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Risk of tuberculosis in patients with rheumatoid arthritis treated with biological and targeted drugs: meta-analysis of randomized clinical trials

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Abstract

Background: Concerns exist regarding the potential development of tuberculosis in patients with rheumatoid arthritis (RA) treated with biological and targeted drugs. We assessed systematically whether biological therapy increased the risk of tuberculosis in patients with RA by meta-analysis of randomized controlled trials (RCTs).

Methods: A systematic literature search was conducted in PubMed, Embase, the Cochrane Library, and China Biology Medicine disc for RCTs evaluating biological therapy in patients with RA from inception through August 2021. Traditional meta-analysis and network meta-analysis were performed to compare the risk of tuberculosis for each biologics class in patients with RA. Peto odds ratio (Peto OR) and its 95% confidence interval (CI) were calculated as the primary effect measure.

Results: In total, 39 studies with 20,354 patients were included in this meta-analysis, and 82 patients developed tuberculosis. The risk of tuberculosis was increased in patients treated with biologics compared with non-biologics (Peto OR: 3.86, 95% CI: 2.36–6.32, $P < 0.001$). Also, tumor necrosis factor-α (TNF-α) inhibitors had a higher probability of developing tuberculosis than placebo (Peto OR: 3.98, 95% CI: 2.30–6.88, $P < 0.001$). However, network meta-analysis demonstrated that there was no significant difference in the risk of tuberculosis for each biologics class in patients with RA. Noticeably, tuberculosis was significantly more common in patients treated with a high dose compared with patients receiving a low dose of tofacitinib (Peto OR: 7.39, 95% CI: 2.00–27.31, $P = 0.003$).

Conclusion: This meta-analysis demonstrates the evidence of an elevated risk of tuberculosis in patients with RA treated with TNF-α inhibitors, and a dose-dependent elevated risk of tuberculosis in patients treated with tofacitinib.

Keywords: Rheumatoid arthritis; Biological therapy; Tuberculosis; Systematic review; Meta-analysis; Network meta-analysis

Introduction

Rheumatoid arthritis (RA) is a chronic and disabling systemic autoimmune disease, which is characterized by synovial joint inflammation and damage, resulting in disability and impaired quality of life.[1,2] The treatment of RA has made important advancements over the past two decades.[3] Biological disease-modifying anti-rheumatic drugs (bDMARDs) provide clinically important improvement in many patients usually failing to respond to symptomatic control with non-steroidal anti-inflammatory drugs or traditional disease-modifying anti-rheumatic drugs.[4,5] Biological agents can reduce inflammation by targeting specific immune pathways, such as tumor necrosis factor-α and interleukin-6 (IL-6), to achieve a better control of symptom and structural damage.[6] The data from European and U.S. RA registries showed that 25% to 56% of patients used biological agents.[7] Although bDMARDs provide clinically important ameliorative effects, they may interfere with the immune system, which has raised concerns about their safety, especially in terms of infection and malignancies.[8] In addition, Janus kinase (JAK) inhibitors such as tofacitinib, a novel small-molecule oral targeted drug, have been approved for the treatment of RA.[9] It works through regulating cytokine signaling pathways involved in lymphocyte function, which may lead to the suppression of immune response, thereby increasing the risk of infection. Although the clinical efficacy and safety of these agents have been tested

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in many randomized controlled trials (RCTs), RCTs are insufficient to detect and quantify sparse adverse events such as tuberculosis.

Tuberculosis is an important infectious disease worldwide associated with significant morbidity and mortality, particularly in developing countries. The increasing use of biologics in the treatment of RA is a matter of concern, particularly in patients with a previous history of tuberculosis onset. Data from nationwide registries in China indicated that these patients with RA receiving anti-TNF therapy had a 10.1-fold to 34.9-fold increased risk of developing tuberculosis when compared to the respective general population.[10] The study showed an increased risk of developing tuberculosis in patients with RA of 2.28-fold than that in the general population, and these patients receiving anti-TNF therapy were at greater risk of developing tuberculosis than those treated with other medications.[11] Thus, the relationship between the treatment of biologics and the risk of developing tuberculosis are an area of interest.

