rates of neutropenia of any severity (as defined by the OMERACT criteria) were low during tofacitinib treatment (moderate-to-severe neutropenia at month 12 in <1% of patients receiving tofacitinib 5 mg twice daily and 1.9% of patients receiving tofacitinib 10 mg twice daily, versus <1% of patients receiving adalimumab). In the overall LTE population, no further decreases in the mean neutrophil count were observed (<1% of patients had moderate-to-severe neutropenia). No patients had life-threatening neutropenia. There was no observed relationship between the presence of neutropenia and the occurrence of either treated or serious infections in the phase III or LTE study populations. In the LTE population, 2.1% of patients with confirmed neutropenia (i.e., identified at 2 sequential visits) and 4.6% of those without neutropenia (95% CI 3.98–5.32) developed a serious infection.

At baseline, the mean lymphocyte counts were <2 × 10^3/mm^3 (lymphopenia, as defined by the OMERACT criteria) in all P3All study groups, and 25% of these patients had OMERACT criteria–defined moderate-to-severe lymphopenia (lymphocyte counts of 0.5–1.5 × 10^3/mm^3). Among the tofacitinib-treated patients in the P3All studies, the mean lymphocyte count decreased ~10% between baseline and month 12. Lymphopenia did not appear to be dose-related, and the frequency of lymphopenia in the P3All studies was similar between tofacitinib-treated patients and placebo-treated patients at month 3 and month 6. Moderate-to-severe lymphopenia developed in a larger number of patients receiving background DMARDs compared with patients receiving tofacitinib monotherapy.

In patients with confirmed absolute lymphocyte counts of ≥0.5 × 10^3/mm^3, no increase in the frequency of serious infections was observed (Table 3). Although confirmed lymphocyte counts of <0.5 × 10^3/mm^3 were infrequent (5 of 2,430 patients in the P3All studies [0.2%; 95% CI 0.07–0.48%] and 17 of 4,088 patients in the LTE studies [0.4%; 95% CI 0.24–0.66%]), the rate of serious infection was increased in patients with confirmed lymphocyte counts of <0.5 × 10^3/mm^3. In the LTE population, 2 of 9 patients (22.2%; 95% CI 2.81–60.01%) and 3 of 8 patients (37.5%; 95% CI 8.52–75.51%) receiving tofacitinib at dosages of 5 mg twice daily and 10 mg twice daily, respectively, who had confirmed lymphocyte counts of <0.5 × 10^3/mm^3 had serious infections compared with 82 of 1,409 patients (5.8%; 95% CI 4.66–7.17%) and 97 of 2,662 patients (3.6%; 95% CI 2.96–4.43%), respectively, with lymphocyte counts of ≥0.5 × 10^3/mm^3. Serious infections in patients with confirmed lymphocyte counts of <0.5 × 10^3/mm^3 in the LTE population included 1 case each of pneumonia, TB, cellulitis, decubitus ulcers, and pyelonephritis.

**Mortality.** The all-cause mortality rate among patients in the P2P3LTE population receiving tofacitinib, including deaths occurring within 30 days of the last dose, was 0.30 events per 100 patient-years (95% CI 0.20–0.44). The mortality rate including deaths occurring at any time after the last dose was 0.53 events per 100 patient-years (95% CI 0.40–0.71). Mortality rates in

| Table 3. Lymphocyte counts and serious infections in the long-term extension studies* |
|---------------------------------|------------------|------------------|
| Confirmed absolute lymphocyte count, × 1,000/m³ | Tofacitinib, 5 mg bid | Tofacitinib, 10 mg bid |
| No. of patients | Serious infection, no. (%) [95% CI] | No. of patients | Serious infection, no. (%) [95% CI] |
| ≥2.0 | 179 | 14 (7.8) [4.34–12.77] | 729 | 28 (3.8) [2.57–5.5] |
| ≥1.5 to <2.0 | 280 | 16 (5.7) [3.30–9.11] | 686 | 26 (3.8) [2.49–5.5] |
| ≥0.5 to <1.5 | 950 | 52 (5.5) [4.11–7.12] | 1,247 | 43 (3.4) [2.51–4.62] |
| <0.5 | 9 | 2 (22.2) [2.81–60.01] | 8 | 3 (37.5) [8.52–75.51] |
| Total | 1,418 | 84 (5.9) [4.75–7.28] | 2,670 | 100 (3.7) [3.06–4.54] |

