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Meta-analysis

# Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies

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## Abstract

**Objective.** The aim of this study was to assess the risk of active tuberculosis (TB) in patients with immune-mediated inflammatory diseases treated with biologics and tofacitinib in randomized controlled trials (RCTs) and long-term extension (LTE) studies.

**Methods.** A systematic review of the English-language literature by was performed by searching the Medline, Embase, Cochrane and Web of Knowledge databases. The search strategy focused on synonyms of diseases, biologics and tofacitinib. Data from RCTs were combined to assess the rate of TB using a random effects model. The incidence rate (IR) of TB and its association with disease, location and treatment were assessed in LTE studies.

**Results.** The search captured 11 130 articles and abstracts. One-hundred RCTs (75 000 patients) and 63 LTE studies (80 774.45 patient-years) met the inclusion criteria. There were 31 TB cases with TNF inhibitors, 1 with abatacept and none with rituximab, tocilizumab, ustekinumab or tofacitinib. The odds ratio for TNF inhibitors was 1.92 (95% CI 0.91, 4.03, $P = 0.085$). In LTE studies, the IR of TB was >40/100 000 with tofacitinib and all biologics except rituximab. IR was higher in RA patients with anti-TNF monoclonal antibodies [307.71 (95% CI 184.79, 454.93)] than in those with rituximab [20.0 (95% CI 0.10, 60)] and etanercept [67.58 (95% CI 12.1, 163.94)] or AS, PsA and psoriasis with etanercept [60.01 (95% CI 3.6, 184.79)]. The IR of TB was higher in high-background TB areas.

**Conclusion.** RCTs are not sensitive enough to assess the risk of reactivation of latent TB infection (LTBI). Disease, treatment and background TB rate are associated with different frequencies of active TB. The benefit/risk balance of preventing reactivation of LTBI in different backgrounds should be considered in clinical practice.

**Key words:** tuberculosis, biologic drugs, tofacitinib, inflammatory diseases, safety.

META-ANALYSIS

## Introduction

The appearance of biologic therapies was an important advancement in the treatment of immune-mediated chronic inflammatory diseases (IMIDs) such as RA, AS, PsA, psoriasis (Ps), ulcerative colitis (UC) and Crohn's disease (CD) [1–4]. The anti-TNF monoclonal antibodies and the soluble TNF receptor etanercept are TNF inhibitors that are approved for the treatment of RA. Rituximab, tocilizumab and abatacept have also been approved for

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the treatment of RA. For the treatment of AS, only TNF inhibitors have been authorized. For PsA, TNF inhibitors and ustekinumab are currently used. Recently the oral small molecule tofacitinib was granted approval for the treatment of RA. Observational studies and clinical trials have reported the occurrence of non-opportunistic and opportunistic infections, including TB, in patients treated with these medications [5, 6].

Most of the individuals infected with mycobacterial tuberculosis (TB) do not develop active disease. They either recover or harbour the dormant mycobacteria as a latent TB infection (LTBI). This diverse response to the infection depends on the host. In LTBI, the mycobacteria are confined by granuloma via recruitment of CD4 and CD8 T cells, B cells and macrophages to the infected site. The T cells produce IFN-$\gamma$ and the macrophages and T cells produce TNF, which maintains the integrity of the granuloma. The currently available information indicates that biologics and tofacitinib cause active TB by disrupting the granuloma.

Controversies have emerged regarding the differences in the risk of active TB during treatment of IMID with biologics [7]. Most information is from observational studies and refers to the risk of TNF inhibitors in patients included in registries. Registries provide sound evidence in selected populations in real life, but they have drawbacks: the recruitment methods and inclusion criteria for both biologic and comparator cohorts are different, the non-exposed internal cohort used for comparison is sometimes missing, the patient demographics and comorbidities are different and the analytic approaches are dissimilar [8, 9]. Recommendations for the management of LTBI in patients treated with biologics are mostly concerned with TNF inhibitors.

The main objective of this review was to assess the risk of the development of active TB in patients suffering from IMID and treated with biologics and tofacitinib in randomized controlled trials (RCTs) and long-term extension (LTE) studies compared with controls. The secondary objective was to investigate the association of the rate of active TB with the type of medication (biologic/tofacitinib), treated disease and location of the study.

## Materials and methods

A systematic literature review to identify all publications that analysed the incidence of TB in IMID patients treated with biologics and tofacitinib in RCTs and LTE studies was performed. Data regarding indications that were not approved were dismissed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) consensus was followed for the review and meta-analysis [10]. The review was divided into two parts: (i) analysis of RCTs that contained a comparator group (treatment and control groups with similar exposure times) and (ii) analysis of LTE studies (only actively treated patients).

### Systematic literature search

A comprehensive search of the literature was performed using the Medline, Embase, Cochrane Library and Web of Knowledge electronic databases for articles published through January 2013. The search strategy focused on synonyms of diseases, biologics and tofacitinib and was limited to human subjects and articles published in the English language. Controlled vocabularies (e.g. Medical Subject Heading terms) were used to identify synonyms (see the example of searching in PubMed in the supplementary data, available at *Rheumatology* Online).

### Selection criteria for articles

The selection criteria were (i) studies including patients at least 18 years of age with a diagnosis of RA, AS, PsA, Ps, UC or CD; (ii) studies of patients treated for at least 12 weeks with infliximab, adalimumab, golimumab, certolizumab, etanercept, abatacept, rituximab, tocilizumab, ustekinumab or tofacitinib; (iii) studies collecting data on TB; (iv) RCTs and (v) studies with a control group.