The aim of this systematic review was to assess and compare the risk for tuberculosis infection accompanying treatments of biological and targeted drugs from RCTs using meta-analysis and network meta-analysis. The method is commonly used as a powerful tool to evaluate drug efficacy or harmful effects, so we performed such an analysis while applying a validated method for pooling sparse event data as a tool for complementing the assessment of drug safety. Besides, while in the absence of RCTs that directly compare the safety of these drugs, indirect comparisons may provide some important information through network meta-analysis to help select the optimal treatment alternative.

Methods

We strictly followed the Preferred Reported Items for Systematic Reviews and Meta-analyses guidelines and the recommendations of the Cochrane Collaboration to conduct this systematic review and meta-analysis.[12] A systematic literature review was performed for identifying all data about tuberculosis infection from published RCTs of the biological and targeted drugs used in patients with RA.

Systematic literature retrieval

Comprehensive literature searches were conducted in the Cochrane Library, PubMed, Web of Science, Embase, Chinese Biomedical Database, and China National Knowledge Infrastructure to identify eligible studies up to August 2021. The search strategy focused on RA, biological and targeted drugs, and was restricted to humans and clinical trials published in English and Chinese. All references cited in the articles were tracked to identify additional studies that were not included in the above electronic databases.

Eligibility criteria

Eligible trials were required to (1) be RCTs collecting data on tuberculosis, (2) include patients (≥18 years old) with RA confirmed by physician/specialist according to valid diagnostic criteria (such as Classification Criteria of the American College of Rheumatology and European League Against Rheumatism); (3) be studies comparing any biologics (adalimumab, abatacept, certolizumab, clazakizumab, etanercept, golimumab, infliximab, tocilizumab, or atacicept) or targeted drug (tofacitinib, baricitinib, or upadacitinib) against non-biologics (placebo or conventional synthetic disease-modifying anti-rheumatic drugs [csDMARDs]) or against each other.

Study selection and data extraction

ENDNOTE X9 (Clarivate Analytics, Philadelphia, PA, USA) was applied to manage the literature search records. A pilot literature selection was conducted to ensure high inter-rater agreement among the researchers. Subsequently, two researchers independently reviewed the titles and abstracts of all the retrieved studies using the predefined criteria. All the studies that potentially met the predefined eligibility criteria and conflicted studies required a full-text assessment. Any disagreement was settled by consensus or a third researcher.

For available studies, two researchers independently extracted data on study characteristics, sample size, phase of the trial, names of drugs used as intervention and control groups, dose, duration of therapy, and the number of patients developing tuberculosis infection in every group. A third researcher compiled the statistical documents and settled the differences between the two researchers to ensure accuracy and consistency in the data collection.

Statistical analysis

We used traditional meta-analysis to compare biologics to non-biologics on the risk of tuberculosis infection. The outcome was presented as Peto odds ratio (OR) with 95% confidence intervals (CIs) based on the fixed-effect model. Peto OR was used to derive the weights for these included studies in meta-analysis since it performed well with sparse events (≤1%).[13] We stratified by biologics classes to investigate how different biologics classes affect the risk of tuberculosis infection.

We used network meta-analysis to compare every biologics class to each other. The Markov Chain Monte Carlo method was used to obtain the ORs and corresponding 95% CI, and all chains were run with 5000 burn-in iterations followed by 10,000 additional iterations.

Traditional meta-analysis was conducted using the "meta" package on R 4.0.2 software and network meta-analysis on Stata/MP 16.0. P value < 0.05 was considered statistically significant in all tests.