* bid = twice daily; 95% CI = 95% confidence interval.
## Table 4. Mortality in phase III and LTE studies of tofacitinib in rheumatoid arthritis*

|                | Phase III studies† | LTE studies          |
|----------------|--------------------|----------------------|
|                | Tofacitinib, 5 mg bid (n = 1,216) | Tofacitinib, 10 mg bid (n = 1,214) | Tofacitinib, all doses (n = 3,030) | Placebo (n = 681) | Adalimumab, 40 mg every other week (n = 204) | Tofacitinib, 5 mg bid (n = 1,421) | Tofacitinib, 10 mg bid (n = 2,681) | Tofacitinib, all doses (n = 4,102) |
| All-cause mortality (up to 30 days after last dose) |                |                     |                     |                   |                                      |                             |                                    |                                   |
| Unique patients with event, no. | 5 | 4 | 10 | 1 | 1 | 10 | 4 | 14 |
| Exposure, patient-years | 903.72 | 910.37 | 2,098.19 | 202.55 | 178.94 | 3,243.11 | 2,790.66 | 6,033.77 |
| IR, patients with event per patient-year (95% CI) | 0.55 (0.23–1.33) | 0.44 (0.17–1.17) | 0.48 (0.26–0.89) | 0.49 (0.07–3.51) | 0.56 (0.08–3.97) | 0.31 (0.17–0.57) | 0.14 (0.05–0.38) | 0.23 (0.14–0.39) |
| All-cause mortality, including deaths occurring >30 days after last dose |                |                     |                     |                   |                                      |                             |                                    |                                   |
| Unique patients with event, no. | 7 | 4 | 12 | 1 | 1 | 21 | 10 | 31 |
| Exposure, patient-years | 903.64 | 910.37 | 2,098.11 | 202.55 | 178.94 | 3,243.11 | 2,790.66 | 6,033.77 |
| IR, patients with event per patient-year (95% CI) | 0.78 (0.37–1.63) | 0.44 (0.17–1.17) | 0.57 (0.33–1.01) | 0.49 (0.07–3.51) | 0.56 (0.08–3.97) | 0.6 (0.4–1.0) | 0.4 (0.2–0.7) | 0.51 (0.36–0.73) |
| Adjudicated mortality attributed to a cardiovascular event‡ |                |                     |                     |                   |                                      |                             |                                    |                                   |
| Unique patients with event, no. | 0 | 2 | 2 | 0 | 1 | 2 | 1 | 3 |
| Exposure, patient-years | 903.72 | 910.37 | 2,098.20 | 202.55 | 178.94 | 2,748.05 | 2,788.86 | 5,536.91 |
| IR, patients with event per patient-year (95% CI) | 0 | 0.22 (0.06–0.88) | 0.10 (0.02–0.38) | 0 | 0.56 (0.08–3.97) | 0.07 (0.02–0.29) | 0.04 (0.01–0.26) | 0.05 (0.02–0.17) |

* LTE = long-term extension; bid = twice daily; IR = incidence rate; 95% CI = 95% confidence interval.
† Patients who advanced from placebo to tofacitinib are counted in the placebo group until advancement and in the tofacitinib group (all doses) after advancement.
‡ Adjudicated in a blinded manner by an independent external cardiovascular safety end point adjudication committee.
the LTE population were generally consistent with those in the P3All population (Table 4) and, within the P3All population, the rates were similar in the groups receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab, and placebo.