The study selection was performed based on the inclusion criteria. Two independent reviewers (A.S. and E.S.) selected the articles in a standardized manner by reading the titles and abstracts. A third reviewer (J.R.M.) selected the articles if the first two reviewers were in disagreement. Abstracts and duplicate publications were dismissed. Additionally, articles including previously biologic-treated patients were dismissed. Once the unrelated articles were excluded, the full texts of the selected studies were examined. Subsequently, articles not fulfilling all selection criteria were excluded. A table with the reasons for exclusion was constructed (see supplementary Table S1, available at *Rheumatology* Online). A reverse search of the included articles and a hand search of the published clinical trials of biologics and tofacitinib were also performed. For the second part of the review, LTE studies were also included. In the LTE studies, some patients had been treated previously with a biologic. The last update of the manual search of the LTE studies was completed in June 2013.

### Data extraction

The data collection included publication details, number of patients, characteristics of the trial participants, study design, study duration, study quality, level of evidence, type of intervention, incidence cases of TB, year of initiation of the study, geographic location of the study classified according to the rate of TB (World Health Organization, incidence TB estimation, 2011), previous latent TB screening and treatment, and characteristics of the current and previous treatments. Countries with an incidence rate (IR) $\geqslant$40/100 000 are considered as high-incidence TB areas.

### Risk of bias

The systematic review included RCTs and their LTE phase. Unblinded studies were permitted. The quality of the studies was assessed by the Jadad scale [11]. The level of evidence of the studies was assessed by the

Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence [12].

### Statistical analysis

Meta-analyses were only performed when at least three studies had comparable outcome measures using a random-effects approach with the DerSimonian and Laird method and the odds ratio (OR) had been computed [13]. An OR >1 suggests a higher risk of TB than the control. Studies without active TB cases were excluded for meta-analysis of RCTs. For each available analysis, the effect was plotted by the inverse of its standard error to identify the risk of publication bias by visually assessing the symmetry of the funnel plots. Its statistical significance was checked using the Egger test [14]. A *P*-value <0.05 was considered indicative of publication bias. The heterogeneity was tested using $I^2$ [15, 16].

The LTE studies were meta-analysed using random effects. The effect estimates were calculated as a pooled estimated IR (per 100 000 patient-years). Explanations for heterogeneity were investigated using sensitivity analysis, meta-regression and stratified analysis. Meta-regression aimed to determine the influence of the type of medication, disease under treatment, study year, TB rate of included areas and previous biologics exposure on the rate of active TB. A *P*-value <0.10 was considered significant in the meta-regression. Stratified analyses were conducted by type of medication, disease under treatment and TB rate of the included area. Stata/IC 11.1 for Windows (StataCorp, College Station, TX, USA) was used for all statistical analyses.

## Results

### Study selection

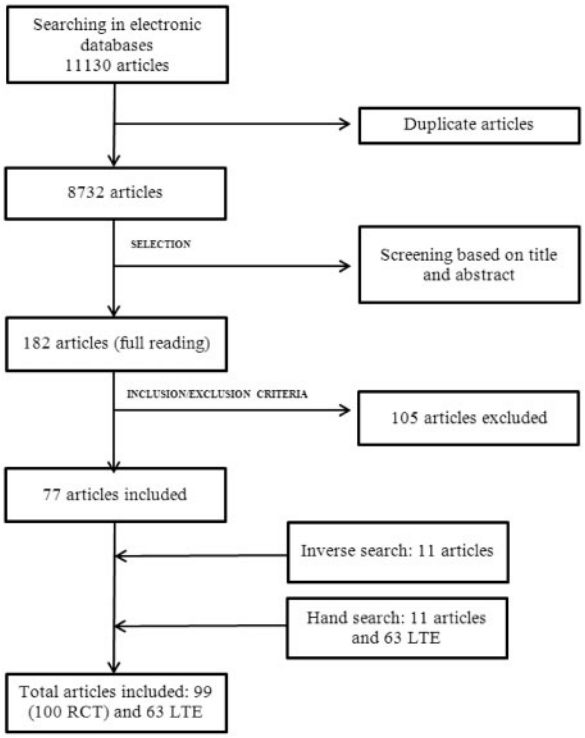
The search identified 11 130 articles and abstracts. After screening, 182 articles were retrieved for review. By hand and reverse searching, 22 articles were additionally included. After reading the full text, 99 articles, including 100 RCTs, were selected for analysis (see Fig. 1). By hand searching, 63 LTE documents, including 1 US Food and Drug Administration (FDA) document, were identified and included for the second objective.

### Meta-analysis of RCTs

A total of 100 RCTs with approximately 75 000 patients were analysed. Fifty-five RCTs were on RA, 18 on Ps, 9 on AS, 8 on PsA, 5 on CD and 5 on UC. Twenty RCTs involved treatment with infliximab, 19 with etanercept, 18 with adalimumab, 9 with tocilizumab, 7 with golimumab, 7 with certolizumab, 6 with abatacept, 5 with ustekinumab, 5 with tofacitinib and 4 with rituximab. Fifty-four RCTs were performed in areas with a low or medium rate of TB and 35 in areas with a high rate of TB, and for 11 RCTs this information was unknown.

Only 19 RCTs reporting active TB cases could be meta-analysed [17–35]. Thirty-two active TB cases were identified in 6599 patients exposed to a biologic or tofacitinib, and only one case was identified in 2702 control patients

**Fig. 1** Flow of information through the different phases of the systematic review




LTEs: long-term extension studies.

(see Tables 1 and 2). In the remaining 81 RCTs there were no cases of TB (see supplementary Tables S2 and S3, available at *Rheumatology* Online).

