EXTENDED REPORT

Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis

K L Winthrop,1 S-H Park,2 A Gul,3 M H Cardiel,4 J J Gomez-Reino,5 Y Tanaka,6 K Kwok,7 T Lukic,7 E Mortensen,8 D Ponce de Leon,9 R Riese,10 H Valdez7

Handling editor Tore K Kvien

ABSTRACT

Objectives To evaluate the risk of opportunistic infections (OIs) in patients with rheumatoid arthritis (RA) treated with tofacitinib.

Methods Phase II, III and long-term extension clinical trial data (April 2013 data-cut) from the tofacitinib RA programme were reviewed. OIs defined a priori included mycobacterial and fungal infections, multidermatomal herpes zoster and other viral infections associated with immunosuppression. For OIs, we calculated crude incidence rates (IRs; per 100 patient-years; 95% CI); for tuberculosis (TB) specifically, we calculated rates stratified by patient enrolment region according to background TB IR (per 100 patient-years): low (<0.01), medium (0.01 to ≤0.05), and high (>0.05).

Results We identified 60 OIs among 5671 subjects; all occurred among tofacitinib-treated patients. TB (crude IR 0.21; 95% CI 0.14 to 0.30)) was the most common OI (n=26); median time between drug start and diagnosis was 64 weeks (range 15–161 weeks). Twenty-one cases (81%) occurred in countries with high background TB IR, and the rate varied with regional background TB IR: low 0.02 (0.003 to 0.15), medium 0.08 (0.03 to 0.21) and high 0.75 (0.49 to 1.15). In Phase III studies, 263 patients diagnosed with latent TB infection were treated with isoniazid and tofacitinib concurrently; none developed TB. For OIs other than TB, 34 events were reported (crude IR 0.25; 95% CI 0.18 to 0.36).

Conclusions Within the global tofacitinib RA development programme, TB was the most common OI reported but was rare in regions of low and medium TB incidence. Patients who screen positive for latent TB can be treated with isoniazid during tofacitinib therapy. Tofacitinib preferentially inhibits JAK3 and ILs 2, 4, 7, 9, 15 and 21 that are integral to lymphocyte development and function.11 Given its mechanism of action, the risk of TB and other OIs could potentially be elevated in tofacitinib-treated patients, and accordingly, we undertook a retrospective evaluation of all OIs reported within the tofacitinib RA clinical development programme.

METHODS

Development programme conduct

Following completion of phase I studies, the global tofacitinib RA development programme comprised six phase II,12–16 six phase III17–24 and two open-label long-term extension (LTE) studies,24 25 with a total of 5671 treated patients and 12 664 patient-years tofacitinib exposure across 48 nations worldwide.

OI case-finding and case description

For phase II, III and open-label LTE studies, we searched all preferred and low-level MedDRA terms (see online supplementary file 1) reported by site investigators containing text consistent with a potential OI using a data cut-off date of 10 April 2013. As of April 2013, data collection for one phase III study,23 and the two LTE studies24 25 were ongoing, and study databases had not yet been locked. For this analysis, the following infections were defined a priori as OIs: TB, non-tuberculous mycobacterium (NTM) infections, all fungal infections (with the exception of oral or vaginal candidiasis and chromomycosis), listeria and viral infections typically associated with immunosuppression, including multidermatomal or disseminated herpes zoster, disseminated herpes virus, cytomegalovirus (CMV), BK virus and progressive multifocal leukoencephalopathy (PML). Legionella was not specified as an OI and was not included in this analysis (one case was reported during the development programme).

For cases classified as ‘OIs’, we reviewed adverse reaction report forms to obtain clinical details, including treatment and outcomes. For all cases, we collected descriptive clinical and epidemiological information at time of randomisation (baseline) including age, sex, race, site of enrolment, corticosteroid use (limited by protocol to ≤10 mg/day prednisone equivalent), concomitant non-biological DMARD use, comorbidities (eg, smoking, diabetes, others), body mass index, measures of RA severity (Disease Activity Score using 28-joint counts and the C reactive protein level (DAS 28-3 CRP)) and disease duration (years since diagnosis), as well as baseline lymphocyte and neutrophil counts.
**TB screening**