Narratives for deaths are included in Supplementary Appendix 3 (available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38779/abstract). Two deaths were reported among patients receiving tofacitinib in phase II studies. In the phase III studies, 12 deaths occurred in the tofacitinib group (10 of which occurred up to 30 days after administration of the last dose of study treatment), and 1 death each occurred in the placebo and adalimumab groups. In the LTE studies, 31 deaths occurred (14 of which occurred within 30 days after administration of the last tofacitinib dose).

All 14 deaths that occurred during the phase III studies and 20 of 31 deaths that occurred during the LTE studies were adjudicated. Among the deaths that occurred during the phase III studies, 6 were attributable to infection, 3 were attributable to noncardiovascular causes classified as “other” (1 in a patient receiving placebo), 2 were attributable to cardiac causes (1 in a patient receiving adalimumab), 1 was due to cancer, 1 was due to trauma, and 1 death was of unknown cause. Among the 20 adjudicated deaths in the LTE studies, 6 were due to infection, 6 were attributable to cancer, 3 were attributable to cardiac causes, 2 were attributable to noncardiovascular causes classified as “other,” 2 were due to suicide, and 1 death was of unknown cause.

DISCUSSION

In this analysis of infection and mortality data from the global tofacitinib RA clinical development program, the overall rates during tofacitinib therapy appear to be similar to those observed during treatment with biologic agents used in RA (9–16). The P2P3LTE data set represents the largest population of RA patients treated with tofacitinib for the longest duration of time and is particularly useful for assessing overall rates in the program and over time. The limitation of this data set is that it is not categorized according to dosage, because patients in several of the phase II studies were treated with tofacitinib dosages other than 5 mg twice daily and 10 mg twice daily, and patients may have changed dosages when they transitioned from the qualifying index study to the LTE study. Additionally, because by study design the duration and extent of exposure in LTE studies were longer and greater with tofacitinib 5 mg twice daily than with tofacitinib 10 mg twice daily, comparisons between dosages in those studies should be interpreted with some caution. Finally, an inherent limitation of all clinical trial data sets is the relatively limited placebo-controlled phase with regard to duration as well as patient numbers; this restricts the strength of any direct comparison between the active-treatment and placebo groups. Therefore, for additional contextualization, the following discussion refers to data from external compilations of clinical trial safety analyses and observational databases.

Infection AEs were the most common cause of permanent discontinuation of tofacitinib in both the P3All and LTE populations; however, this was attributable in part to protocol-mandated discontinuation criteria requiring study withdrawal in the case of serious infection. The overall rates of serious infection reported in patients treated with tofacitinib (3.1 events per 100 patient-years) were consistent with the rates previously reported in clinical trial safety analyses of adalimumab (3.9–5.1 events per 100 patient-years [17]), rituximab (3.9–4.3 events per 100 patient-years [15]), tocilizumab (3.8–5.1 events per 100 patient-years [16]), etanercept (3.8 events per 100 patient-years [18]), abatacept (2.0–3.1 events per 100 patient-years [19,20]), and golimumab (5.09 events per 100 patient-years [21]). Furthermore, a meta-analysis of published data (22) showed that the rates of serious infection in patients treated with tofacitinib and in those treated with approved biologic DMARDs were similar. The rates of serious infection associated with tofacitinib treatment are also within the ranges demonstrated in various large observational databases of patients receiving tumor necrosis factor (TNF) inhibitor therapies (10–14).