Fourteen active TB cases occurred out of 3158 patients treated with infliximab, 10 of 1275 patients treated with certolizumab, 2 of 658 patients treated with etanercept, 4 of 598 patients treated with adalimumab, 1 of 477 patients treated with golimumab and 1 of 433 patients treated with abatacept. No TB cases occurred in patients treated with rituximab, tocilizumab or tofacitinib. Only data on the TNF inhibitors were enough to perform a meta-analysis. The OR for all TNF inhibitors was 1.92 (95% CI 0.91, 4.03, $P = 0.085$), without heterogeneity ($I^2 = 0.0\%$) (see Fig. 2). No asymmetries were found in the funnel plot (Egger test $P = 0.035$).

There were 26 active TB cases out of 5253 RA patients, 2 of 55 AS patients, 1 of 57 PsA patients, 1 of 653 Ps patients, 1 of 243 UC patients and 1 of 338 CD patients. The OR for RA was 1.87 (95% CI 0.76, 4.60, $P = 0.169$), without heterogeneity ($I^2 = 0.0\%$). No asymmetries were found in the funnel plot (Egger test $P = 0.012$). The data for AS, PsA, Ps, CD and UC could not be independently meta-analysed, therefore they were pooled and compared with RA. The OR for the non-RA diseases was 2.01 (95% CI 0.54, 7.50, $P = 0.297$). No asymmetries were found in the funnel plot (Egger test $P = 0.056$).

The OR for studies that did not include high TB rate areas was 1.89 (95% CI 0.52, 6.90, $P = 0.334$), without

**Table 1** Evidence in randomized controlled trials with tuberculosis cases

| Article | Drug | Disease | Design | *D* | *Q* | LE | EA | Treatment arms | *n* | Age[a] | DD[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Combe *et al*. [17] | ETA | RA | III. R. DB | 104 | 5 | 2 | | SSZ/ETA 50 mg/wk ETA 50 mg/wk + SSZ | 50/103/101 | 53/51.3/50.6 | 5.6/7.1/6.5 |
| Maini *et al*. [18] | IFX | RA | III. R. DB | 102 | 5 | 2 | No | DMARD/DMARD + IFX 3 mg 8 wk/DMARD + IFX 3 mg 4 wk/DMARD + IFX 5 mg 8 wk/DMARD + IFX 5 mg 4 wk | 88/86/86/87/81 | 51/56/51/55/52 | 8.9/8.4/7.2/9/8.7 |
| Barker *et al*. [19] | IFX | Ps | IIIb. R. OL | 24 | 3 | 2 | | MTX/IFX 5 mg/kg | 215/653 | 41.9/44.1 | 17/18.8 |
| Emery *et al*. [20] | GOL | RA | III. R. DB | 24 | 5 | 2 | Yes | MTX + placebo/placebo + GOL 100 mg/MTX + GOL 50 mg/MTX + GOL 100 mg | 160/159/159/159 | 48.6/48.2/50.9/50 | 209/4.1/3.5/3.6 |
| Chen *et al*. [21] | ADA | RA | III. R. DB | 12 | 5 | 2 | No | MTX/ADA 40 mg | 12/35 | 53/53 | 6.2/8.3 |
| Keystone *et al*. [22] | ADA | RA | III. R. DB | 52 | 5 | 2 | No | MTX + placebo/MTX + ADA 20 mg/wk/MTX + ADA 40 eow | 200/212/207 | 56.1/57.3/56.1 | 10.9/11/11 |
| Rutgeerts *et al*. [23] | IFX | UC | III. R. DB | 54 | 5 | 2 | Yes | Placebo/IFX 5 mg/kg/IFX 10 mg/kg | 121/121/122 | 41.4/42.4/41.8 | 6.2/5.9/8.4 |
| Heijde *et al*. [24] | ETA | RA | III. R. DB | 156 | 5 | 2 | Yes | MTX/ETA 50 mg wk/MTX + ETA 50 mg/wk | 228/223/231 | 53/53.2/52.5 | 6.8/6.3/6.8 |
| Colombel *et al*. [25] | IFX | CD | III. R. DB | 20 | 5 | 2 | | AZA/IFX 5 mg/kg/AZA + IFX 5 mg/kg | 170/169/169 | 35/35/34 | 2.4/2.2/2.2[b] |
| Keystone *et al*. [26] | CZP | RA | III. R. DB | 52 | 4 | 2 | Yes | MTX + placebo/CZP 200 mg + MTX/CZP 400 mg + MTX | 199/393/390 | 52.2/51.4/52.4 | 6.2/6.1/6.2 |
| Smolen *et al*. [27] | CZP | RA | III. R. DB | 24 | 5 | 2 | Yes | MTX + placebo/CZP 200 mg + MTX/CZP 400 mg + MTX | 127/246 /246 | 51.5/52.2/51.9 | 5.6/6.1/6.5 |
| Vollenhoven *et al*. [28] | ADA | RA | II. R. OL | 24 | 3 | 2 | Yes | MTX + placebo/MTX + ADA 40 mg eow | 76/79 | 54/53 | 8.4/8.8 |
| Kim *et al*. [29] | ADA | RA | III. R. DB | 24 | 5 | 2 | No | MTX/MTX + ADA 40 eow | 63/65 | 49.8/48.5 | 6.9/6.8 |
| Braun *et al*. [30] | IFX | AS | III. R. DB | 12 | 3 | 2 | No | Placebo/IFX 5 mg/kg | 35/35 | 30/40.6 | 14.9/16.4 |
| Baranauskaite *et al*. [31] | IFX | PsA | IIIb. R. DB | 16 | 5 | 2 | Yes | MTX/MTX + IFX 5 mg/kg | 58/57 | 42.3/40.1 | 3.7/2.8 |
| Van den Bosch *et al*. [32] | IFX | AS | III. R. DB | 12 | 4 | 2 | | Placebo/IFX 5 mg/kg | 20/20 | 47.5/46 | 13/8.5 |
| Westhovens *et al*. [33] | IFX | RA | III. R. DB | 24 | 5 | 2 | Yes | MTX + placebo/MTX + IFX 3 mg/kg/MTX + IFX 10 mg/kg | 363/360/361 | 52/53/52 | 8.4/7.8/6.3 |
| Clair *et al*. [35] | IFX | RA | III. R. DB | 54 | 5 | 2 | No | MTX + placebo/MTX + IFX 3 mg/kg/MTX + IFX 6 mg/kg | 298/373/378 | 50/51/50 | 0.9/0.8/0.9 |
| Kremer *et al*. [34] | ABA | RA | III. R. DB | 52 | 5 | 2 | Yes | MTX + placebo/MTX + ABA 10 mg/kg | 219/433 | 50.4/51.5 | 8.9/8.5 |