In phase II studies, patients with positive TB screening were excluded from entering the trial. In phase III studies, all potential study subjects were queried regarding a history of prior diagnosis or treatment of active or latent TB infection (LTBI). All patients underwent chest radiography (within 3 months of screening), and for those with no prior history of positive screening results, at least one screening test for LTBI was performed at discretion of the site primary investigator; QuantiFERON-TB Gold In-Tube (QFT-IT; Quest Diagnostics, Madison, New Jersey, USA) or tuberculin skin test (TST; using ≥5 mm induration cut-off outside Japan and ≥20 mm erythema for Japan). Patients diagnosed with LTBI and patients with a history of inadequately or untreated LTBI prior to screening were allowed entry into phase III trials after receiving at least 1 month of a planned 9-month isoniazid preventive therapy regimen.

**OI incidence rate calculations and evaluation of comparative risk**

OIs were attributed either to tofacitinib, placebo, adalimumab or methotrexate based on exposure at time of event. Given all OIs occurred in tofacitinib patients, we calculated OI crude incidence rates (IRs) per 100 patient-years (95% CI) only for tofacitinib-exposed patients. Given that no OIs occurred in phase II studies, these calculations were limited to the phase III and LTE studies. Patients were censored at time of event, death or withdrawal from study.

**TB substudy**

For TB cases, we obtained detailed information regarding date of onset, type of presentation and clinical outcomes. We also evaluated TB screening results among patients who entered the phase II, III and LTE studies. In addition, for patients who started isoniazid preventive therapy and entered trials, we described the proportion of individuals who developed elevated transaminases. We calculated crude TB IRs overall, as well as stratified by enrolment region, age, sex and baseline corticosteroid use. In order to contextualise the regional variation in TB rates, we presented TB rates according to regional background TB incidence. We used WHO TB incidence data from 2011,26 to categorise countries where enrolment took place according to background TB IR (per 100 patient-years) defined as follows: low-incidence regions (IR<0.01 per 100 patient-years), medium-incidence regions (IR>0.01 to ≤0.05 per 100 patient-years) and high-incidence regions (IR>0.05 per 100 patient-years). We conducted all statistical analyses using SAS software (SAS Institute, Cary, North Carolina, USA).

**RESULTS**

Patient baseline characteristics are described in table 1. We identified 60 OIs (58 patients) among 5671 patients enrolled in phase II, phase III and LTE studies (crude IR (95% CI) of 0.46 (0.36 to 0.59) per 100 patient-years); no events occurred during phase II studies and all events occurred in tofacitinib-treated patients. Crude IRs for TB and non-TB OIs were 0.21 (95% CI 0.14 to 0.30) and 0.25 (95% CI 0.18 to 0.36), respectively. OIs included TB (n=26), oesophageal candidiasis (n=9), Pneumocystis jirovecii pneumonia (n=4), CMV infection (n=6), NTM pulmonary infection (n=2), cryptococcal infection (pneumonia n=2, meningitis n=1), disseminated or multidermatomal herpes zoster (n=8), BK encephalopathy (n=1) and toxoplasmosis (n=1). No cases of disseminated herpes virus or PML were reported. Of the 58 patients with OIs, one patient died due to pneumocystis, and most (n=40) permanently discontinued treatment with the study drug. The CMV cases presented differently: antigenemia without evidence of other infection (n=1); an oesophageal ulcer, which resolved without antiviral therapy while tofacitinib treatment was continued (n=1); sialadenitis with CMV on biopsy (n=1); hepatitis in which CMV was also detected in cerebrospinal fluid (CSF) by PCR (n=1); and gastritis with little clinical information provided (n=1). The final case involved CMV retinitis with characteristic retinal pathology and a positive anterior chamber PCR; the infection responded appropriately to antiviral therapy. The case of BK encephalitis was diagnosed using PCR of CSF in a patient during an episode of bacterial sepsis; it resolved as the patient’s overall status improved.