The risk of serious infection associated with tofacitinib treatment was increased in older patients and was numerically higher in those receiving tofacitinib with background DMARDs and/or glucocorticoids, compared with patients receiving tofacitinib monotherapy. In the LTE but not the P3All populations, the tofacitinib dosage was also an independent risk factor for serious infection. This was confirmed by a Cox proportional hazards model that identified tofacitinib dosage, age, diabetes, and corticosteroid dose as independent risk factors and is consistent with reports derived from multiple databases of RA patients receiving biologic DMARDs (16,23–25). However, the results of interaction tests suggest that the other risk factors are independent of tofacitinib treatment and reflect the underlying characteristics of the population of RA patients treated with DMARDs. A separate analysis of infection of any
severity (i.e., mild, moderate, and severe) did not show differences between elderly patients compared with younger patients or patients with diabetes (26).

In the P3All population, the incidence rate for all herpes zoster events occurring in tofacitinib-treated patients (4.36 per 100 patient-years [95% CI 3.54–5.35]) was higher than that in adalimumab-treated patients (2.81 per 100 patient-years [95% CI 1.17–6.76]) and in the placebo group (1.49 per 100 patient-years [95% CI 0.48–4.61]). Each of these rates was also higher than the rates reported in the literature for RA patients treated with biologic agents (0.89–1.6 events per 100 patient-years) (15–21). In the tofacitinib RA clinical development program, approximately one-quarter of patients were Asian, and a higher incidence of herpes zoster was observed in Asian countries compared with other countries. Most cases of herpes zoster infection were mild to moderate, cases of serious herpes zoster infection were rare, and patients recovered after receiving appropriate medical management.

The higher rates of herpes zoster infection among patients treated with tofacitinib may be related to the mechanism of action of tofacitinib, which involves a decrease in lymphocyte activation and proliferation. The human antiviral defense is also associated with intact responses to type I IFN (IFNα and IFNβ) and type II IFN (IFNγ) (27), the receptors of which signal via JAK-1. Because tofacitinib inhibits signaling through JAK-1, it is possible that such a mechanism is related to an increased risk of herpes zoster infection. The higher rates of herpes zoster infection observed in control groups may reflect the increasing absolute or reporting rate of herpes zoster infection in the overall population as well as the possibility of an increased background prevalence in certain Asian countries. The American College of Rheumatology recommends that RA patients who are ≥60 years of age should receive a herpes zoster vaccination prior to beginning treatment with a biologic agent (28).

The incidence of TB in the tofacitinib program was consistent with the incidence reported for TNF inhibitors (0.02 [global] to 2.56 [South Korea]) and nonbiologic DMARDs (0.01 [global] to 0.28 [South Korea]) (9,29–39). The majority of cases were reported in countries where TB is endemic. Opportunistic infections other than TB have also been reported in association with DMARD therapy (5,16,40). There is no established definition of opportunistic infection, which makes comparisons between studies and agents difficult. In addition, differences in endemic rates of certain types of opportunistic infection make comparisons across global studies uncertain. The opportunistic infections observed in the tofacitinib program are consistent with the types of opportunistic infection reported in association with biologic therapies (5,16,41–43).

A higher rate of serious infection was observed in patients with absolute lymphocyte counts of <0.5 × 10^3/mm^3. Although it was unclear whether the occurrence of a serious infection was the result of lymphopenia or whether lymphopenia was the result of infection, lymphocyte counts should be determined prior to initiation of tofacitinib therapy and should be monitored regularly (e.g., every 3 months) during therapy, to inform decisions regarding treatment discontinuation.

Mortality rates in patients with RA are generally 1.5–1.6-fold higher than those in the general population (2). The reported mortality rates in RA patients treated with tofacitinib are similar to those reported in RA patients treated with biologic DMARDs: 0.51 deaths per 100 patient-years with rituximab (15), 0.53 events per 100 patient-years with tocilizumab (16), and 1.1 events per 100 patient-years with etanercept, infliximab, or adalimumab (44) compared with tofacitinib, with events per 100 patient-years of 0.30 (including deaths occurring within 30 days of the last dose) and 0.53 (including deaths occurring at any time after the last dose).