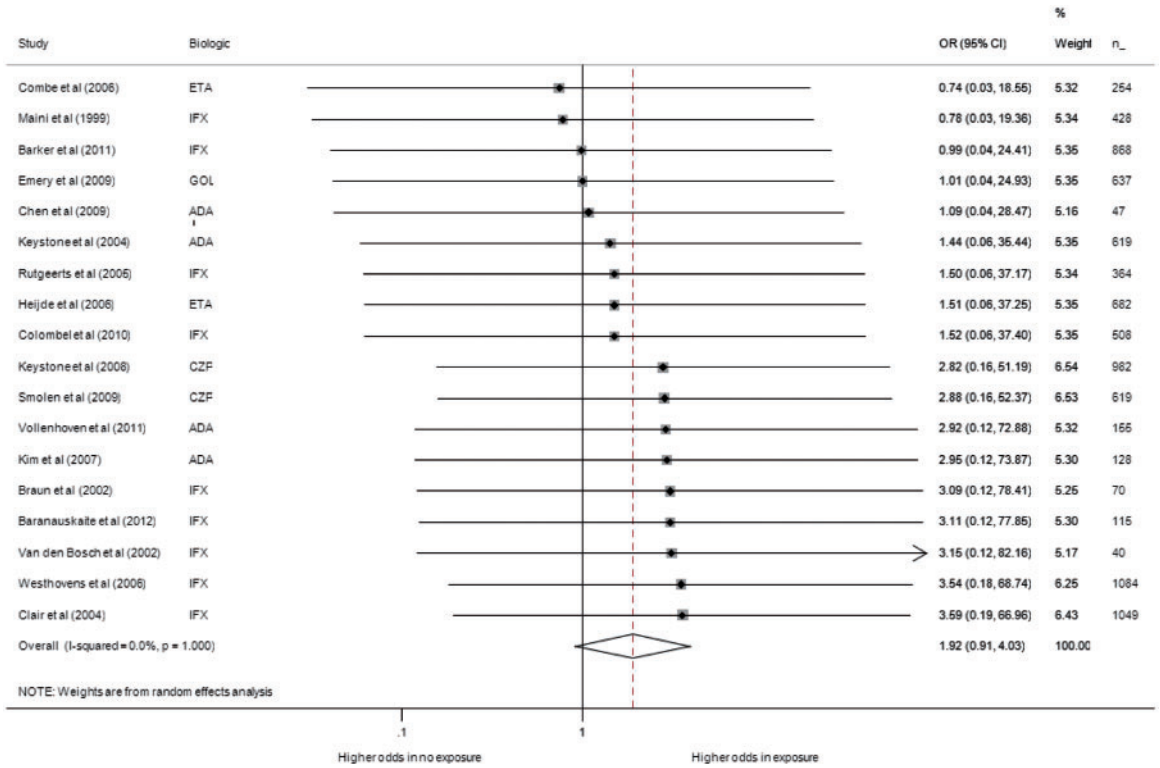
*D*: duration of study (weeks); *Q*: study quality; LE: level of evidence; EA: endemic area of TB; *n*: number of patients; DD: disease duration; IFX: infliximab; ADA: adalimumab; ETA: etanercept; CZP: certolizumab; GOL: golimumab; ABA: abatacept; Ps: psoriasis; CD: Crohn's disease. UC: ulcerative colitis; R: randomized; DB: double blind; OL: open label; wk: week; eow: every other week. [a]Age and disease duration are given as the mean (years). [b]Median years.