### All OIs (TB and non-TB OIs combined)

In phase III studies, crude OI incidence was numerically higher in patients treated with tofacitinib 10 mg twice daily (0.93 (95% CI 0.55 to 1.58)) vs 5 mg twice daily (0.20 (95% CI 0.07 to 0.64)). In LTE studies, rates were more similar in tofacitinib 5 mg (0.38 (95% CI 0.23 to 0.62)) and 10 mg treated patients (0.48 (95% CI 0.33 to 0.71)). Across treatment arms, the crude incidence of all OIs among all tofacitinib users was slightly higher among glucocorticoid users (0.55 (95% CI 0.38 to 0.81)) than non-users (0.31 (95% CI 0.19 to 0.53)). Rates were similar in those aged ≥65 and <65 years (0.49 (95% CI 0.24 to 1.04) vs 0.43 (95% CI 0.30 to 0.60)), respectively.

### OIs other than TB

Non-TB OIs occurred at a median of 40 weeks (range, 6–179 weeks) after tofacitinib start. In phase III studies, the incidence of non-TB OIs was numerically higher in patients treated with tofacitinib 10 mg twice daily (0.40 (95% CI 0.18 to 0.90) compared with 5 mg twice daily (0.21 (95% CI 0.07 to 0.64))). In LTE studies, rates were similar in tofacitinib 5 mg (0.23 (95% CI 0.12 to 0.43)) and 10 mg treated patients (0.27 (95% CI 0.16 to 0.46)). Across treatment arms, the crude incidence of non-TB OIs among all tofacitinib users was higher among glucocorticoid users (0.36 (95% CI 0.22 to 0.58)) than non-users (0.13 (95% CI 0.06 to 0.30)). Rates were similar in those aged ≥65 and <65 years (0.21 (95% CI 0.07 to 0.66) vs 0.26 (95% CI 0.17 to 0.40)).

### Tuberculosis

There were 26 cases of active TB reported by investigators, all within tofacitinib-treated individuals from phase III (n=9 cases) and LTE studies (n=17 cases). The median time between tofacitinib start and TB diagnosis was 64 weeks (range, 15–161 weeks). Fifteen (58%) cases involved extrapulmonary infection sites. Few were culture-confirmed, and most (20/26, 77%) occurred in those taking tofacitinib 10 mg twice daily (table 2). All but two cases had negative screening results at entry. The two cases with positive screening results at baseline had a history of receiving an adequate course of therapy for active TB or LTBI in the past (one each). These patients, given the adequate treatment history, were allowed into the trial without isoniazid treatment, per protocol. The TB rate varied according to regional background IR: 21 cases (81%) occurred in countries with high background TB IR (characteristics of the 26 reported active TB cases from phase II, III and LTE studies of tofacitinib are presented in online supplementary file 3).

In phase III studies, crude IR of TB among all tofacitinib users was 0.27 (95% CI 0.14 to 0.54) and all cases occurred in...
The 10 mg twice daily group (crude incidence, 0.53 (95% CI 0.27 to 1.07)). IRs were similar between those aged <65 years (0.54 (95% CI 0.26 to 1.13)) and those ≥65 years (0.51 (95% CI 0.07 to 3.63)), among those with and without baseline glucocorticoid use (0.50 (95% CI 0.19 to 1.33) vs 0.57 (95% CI 0.22 to 1.53)), but trended higher in males (1.26 (95% CI 0.41 to 3.90)) vs females (0.40 (95% CI 0.17 to 0.95)). Within LTE studies, cases occurred at similar incidence in both 5 and 10 mg twice daily arms (0.15 (95% CI 0.07 to 0.33) vs 0.21 (95% CI 0.12 to 0.38)). When examining IRs across dosage arms within the LTE experience, we observed higher incidence in patients aged ≥65 years (0.28 (95% CI 0.11 to 0.75)) compared with those <65 years (0.17 (95% CI 0.10 to 0.29)). Rates were similar among patients using glucocorticoids (0.19 (95% CI 0.10 to 0.37)) and those not using glucocorticoids (0.18 (95% CI 0.09 to 0.36)).