This analysis provides important safety information regarding treatment with tofacitinib in patients with RA. Overall, the risk of infection, including serious infection, appears to be stable over time and similar to that observed in RA patients treated with biologic agents. Mortality rates are consistent with published rates in patients with active RA, including those receiving other DMARDs. It will be important to be vigilant for the emergence of any new safety signals or changes in the trends of AE profiles.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Cohen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ROLE OF THE STUDY SPONSOR

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REFERENCES

1. Meyer DM, Jesson MI, Li X, Elrick MM, Funde-Shippey CL, Warner JD, et al. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm (Lond) 2010;7:41.
2. Sokka T, Abelso B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol 2008;26:535–61.
3. Done MF, Crowson CS, Pond GR, O’Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46:2294–300.
4. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275–85.
5. Greenberg JD, Reed G, Kremer JM, Tindall E, Kavanaugh A, Zheng C, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis 2010;69:380–6.
6. Woodworth TG, Forst DE, Strand V, Kempeni J, Fenner H, Lau CS, et al. Standardizing assessment of adverse effects in rheumatology clinical trials. Status of OMERACT Toxicity Working Group March 2000: towards a common understanding of comparative toxicity/safety profiles for antirheumatic therapies. J Rheumatol 2001;28:1163–9.
7. Prevoo ML, van ’t Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
8. Winthrop KL, Yamanaka H, Valdez H, Mortensen E, Chew R, Krishnaswami S, et al. Risk of herpes zoster in patients with rheumatoid arthritis following tofacitinib therapy. Arthritis Rheum 2014;66:2675–84.
9. Burmester GR, Mariette X, Montecucco C, Montagudo-Saez I, Malaise M, Tzioufas AG, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 2007;66:732–9.
10. Kievit W, Fransen J, Adang EM, den Broeder AA, Bernelot Moen HJ, Visser H, et al. Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. Rheumatology (Oxford) 2011;50:196–203.
11. Curtis JR, Patkar N, Xie A, Martin C, Allison JJ, Saag M, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor α antagonists. Arthritis Rheum 2007;56:1125–33.
12. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, British Society for Rheumatology Biologics Register Control Centre Consortium, et al, on behalf of the British Society for Rheumatology Biologics Register. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti–tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54:2368–76.
13. Fumagalli EG, Desai R, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, et al. Serious infections during anti-TNFα treatment in rheumatoid arthritis patients. Autoimmun Rev 2009;8:266–73.
14. Galloway JB, Hyrich KL, Mercer IK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford) 2011;50:124–31.
15. Van Vollenhoven RF, Emery P, Bingham CO III, Keystone EC, Fleischmann RM, Forst DE, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis 2013;72:1496–502.
16. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther 2011;13:R141.
17. Schiff MH, Burmester GR, Kent JD, Pangan AL, Kupper H, Fitzpatrick SB, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:889–94.
18. Gottlieb AB, Gordon K, Giannini EH, Mease P, Li J, Chan Y, et al. Clinical trial safety and mortality analyses in patients receiving etanercept across approved indications. J Drugs Dermatol 2011;10:289–300.
19. Lacaille D, Smitten A, Simon T, Qi K, Franklin J, Askling J, et al. Hospitalized infections in the Abatacept Rheumatoid Arthritis Clinical Development Program: an epidemiological assessment with >10,000 person-years of exposure [abstract]. J Rheumatol 2009;36:2568.
20. Schiff M, Keiserman M, Codding C, Songharaen S, Berman A, Nayiager S, et al. Clinical response and tolerability to abatacept in patients with rheumatoid arthritis previously treated with infliximab or abatacept: open-label extension of the ATTEST Study. Ann Rheum Dis 2011;70:2003–7.
21. Kay J, Fleischmann R, Keystone E, Hsia EC, Hsu B, Mack M, et al. Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Ann Rheum Dis 2013. E-pub ahead of print.
22. Ahadieh S, Checchio T, Tensfeldt T, French J, Krishnaswami S, Riese R, et al. Meta-analysis of malignancies, serious infections, and serious adverse events with tofacitinib and biologic treatment in rheumatoid arthritis clinical trials [abstract]. Arthritis Rheum 2012;64 Suppl:S726.
23. Lane MA, McDonald JR, Zeringue AL, Caplan L, Curtis JR, Ranganathan P, et al. TNF-α antagonist use and risk of hospitalization for infection in a national cohort of veterans with rheumatoid arthritis. Medicine (Baltimore) 2011;90:139–45.
24. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology (Oxford) 2013;52:53–61.
25. Strangfeld A, Eveslage M, Schneider M, Bergerhausen HJ, Klochsch T, Zink A, et al. Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Ann Rheum Dis 2011;70:1914–20.
26. Rigby WF, Takiya L, Wood SP, Fan H, Jones TV. Assessment of lipid changes and infection risk in diabetic and non-diabetic patients with rheumatoid arthritis treated with tofacitinib [abstract]. Arthritis Rheum 2013;65 Suppl:S995.