**Table 2** Results of randomized clinical trials with tuberculosis cases

| Study | Drug | *n* | Disease | *D* | Comparator | $TB^+BIO^+$ | $TB^-BIO^+$ | $TB^+BIO^-$ | $TB^-BIO^-$ |
|---|---|---|---|---|---|---|---|---|---|
| Combe *et al*. [17] | ETA | 254 | RA | 104 | SSZ/ETA 50 mg/wk/ETA 50 mg/wk + SSZ | 1 | 203 | 0 | 50 |
| Maini *et al*. [18] | IFX | 428 | RA | 102 | DMARD/DMARD + IFX 3 mg 8 wk/DMARD + IFX 3 mg 4 wk/DMARD + IFX 5 mg 8 wk/DMARD + IFX 5 mg 4 wk | 1 | 339 | 0 | 88 |
| Barker *et al*. [19] | IFX | 868 | Ps | 24 | MTX/IFX 5 mg/kg | 1 | 652 | 0 | 215 |
| Emery *et al*. [20] | GOL | 637 | RA | 24 | MTX + placebo/placebo + GOL 100 mg/MTX + GOL 50 mg/MTX + GOL 100 mg | 1 | 476 | 0 | 160 |
| Chen *et al*. [21] | ADA | 47 | RA | 12 | MTX/ADA 40 mg | 1 | 34 | 0 | 12 |
| Keystone *et al*. [22] | ADA | 619 | RA | 52 | MTX + placebo/MTX + ADA 20 mg/wk/MTX + ADA 40 eow | 1 | 418 | 0 | 200 |
| Rutgeerts *et al*. [23] | IFX | 364 | UC | 54 | Placebo/IFX 5 mg/kg/IFX 10 mg/kg | 1 | 242 | 0 | 121 |
| Heijde *et al*. [24] | ETA | 682 | RA | 156 | MTX/ETA 50 mg/wk/MTX + ETA 50 mg/week | 1 | 453 | 0 | 228 |
| Colombel *et al*. [25] | IFX | 508 | CD | 20 | AZA/IFX 5 mg/kg/AZA + IFX 5 mg/kg | 1 | 337 | 0 | 170 |
| Keystone *et al*. [26] | CZP | 982 | RA | 52 | MTX + placebo/CZP 200 mg + MTX/CZP 400 mg + MTX | 5 | 778 | 0 | 199 |
| Smolen *et al*. [27] | CZP | 619 | RA | 24 | MTX + placebo/CZP 200 mg + MTX/CZP 400 mg + MTX | 5 | 487 | 0 | 127 |
| Vollenhoven *et al*. [28] | ADA | 155 | RA | 24 | MTX + placebo/MTX + ADA 40 mg eow | 1 | 78 | 0 | 76 |
| Kim *et al*. [29] | ADA | 128 | RA | 24 | MTX/MTX + ADA 40 eow | 1 | 64 | 0 | 63 |
| Braun *et al*. [30] | IFX | 70 | AS | 12 | Placebo/IFX 5 mg/kg | 1 | 34 | 0 | 35 |
| Baranauskaite *et al*. [31] | IFX | 115 | PsA | 16 | MTX/MTX + IFX 5 mg/kg | 1 | 56 | 0 | 58 |
| Van den Bosch *et al*. [32] | IFX | 40 | AS | 12 | Placebo/IFX 5 mg/kg | 1 | 19 | 0 | 20 |
| Westhovens *et al*. [33] | IFX | 1084 | RA | 24 | MTX + placebo/MTX + IFX 3 mg/kg/MTX + IFX 10 mg/kg | 3 | 718 | 0 | 363 |
| Clair *et al*. [35] | IFX | 1049 | RA | 54 | MTX + placebo/MTX + IFX 3 mg/kg/MTX + IFX 6 mg/kg | 4 | 747 | 0 | 298 |
| Kremer *et al*. [34] | ABA | 652 | RA | 52 | MTX + placebo/MTX + ABA 10 mg/kg | 1 | 432 | 1 | 218 |

TB: active tuberculosis; BIO: biologics and tofacitinib; *D*: duration of study (weeks); *n*: number of patients; $TB^+BIO^+$: TB cases in patients exposed to drug; $TB^-BIO^+$: patients without TB exposed to drugs; $TB^+BIO^-$: TB cases in patients exposed to placebo; $TB^-BIO^-$: patients without TB exposed to placebo; IFX: infliximab; ADA: adalimumab; ETA: etanercept; CZP: certolizumab; GOL: golimumab; ABA: abatacept; Ps: psoriasis; CD: Crohn's disease; UC: ulcerative colitis; wk: week; eow: every other week.

FIG. 2 Meta-analysis of odd ratios of cases of active tuberculosis in randomized controlled trials treated with TNF inhibitors




ETA: etanercept; IFX: infliximab; GOL: golimumab; ADA: adalimumab; CZP: certolizumab; OR: odds ratio.

heterogeneity ($I^2 = 0.0\%$). No asymmetries were found in the funnel plot (Egger test $P = 0.275$). The OR for active TB cases in RCTs that included high TB rate areas was 2.27 (95% CI 0.76, 6.78, $P = 0.141$), without heterogeneity ($I^2 = 0.0\%$). No asymmetries were found in the funnel plot (Egger test $P = 0.158$).