Results

Literature selection and study characteristics

A total of 34,956 unique citations were initially identified through electronic bibliographic databases. After preliminary screening of the titles and abstracts of these literatures for potentially relevant to our topic, the remaining 256 clinical trials were deemed eligible for further full-text

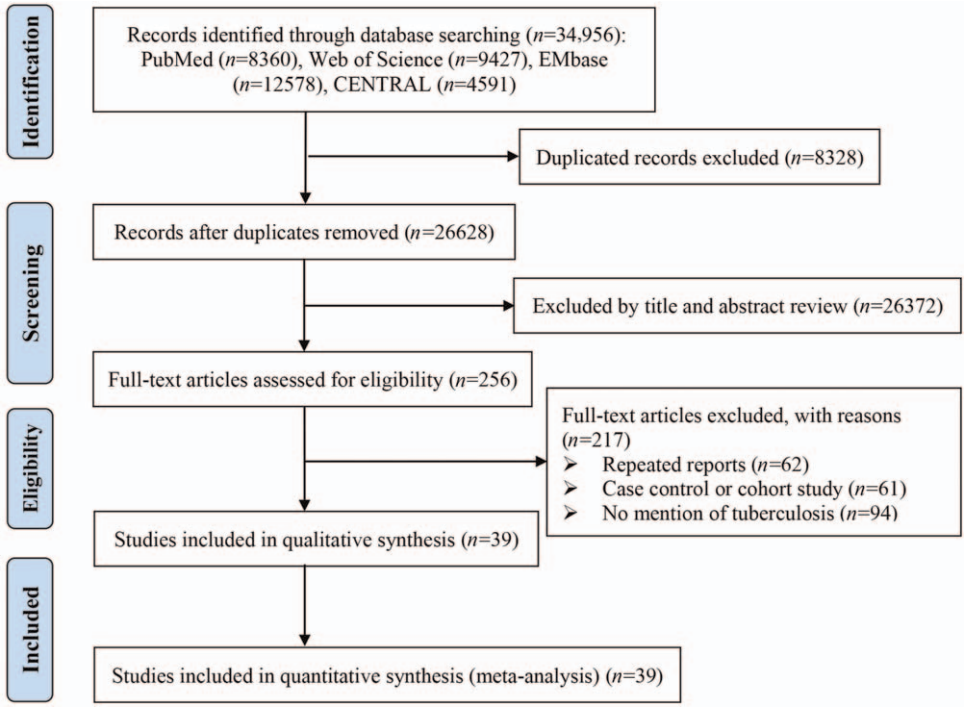

Figure 1: Flowchart of literature selection.

review. Of these clinical trials, only 39 trials, providing the available data on tuberculosis infection, met the inclusion criteria and then were included in our traditional meta-analysis and network meta-analysis. All the included trials were reported in Chinese or English. The details of the study selection process were showed in [Figure 1]. A total of 76.9% (30/39) of studies were two-arm trials [Table 1]. Overall, 20,354 patients with RA were included in the meta-analysis, of whom, 82 patients developed tuberculosis during treatments. The characteristics of the included studies were summarized in Table 1, and detailed characteristics of individuals including studies were available in [Supplementary Table 1, http://links.lww.com/CM9/A892].

Among the RA patients who developed active tuberculosis treated with biologics, 24 patients (29.3%) presented with pulmonary tuberculosis, followed by lymph node tuberculosis (12.2%), disseminated tuberculosis (8.5%), peritoneal tuberculosis (6.1%), pleural tuberculosis (6.1%), and bone tuberculosis (1.2%). We identified three mortality cases (3.7%), of which two were attributed to disseminated tuberculosis that occurred, respectively, after 4 and 14 weeks of infliximab infusion, and the other died from septic shock following peritoneal tuberculosis. Most tuberculosis patients (32%) were of Asia origin, followed by Eastern Europe (22%), South America (18%), Western Europe (12%), and North America (5%).

Direct comparison against non-biologics

Overall, the risk of tuberculosis infection was elevated in the patients receiving biologics therapy compared with non-biologics (Peto OR: 3.86, 95% CI: 2.36–6.32, $P < 0.001$; Figure 2). A funnel plot was used to detect potential publication bias, and the result showed no significant risk of publication bias [Supplementary Figure 1, http://links.lww.com/CM9/A891]. We stratified by biologics classes to investigate how different biologics classes affect the risk of tuberculosis infection. The results demonstrated that the

Table 1: Characteristics of included studies.