### DISCUSSION

We have conducted the largest analyses to date examining the risk of OIs in the context of JAK inhibition by tofacitinib. Within the global RA clinical development programme, TB was

---

**Table 1** Baseline characteristics of patients entering phase III tofacitinib trials by exposure group

| & Tofacitinib 5 mg twice daily (N=1587; PY=1646.18) | Tofacitinib 10 mg twice daily (N=1609; PY=1501.03) | Placebo (N=681; PY=202.71) | Adalimumab (N=204; PY=178.04) | Methotrexate (N=186; PY=152.07) |
|---|---|---|---|---|---|
| **Age, median years (range)** | 54 (18–86) | 54 (18–86) | 54 (18–82) | 54 (24–78) | 50.5 (20–80) |
| **Female, n (%)** | 1310 (82.5) | 1355 (84.2) | 553 (81.2) | 162 (79.4) | 145 (78.0) |
| **Race, n (%)** | | | | | |
| **White** | 976 (61.5) | 1006 (62.5) | 439 (64.5) | 148 (72.5) | 127 (68.3) |
| **Black** | 58 (3.7) | 47 (2.9) | 24 (3.5) | 3 (1.5) | 4 (2.2) |
| **Asian** | 394 (24.8) | 375 (23.3) | 166 (24.4) | 29 (14.2) | 33 (17.7) |
| **Other** | 159 (10) | 181 (11.2) | 52 (7.6) | 24 (11.8) | 22 (11.8) |
| **BMI, mean (range)** | 26.9 (14.3–70.8) | 27.0 (12.1–63.3) | 27.2 (14.7–55.1) | 27.1 (13.9–45.7) | 26.7 (14.9–49.4) |
| **RA duration, mean, years** | 7.4 | 7.7 | 9.3 | 8.1 | 2.6 |
| **Diabetes mellitus, n (%)** | 130 (8.2) | 127 (7.9) | 48 (7.0) | 16 (7.8) | 8 (4.3) |
| **Smoking history, n (%)** | 534 (33.7) | 520 (32.3) | 254 (37.4) | 71 (35.1) | 61 (32.8) |
| **BMI, mean (range)** | 26.9 (14.3–70.8) | 27.0 (12.1–63.3) | 27.2 (14.7–55.1) | 27.1 (13.9–45.7) | 26.7 (14.9–49.4) |
| **RA severity (DAS28-3 CRP)** | 5.4 | 5.4 | 5.3 | 5.3 | 5.6 |
| **Concomitant DMARD, n (%)** | | | | | |
| **Methotrexate** | 904 (57.0) | 902 (56.1) | 520 (76.4) | 199 (97.5) | 1 (0.5) |
| **Leflunomide** | 91 (5.7) | 84 (5.2) | 34 (5.0) | 0 (0) | 0 (0) |
| **Hydroxychloroquine** | 152 (9.6) | 157 (9.8) | 51 (7.5) | 2 (<1.0) | 10 (5.4) |
| **Baseline glucocorticoid use, n (%)** | 866 (54.6) | 834 (51.8) | 376 (55.2) | 116 (5.4) | 79 (42.5) |
| **>0 mg to <5 mg daily** | 114 (7.2) | 113 (7.0) | 48 (7.0) | 16 (7.8) | 10 (5.4) |
| **5 to 10 mg daily** | 731 (46.1) | 698 (43.4) | 315 (46.3) | 90 (44.1) | 68 (36.6) |
| **>10 mg daily** | 9 (<1.0) | 9 (<1.0) | 5 (<1.0) | 7 (3.4) | 0 (0) |
| **Unknown dose** | 24 (1.5) | 20 (1.2) | 19 (2.8) | 3 (1.5) | 3 (1.6) |

BMl, body mass index; COPD, chronic obstructive pulmonary disease; DAS28-3 CRP, Disease Activity Score using 28-joint counts and the C reactive protein level; DMARD, disease-modifying antirheumatic drugs; PY, person-years exposure; RA, rheumatoid arthritis.

---

**Table 2** TB IRs for tofacitinib patients by background country IRs* (phase II, III and LTE studies)

<table>
<thead>
<tr>
<th>TB cases with tofacitinib (n)</th>
<th>Tofacitinib exposure (patient-years)</th>
<th>Crude TB IR † (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low† (≤0.10)</strong></td>
<td>1</td>
<td>4852.3</td>
</tr>
<tr>
<td><strong>Medium§ (0.01 and ≤0.50)</strong></td>
<td>4</td>
<td>5020.5</td>
</tr>
<tr>
<td><strong>High¶ (&gt;0.05)</strong></td>
<td>21</td>
<td>2791.1</td>
</tr>
</tbody>
</table>