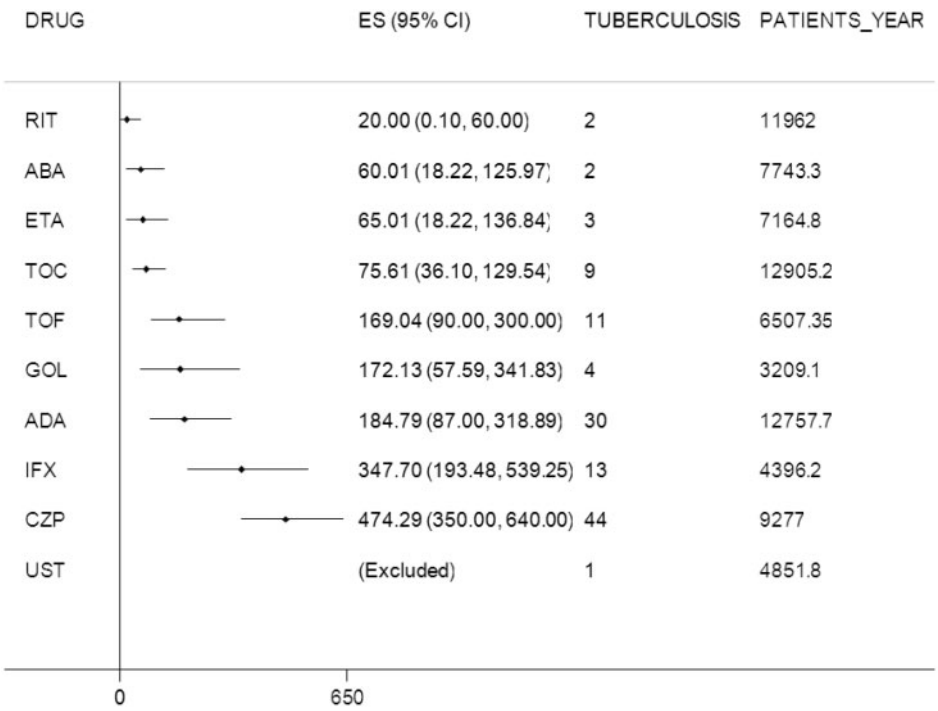
## Meta-analysis of the LTE studies

A total of 119 active TB cases were detected in 80 774.45 patient-years of exposure to biologics or tofacitinib in the LTE studies [1, 19, 20, 25, 31, 35–92]. TB cases occurred 4 weeks to 5 years after the initiation of the treatment (see supplementary Table S4, available at *Rheumatology* Online).

The pooled estimated IR of active TB was calculated by the type of medication and treated disease. The IR of active TB was 474.2 (95% CI 350.0, 640.0), without heterogeneity ($I^2 = 0.0\%$), with certolizumab treatment; 347.7 (95% CI 193.4, 539.2), without heterogeneity ($I^2 = 0.0$), with infliximab treatment; 172.1 (95% CI 57.6, 341.8), without heterogeneity ($I^2 = 0.0\%$), with golimumab treatment; 169.0 (95% CI 90.0, 300.0), without heterogeneity ($I^2 = 0.0\%$), with tofacitinib treatment; 75.6 (95% CI 36.1, 129.5), without heterogeneity ($I^2 = 0.0\%$), with tocilizumab treatment; 65.01 (95% CI 18.22, 136.84), without heterogeneity ($I^2 = 0.0\%$), with etanercept treatment; 60.0 (95% CI 18.2, 125.9), without heterogeneity ($I^2 = 0.0\%$), with abatacept treatment and 20.0 (95% CI 0.1, 60.0), without heterogeneity ($I^2 = 0.0\%$), with rituximab treatment. The IR with adalimumab treatment was 184.7 (95% CI 87.0, 318.8), with heterogeneity ($I^2 = 41.1\%$) (Fig. 3). Treated disease, study year, gender and age of patients, concomitant medications, inclusion of areas with a high rate of TB (countries where trials were conducted), treatment of LTBI and previous biologics failure were not identified as causes of heterogeneity by meta-regression. The sensitivity analysis showed that the heterogeneity was due primarily to one study [48]. When this study was excluded from the analysis, the heterogeneity disappeared. A subanalysis by study year was performed. The IR of the active TB cases in the trials starting later than 2003 (when an awareness of the risk of TB in these patients was first established) was 57.6 (95% CI 15.4, 129.5) with etanercept treatment and 654.7 (95% CI 140.6, 1542.0) with the infliximab and adalimumab treatment data pooled together. The IR with ustekinumab treatment was not estimated because of the heterogeneity of the pooled data.

The IR of active TB cases was 136.8 (95% CI 78.4, 211.4), with heterogeneity ($I^2 = 70.3\%$), in RA patients treated with biologics and tofacitinib and 225.4 (95% CI 125.9, 353.6), with heterogeneity ($I^2 = 60.5\%$), in RA patients treated with TNF inhibitors. Treated disease, study year,

**Fig. 3** Meta-analysis of incidence rates by treatment of long-term extension studies




ES: incidence rate per 100 000 patient-years; ABA: abatacept; ETA: etanercept; TOC: tocilizumab; TOF: tofacitinib; GOL: golimumab; ADA: adalimumab; IFX: infliximab; CZP: certolizumab; UST: ustekinumab; RIT: rituximab.

gender and age of patients, concomitant medications, inclusion of areas with a high rate of TB, treatment of LTBI and previous biologics failure were not identified as causes of heterogeneity by meta-regression. The sensitivity analysis showed that the heterogeneity was due to the inclusion of two studies [48, 60]. When these two studies were excluded from the meta-analysis, the heterogeneity disappeared. The IR was 654.6 (95% CI 193.4, 1374.2) with infliximab treatment, 474.3 (95% CI 350.0, 640.0) with certolizumab treatment, 254.8 (95% CI 70.2, 546.6) with golimumab treatment, 193.48 (95% CI 55.21, 409.04) with adalimumab treatment and 67.5 (95% CI 12.1, 163.9) with etanercept treatment. The IR with etanercept was lower than with anti-TNF monoclonal antibodies [67.6 (95% CI 12.1, 163.9) *vs* 307.7 (184.8, 454.9)].