27. Malmgaard L. Induction and regulation of IFNs during viral infections. J Interferon Cytokine Res 2004;24:439–54.

28. American College of Rheumatology. Update on Herpes zoster (shingles) vaccine for autoimmune disease patients. September 2012. URL: http://www.rheumatology.org/Publications/Hotline/Update_on_Herpes_Zoster_Shingles_Vaccine_for_Autoimmune_Disease_Patients/.

29. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α-neutralizing agent. N Engl J Med 2001;345:1098–104.

30. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004;50:372–9.

31. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 2006;43:717–22.

32. Carmona L, Hernandez-Garcia C, Vadillo C, Pato E, Balsa A, Gonzalez-Alvaro I, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol 2003;30:1436–9.

33. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, Montero D, Pascual-Gomez E, Mola EM, et al, on behalf of the BIOBADASER Group. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum 2005;52:1766–72.

34. Seong SS, Choi CB, Woo JH, Bae KW, Joung CL, Uhm WS, et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA); effects of RA itself and of tumor necrosis factor blockers. J Rheumatol 2007;34:706–11.

35. Yamada T, Nakajima A, Inoue E, Tanaka E, Hara M, Tomatsu T, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan. Ann Rheum Dis 2006;65:1661–3.

36. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, et al, on behalf of the BSR Biologics Register. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010;69:522–8.

37. Baldin B, Dozol A, Speaux A, Chichemanian RM. Tuberculosis and infliximab treatment: national surveillance from January 1, 2000, through June 30, 2003. Presse Med 2005;34:353–7. In French.

38. Sicilhedis L, Settas L, Spyrtos D, Chloros D, Patakasis D. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis 2006;10:1127–32.

39. Solovie I, Sester M, Gomez-Reino JJ, Rieder HL, Ethiers S, Milburn HJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. Eur Respir J 2010;36:1185–206.

40. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda AP. 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;72:517–24.

41. Keystone EC, van der Heijde D, Kavanaugh A, Kupper H, Liu S, Guerette B, et al. Clinical, functional, and radiographic benefits of longterm adalimumab plus methotrexate: final 10-year data in longstanding rheumatoid arthritis. J Rheumatol 2013;40:1487–97.

42. Mariette X, Gottenberg JE, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. Rheumatology (Oxford) 2011;50:222–9.

43. Galloway JB, Low AS, Mercer IK, Dixon WG, Ustianowski A, Lunt M, et al, British Society for Rheumatology Biologics Register (BSRBR). Opportunistic infections in patients exposed to anti-tumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register [abstract]. Arthritis Rheum 2011;63 Suppl:S988.

44. Simard JF, Neovius M, Askling J, for the ARTIS Study Group. Mortality rates in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: drug-specific comparisons in the Swedish Biologics Register. Arthritis Rheum 2012;64:3502–10.