† Crude incidence calculated TB cases per 100 patient-years.
‡ Low TB incidence region (total study enrolment, n=2213); the USA (n=1098), Czech Republic (n=378), Germany (n=238), Slovakia (n=126), Australia (n=114), Canada (n=103), Austria (n=36), Italy (n=28), Sweden (n=17), Finland (n=16), Greece (n=15), Belgium (n=13), France (n=10), Denmark (n=9), New Zealand (n=9), Ireland (n=3), Norway (n=45), and Taiwan (n=36).
§ Medium TB incidence region (total study enrolment, n=2112); Japan (n=556), Brazil (n=306), Mexico (n=259), Poland (n=254), Chile (n=174), Bulgaria (n=169), Spain (n=128), Colombia (n=120), Argentina (n=61), Croatia (n=27), Hungary (n=27), the UK (n=17), Costa Rica (n=16), Venezuela (n=7), Bosnia-Herzegovina (n=6), Turkey (n=5).
¶ High TB IR (total study enrolment, n=1326); Korea (n=284), Ukraine (n=227), China (n=213), India (n=194), Russia (n=149), Thailand (n=63), Philippines (n=61), Malaysia (n=46), Taiwan (n=36), Dominican-Republic (n=27), Peru (n=14), Romania (n=12), and the USA (n=1098).
the most commonly reported OI but was rare in regions of low and medium background TB prevalence. In phase III trials, the incidence of OIs was higher in patients using tofacitinib 10 mg twice daily dosing compared with tofacitinib 5 mg twice daily dosing, and overall most TB cases occurred in patients using the higher dose. Importantly, our data suggest the utility of screening for TB prior to tofacitinib start, and the ability to successfully treat LTBI with isoniazid during tofacitinib therapy.

Patients with RA are known to be at higher risk for OIs, in part due to their therapies. For anti-TNF therapies, this increased risk has been most clearly described for those pathogens that rely upon granulomatous immunity, with TB the best studied example and generally the most common OI (other than routine uncomplicated herpetic zoster) reported in that setting. Further, no matter the immunosuppressive therapy, the risk of TB varies directly with background TB rate in the underlying population, and for those starting TNF blockade, screening and treatment of LTBI effectively reduces the risk of subsequent TB. In this regard, our experience within the tofacitinib population, and for those starting TNF blockade, screening and treatment of LTBI effectively reduces the risk of subsequent TB. In our population, and for those starting TNF blockade, screening and treatment of LTBI effectively reduces the risk of subsequent TB. In our study, only two cases of TB occurred in North America and Western Europe. While our data suggest an increased risk of such infections in patients using tofacitinib, it is unclear whether this risk is any different than that associated with biological therapy. It is difficult to compare rates between studies conducted in regions where the background risk of TB may vary. The comparative risk between biologics and tofacitinib, and the potential risk modification of steroids, is not clear and deserves further population-based study.

Screening and treatment for LTBI prior to biological therapy has been shown to effectively reduce subsequent TB rates. Our data also suggest a benefit of starting antimicrobial treatment in patients diagnosed with LTBI prior to tofacitinib start. All but two of the TB cases reported in this study occurred in individuals with negative screening test results at baseline. This is not dissimilar to other clinical trial experiences with anti-TNF therapy, and it suggests the likelihood that some patients have false-negative screening test results at baseline. False-negative TST or Interferon-Gamma Release Assay results are more common in immunosuppressed and older patients, and it is possible that a strategy that uses both tests, rather than a single test as reported herein, could improve the sensitivity (and potentially decrease the specificity) of screening prior to starting biologics or tofacitinib. It is also possible that some of the observed TB cases were instances of newly acquired infection during the trial, given that nearly all the cases occurred in regions of high TB endemicity where exposure would be more likely. The long time between tofacitinib start and TB diagnosis for most of the observed cases, and their negative baseline screening results, lends further support to this idea. Lastly, it is possible that some of the TB cases were not true cases. We attempted to use US Centers for Disease Control and Prevention case criteria for TB in order to confirm them, but most case reports were lacking in follow-up information, making such adjudication impossible. Only 8 of the 26 cases had microbiological confirmation, and many of the patients were worked-up and diagnosed only by positive acid-fast bacilli smear and no culture was performed. In some of these cases, particularly the pulmonary cases, infection due to NTM was possible and also consistent with the negative screening test results for TB at baseline. There were at least two pulmonary NTM cases reported within the development programme. In regions of low TB prevalence, such as North America and Western Europe, NTM disease is more common than TB, and in fact in our study only two cases of TB occurred in North America and Europe.