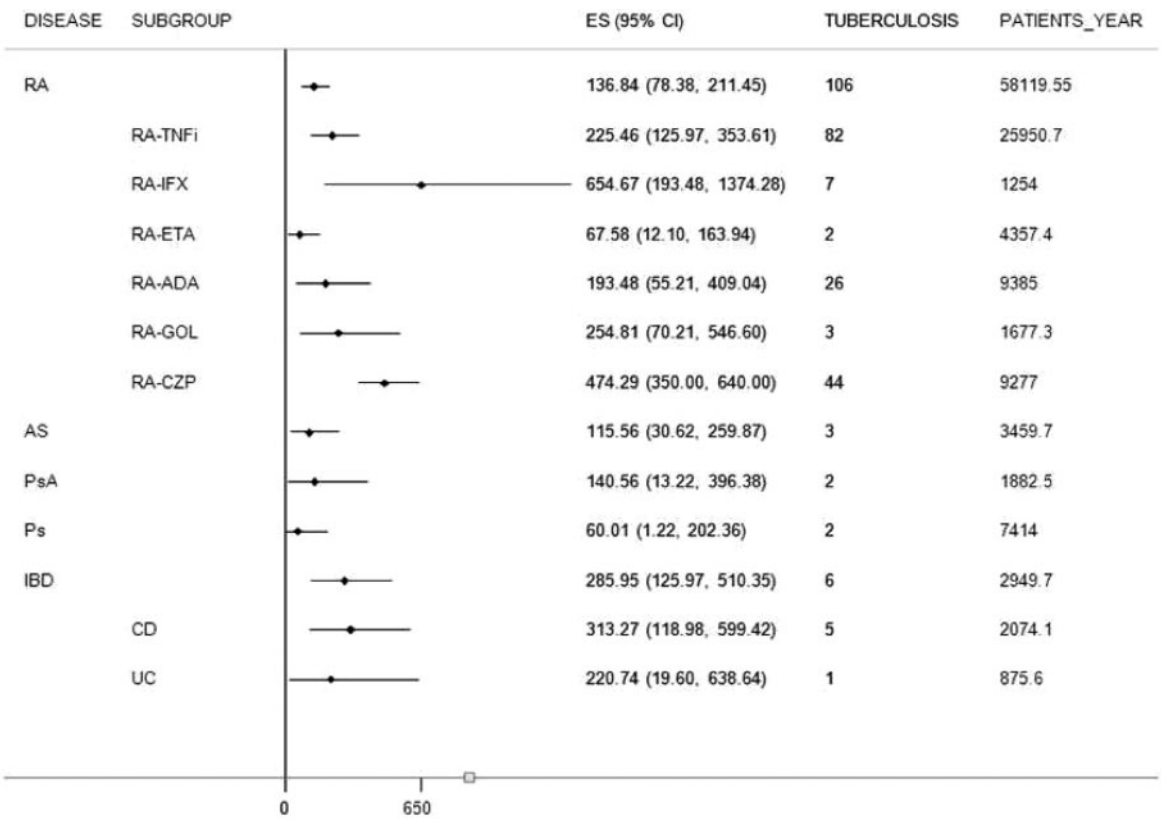
The IR of active TB in patients with IBD treated with biologics was 285.9 (95% CI 125.9, 510.3), without heterogeneity ($I^2 = 0.0\%$). The IR in patients with CD was higher than in patients with UC [313.3 (95% CI 119.0, 99.4) vs. 220.7 (19.6, 638.6)]. The IR in patients with PsA was 140.6 (95% CI 13.2, 396.4), without heterogeneity ($I^2 = 14.4\%$); in patients with AS it was 115.6 (95% CI 30.6, 259.9), without heterogeneity ($I^2 = 0.0\%$); and in patients with Ps it was 60.0 (95% CI 1.2, 202.4), with heterogeneity ($I^2 = 42.7\%$) (see Fig. 4). Treated disease, study year, gender and age of patients, concomitant medications, inclusion of areas with a high rate of TB, treatment of LTBI and previous biologics failure were not identified as causes of heterogeneity by meta-regression. Heterogeneity was due to the inclusion of the two studies with ustekinumab [89, 90]. When only trials with TNF inhibitors were analysed, the heterogeneity disappeared. The IR in AS, PsA and Ps patients pooled together was lower with etanercept than anti-TNF monoclonal antibodies [60.01 (95% CI 3.6, 184.8) *vs* 122.4 (34.2, 264.9)].

The proportion of patients from each individual country in the trials is not available. Seven of the nine cases of active TB in patients treated with tocilizumab occurred in medium/high TB rate areas in LTE studies [60, 86, 93]. For the tofacitinib-treated patients, the IR of active TB per 100 000 was 781, 36 and 37 in high, medium and low TB rate areas, respectively [94]. For certolizumab-treated patients, the IR was 50, 230, 580, and 1020 in North America, Western Europe, Central Europe and Eastern Europe, respectively [95].

## Discussion

Our work shows that an increased rate of reactivation of LTBI with biologics and tofacitinib cannot be demonstrated in RCTs. Only 19% of the RCTs had TB cases. The meta-analysis was only performed for the TNF inhibitor trials because there was only one case of TB in the RCTs with abatacept and none with other biologics and tofacitinib. Moreover, for the individual RCTs of patients treated with TNF inhibitors, a rate could not be assessed

FIG. 4 Meta-analysis of incidence rates by disease of long-term extension studies




ES: incidence rate per 100 000 patient-years; Ps: psoriasis; CD: Crohn's disease; UC: ulcerative colitis; RA-TNFi: RA treated with a TNF inhibitor; RA-IFX: RA treated with infliximab; RA-ETA: RA treated with etanercept; RA-ADA: RA treated with adalimumab; RA-GOL: RA treated with golimumab; RA-CZP: RA treated with certolizumab.

or was not different from the controls. This is likely due to insufficient exposure pertaining to the design of the RCTs and the number of patients. In line with this, the first study that indicated the reactivation of LTBI in patients with RA was an analysis of all cases of active TB after infliximab therapy through the MedWatch spontaneous reporting system of the FDA [96].

In LTE studies, the IR of active TB was high (>40/100 000) for patients with tofacitinib and all biologics but rituximab. In addition, treated disease, the rate of TB in the background population and treatment were associated with a higher rate of TB. Interestingly, the rate of TB in RA patients, but not in the patients with the other diseases, not treated with biologics was increased compared with the control population, and treatment with biologics further increased this rate [5, 97–101]. This would explain the higher risk in RA patients compared with the other IMIDs in our work. Heterogeneity was found in RA and Ps, and a sensitivity analysis showed that it was partially due to three studies. When these studies were excluded, the heterogeneity disappeared. One study on RA with the largest number of patients included quite dissimilar patients [48]. The second study had a very large exposure and reported a large number of TB cases [60]. In Ps, the heterogeneity was primarily due to ustekinumab studies. In one study, no cases of TB in an exposure of 4782 patient-years were reported [90]. In another study on Taiwanese and Korean patients, one case occurred in 69.8 patient-years [89].