Both fungal and viral OIs were also identified in this study. While our data suggest an increased risk of such infections in patients using tofacitinib, it is unclear whether this risk is any different than that associated with biological therapy. It is difficult to compare overall rates of OIs between various studies due to heterogeneity in methods, and particularly due to differences in defining which OIs are considered ‘opportunistic’. In population-based studies from France, Britain and the USA, reported rates vary between 152 and 3000 per 100 000, with the wide variance due to differences in case-finding methodology and OI definitions (specifically some studies included herpes zoster as an OI and others did not). We have included only complicated cases of herpes zoster within this current analysis and have recently reported uncomplicated herpes zoster cases associated with the development programme. In that analysis, zoster rates were observed to be elevated with tofacitinib and to vary considerably according to enrolment region, with rates in some Asian countries approximately double those seen in Western Europe or North America. Intracellular infections with Pneumocystis, Cryptococcus and CMV were also observed in the development programme. No cases of endemic mycotic infections (histoplasmosis, coccidioidomycosis and blastomycosis) were observed, but presumably few patients were enrolled within regions where these organisms are endemic.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Patients in phase III studies who experienced ALT elevations according to study exposure group and isoniazid usage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;1×ULN n (%)</td>
</tr>
<tr>
<td>Isoniazid/tofacitinib*</td>
<td>58 (22.1%)</td>
</tr>
<tr>
<td>(n=263)</td>
<td></td>
</tr>
<tr>
<td>No isoniazid/tofacitinib*</td>
<td>550 (15.2%)</td>
</tr>
<tr>
<td>(n=3614)</td>
<td></td>
</tr>
<tr>
<td>Isoniazid/adalimumab</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>(n=15)</td>
<td></td>
</tr>
<tr>
<td>No isoniazid/adalimumab</td>
<td>24 (12.7%)</td>
</tr>
<tr>
<td>(n=189)</td>
<td></td>
</tr>
<tr>
<td>Isoniazid/methotrexate</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
</tr>
<tr>
<td>No isoniazid methotrexate</td>
<td>19 (10.7%)</td>
</tr>
<tr>
<td>(n=178)</td>
<td></td>
</tr>
</tbody>
</table>

*Includes patients who were randomised to tofacitinib at study start and those randomised to placebo who later took tofacitinib during their isoniazid treatment course.

ALT, alanine aminotransferase; LTBI, latent tuberculosis infection; ULN, upper limit of normal.
A biological mechanism for how tofacitinib could increase the risk of TB or other intracellular infections is not yet clear. It could theoretically inhibit the development and/or maintenance of pathogen-specific memory T cells by inhibiting the intracellular signalling of IL-12, interferon (IFN)-γ and other relevant cytokines. An increased risk for serious TB disease has been documented with mutations affecting IL-12, IFN-γ and STAT1 pathways. Therefore, it is possible that down-modulation of these pathways by JAK inhibition could diminish the ability of macrophages to contain infections such as TB. Further, it is likely that JAK inhibition diminishes type 1 (IFN-α and IFN-β) and type 2 (IFN-γ) antiviral responses, both of which signal via the JAK1 receptor. This could explain the spectrum of viral infections observed in the development programme, and such hypotheses deserve further testing.

Our experience suggests that patients can use isoniazid therapy during tofacitinib therapy with good tolerance and apparent efficacy in TB prevention. None of the >200 patients treated in this fashion developed clinically significant hepatitis, all completed isoniazid therapy and none developed active TB. Importantly, it should be noted that a drug–drug interaction exists between rifampin and tofacitinib such that tofacitinib could be less effective during rifampin therapy due to an 80% reduction in bioavailability of tofacitinib. For this reason, isoniazid should remain the drug of choice when treating LTBI during tofacitinib therapy, and periodic liver function testing should be conducted during such therapy in accordance with Centers for Disease Control and Prevention guidance.