Extensive reviews of the risk of reactivation of latent TB following therapy with TNF antagonists, largely from observational studies, have been published [102, 103]. Following TNF antagonist therapy, the relative risk for TB is increased, depending on the clinical setting and the TNF antagonist used. However, significant differences in the rate of active TB from study to study are reported with adalimumab, etanercept and infliximab. Data for golimumab, certolizumab, abatacept, tocilizumab, rituximab and tofacitinib are meagre.

A large number of active TB cases occurred in patients treated with certolizumab, tocilizumab and tofacitinib in areas with high background rates of TB [60, 86, 93, 94]. Hence, safety studies should include patients from these areas to develop a true picture of the risk of this infection.

A higher IR of active TB with anti-TNF monoclonal antibodies than with etanercept was observed. This difference was also observed in sub-analyses of RA, AS, PsA and Ps. In observational studies, whether the IR with anti-

TNF monoclonal antibodies is greater than that with etanercept is controversial [7, 104–107]. The first trials reporting TB cases were conducted before the dissemination of the general recommendations for the management of LTBI. Nevertheless, in the trials starting later than 2003, a lower rate of TB with etanercept than with infliximab or adalimumab was also demonstrated, excluding the bias related to the trial starting date. Interestingly, certolizumab has the highest IR. However, this should be carefully interpreted because the certolizumab trials included a much higher percentage of patients from TB endemic areas than the other trials. Of additional interest is the lower rate of active TB in patients with spondyloarthritis treated with etanercept, and possibly in Ps patients treated with ustekinumab and RA patients treated with rituximab, compared with RA patients treated with monoclonal antibodies. This low rate of rituximab could merely represent the background rate of TB in RA patients. The IR of tofacitinib was similar to that for anti-TNF monoclonal antibodies. Other biologics, such as abatacept or tocilizumab, had a lower IR.

One possible explanation for the differences regarding the reactivation of latent TB is the mechanism of action of these medications. *In vitro* and *in vivo*, monoclonal antibodies cross-link trans-membrane TNF and induce apoptosis of T cells, which are relevant for granuloma integrity. Etanercept is a soluble receptor and does not have this activity. Moreover, the complement-mediated lysis of TNF-expressing T cells is different. Etanercept, but not the monoclonal antibodies, lacks the CH1 domain where C3 attaches, resulting in a different interaction of etanercept with the complement system. Insufficient IFN-$\gamma$ production is also important in the reactivation of latent TB. TNF inhibitors inhibit the IFN-$\gamma$ production induced by TB antigens, while abatacept, tocilizumab and rituximab do not. Additionally, the CTLA-4 fusion protein abatacept does not affect mycobacterial infection-induced lymphocyte expansion or cytokine production and does not alter the number or function of the lymphocytes that maintain the integrity of the granuloma [108, 109]. Inhibition of Janus kinase 1 (JAK1) and JAK3 by tofacitinib blocks intracellular signals by cytokines that are important for lymphocyte function and modulate the immune response. Animal models have demonstrated that tofacitinib reduces the ability of the host to contain latent TB and enhances the reactivation of latent infection [94, 110, 111]. Differences in TB reactivation might be related to the different roles of biologics and tofacitinib in the modulation of the acquired immune response and the preservation of granuloma integrity [112].

The inclusion of a large number of patients, the concordance and the low heterogeneity of the results, and the analysis of long time exposures to biologics in LTE studies are among the strengths of our review. The limitations of our review are the short time exposures of the RCTs and the lack of patients from high TB rate countries in the early studies. The short exposures to treatments in the RCTs might have caused an underestimation of the TB rates. Undoubtedly there are design differences in the trials. Another weakness is how the analysis of areas included in the trials was reported. Some studies reported the areas where the trial was conducted but not the number of patients from those areas. Information regarding the screening of TB was not consistently reported. In the studies with the highest rates, screening was included in the selection of patients. However, management of positive cases was based on local guidelines (not described in reports). Thus the results must be carefully interpreted. Publication bias might be considered in the meta-analysis of TNF inhibitors in RCTs, although ORs were not significant and funnel plots were symmetric.

Our results may have direct implications in the management of a large number of patients treated currently with biologics and tofacitinib. Isoniazid is the current standard treatment for LTBI, but its liver toxicity is a major concern. The risk factors for this complication have been established, and the selection of candidates to avert this rare but severely adverse event has been proposed [113–115]. In selected populations, the benefit/risk balance may not favour the implementation of recommendations to prevent the reactivation of LTBI. Future studies should answer this question in patients treated with biologics and tofacitinib with a low risk of TB and a high risk of liver toxicity. On the other hand, reinforcement of the recommendations in patients with high risk is essential for all biologics and tofacitinib. Of note, observational studies and clinical trials have demonstrated the benefit of the treatment of LTBI [95, 104]. Finally, RCTs are not sensitive enough to assess the risk of reactivation of LTBI. This should be taken into account before definitive statements about the risk of TB in patients treated with biologics and the new small molecule tofacitinib are made.

**Rheumatology key messages**

- Different risk of tuberculosis is related to disease, selected treatment and background tuberculosis.
- The benefit/risk balance of preventing reactivation of latent tuberculosis infection should be considered individually.

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## Supplementary data

Supplementary data are available at *Rheumatology* Online.

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