In summary, we observed an increased risk of OIs among patients with RA using tofacitinib, although they occur rarely and are less frequent in those treated with 5 mg twice daily. TB was the most common OI reported in this setting, but remained rare in regions of low TB prevalence. As with biological therapy, screening and treating for LTBI should be employed prior to starting tofacitinib, and long-term population-based studies are necessary to better understand the comparative risk of tofacitinib with other DMARD therapies.

**Author affiliations**

1. Oregon Health and Science University, Portland, Oregon, USA
2. Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary’s Hospital, The Catholic University of Korea, Seoul, South Korea
3. Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
4. Centro de Investigación Clínica de Morelia SC, Morelia, Mexico
5. Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain
6. University of Occupational and Environmental Health, Kitakyushu, Japan
7. Pfizer Inc, New York, New York, USA
8. Pfizer Inc, Collegeville, Pennsylvania, USA
9. Pfizer Inc, Lima, Peru
10. Pfizer Inc, Groton, Connecticut, USA

**Twitter** Follow Mario Cardiel at @mcardiel

**Acknowledgements** We wish to thank Jennifer Ku at Oregon Health & Science University and Jason Gardner from Complete Medical Communications for assistance in formatting the manuscript. We also wish to thank Bob Bumside and Robert Chew for their statistical support and Thomas Kawabata for his input into the interpretation of the data.

**Contributors** For each study, adverse event data were reported by site investigators and entered within the Pfizer clinical database. Standard MedDRA codes were used to categorise adverse events. For the retrospective analysis reported herein, the analysis plan was conceived by the primary author in conjunction with collaborating authors, with statistical analysis conducted using a Pfizer statistician (RC).

**Funding** Pfizer Inc.

**Competing interests** KIW reported consulting for Genentech, Pfizer Inc, UCBB and AbbVie, and research grant support from Pfizer Inc. AG reported consulting for Pfizer Inc, MSD, AbbVie, UCB, Servier, Xoma, Novartis, Bristol-Myers Squibb and Roche. MHC has received research grants, consulting fees and/or speaking fees from Pfizer Inc, Roche, Bristol-Myers Squibb, Merck, Sanofi, Janssen, Anthera, Astellas, AbbVie, UCBB and Amgen. J-G-R reported consulting for Pfizer Inc and research grant support from AbbVie, MSD, Pfizer Inc, Roche and UCB. YT has received consulting fees, speaking fees and/or honoraria from AbbVie, Chugai, Astellas, Takeda, Santen, Mitsubishi-Tanabe, Pfizer Inc, Janssen, Eisai, Daiichi-Sankyo, UCB, GlaxoSmithKline and Bristol-Myers Squibb, and has received research grants from Mitsubishi-Tanabe, Chugai, MSD, Astellas and Novartis. KK, TL, EM, DP4, RR and HV are employees of Pfizer Inc. The contributions of JG, BB and RC were supported by Pfizer Inc.

**Patient consent** Obtained.

**Ethics approval** All clinical studies were conducted in compliance with the Helsinki declaration of Good Clinical Practice guidelines of the International Conference on Harmonisation, and all participating institutions provided ethics board approval.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Open Access** This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/
Clinical and epidemiological research


Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis

K L Winthrop, S-H Park, A Gul, M H Cardiel, J J Gomez-Reino, Y Tanaka, K Kwok, T Lukic, E Mortensen, D Ponce de Leon, R Riese and H Valdez

Ann Rheum Dis published online August 28, 2015

Updated information and services can be found at: http://ard.bmj.com/content/early/2015/08/28/annrheumdis-2015-207319

These include:

Supplementary Material
Supplementary material can be found at: http://ard.bmj.com/content/suppl/2015/08/27/annrheumdis-2015-207319.DC1

References
This article cites 51 articles, 20 of which you can access for free at: http://ard.bmj.com/content/early/2015/08/28/annrheumdis-2015-207319#BIBL

Open Access
This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Open access (605)
Connective tissue disease (4253)
Degenerative joint disease (4641)
Immunology (including allergy) (5144)
Musculoskeletal syndromes (4951)
Rheumatoid arthritis (3258)

Notes

To request permissions go to: http://group.bmj.com/group/rights-licensing/permissions
To order reprints go to: http://journals.bmj.com/cgi/reprintform
To subscribe to BMJ go to: http://group.bmj.com/subscribe/