Items	Results
Median year of publication (range)	2013 (1999–2021)
Number of trials	39
Study arms	
Two-arm trials, *n* (%)	30 (76.9)
Multi-arm trials, *n* (%)	9 (23.1)
Follow-up	
Follow-up duration (weeks), mean ± SD	54 ± 36
Follow-up duration ≥52 weeks, *n* (%)	21 (53.8)
Tuberculosis cases	
Observed tuberculosis at the end of follow-up, *n*	82
Classes of biological agents	
IL-6 inhibitors, *n* (%)	3 (7.7)
TNF-α inhibitors, *n* (%)	28 (71.8)
JAK inhibitors, *n* (%)	8 (20.5)
Sponsorship	
Pharmaceutical companies, *n* (%)	35 (89.7)
Non-pharmaceutical companies, *n* (%)	4 (10.3)
Sample size	
Number of patients	20,354
Number of female patients	16,335
Analysis approach	
Per protocol, *n* (%)	12 (30.8)
Intention to treat, *n* (%)	21 (53.8)
Modified intention to treat, *n* (%)	6 (15.4)

IL-6: Interleukin-6; JAK: Janus kinase; RA: Rheumatoid arthritis; SD: Standard deviation; TNF-α: Tumor necrosis factor-α.

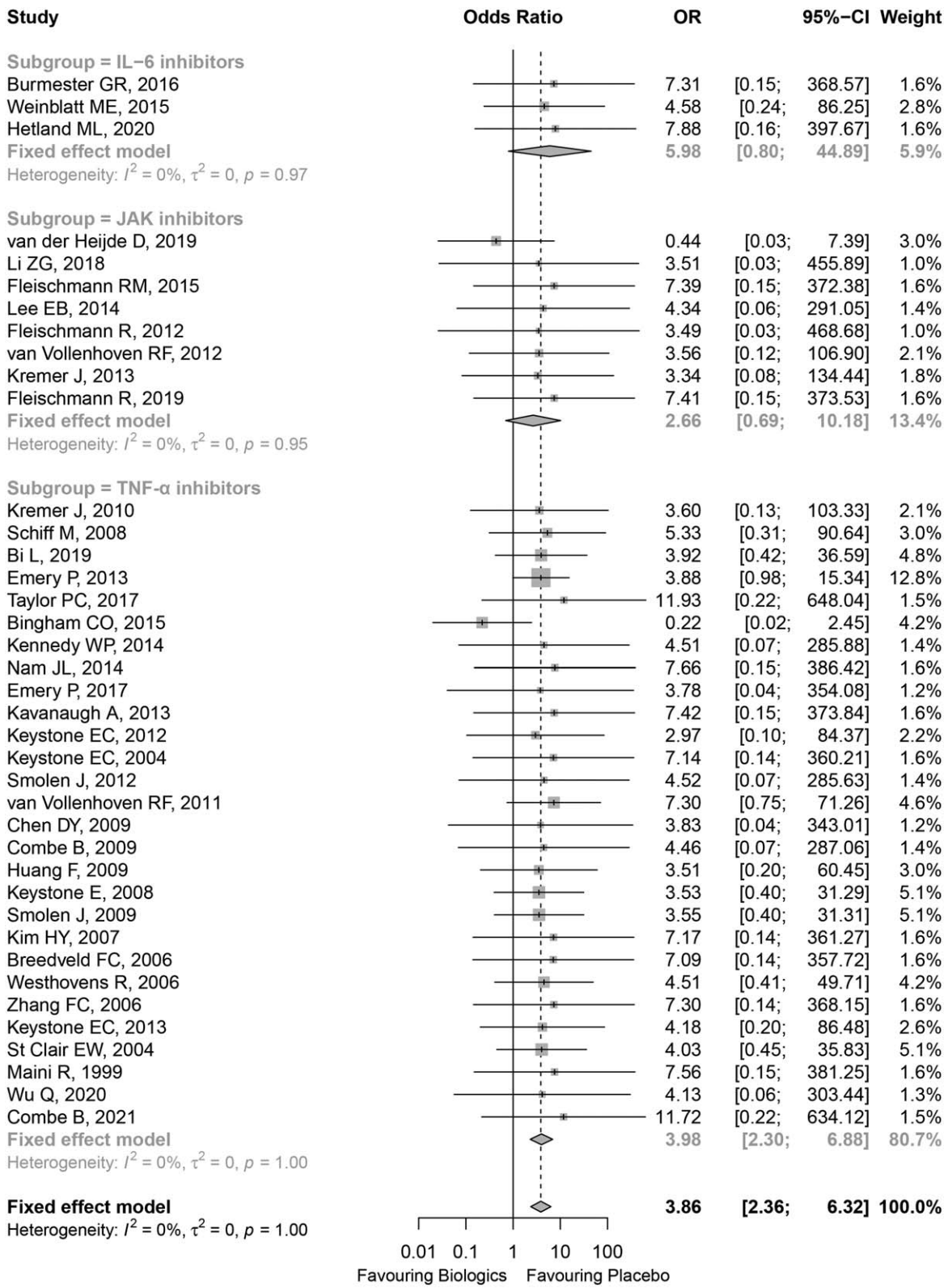

Figure 2: Forest plot of meta-analyses comparing biologics *vs.* placebo for risk of tuberculosis. CI: Confidence interval; IL-6: Interleukin-6; JAK: Janus kinase; TNF-α: Tumor necrosis factor-α.

risk of tuberculosis infection was higher than non-biologics for TNF-α inhibitors (Peto OR: 3.98, 95% CI: 2.30–6.88, $P < 0.001$). There was no significant difference in the risk of tuberculosis infection between other biologics and non-biologics groups, such as IL-6 inhibitors (Peto OR: 5.98, 95% CI: 0.80–44.89, $P > 0.05$) and JAK inhibitors (Peto OR: 2.66, 95% CI: 0.69–10.18, $P > 0.05$; Figure 2). However, subgroup analysis indicated that tofacitinib

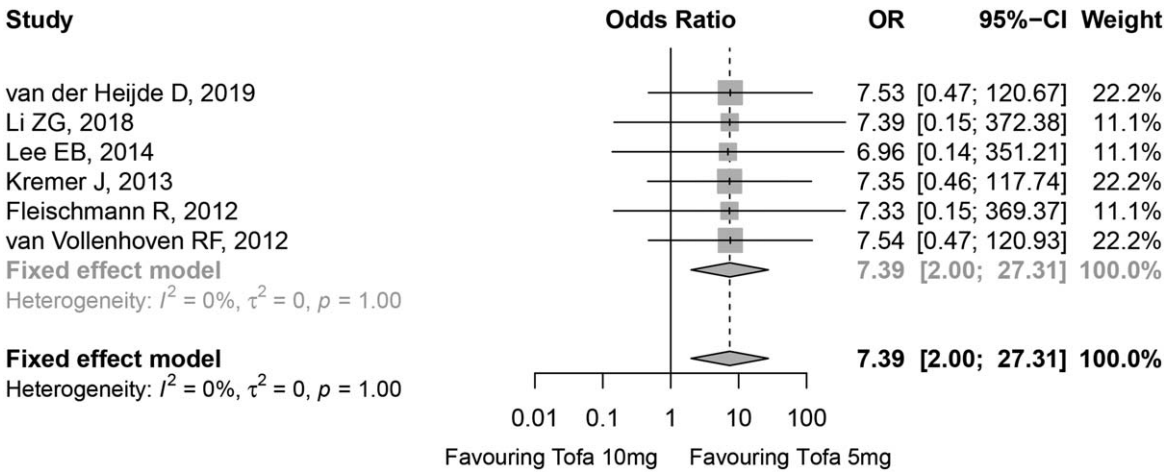

Figure 3: Forest plot of meta-analysis comparing tofacitinib 10 mg *vs.* 5 mg for risk of tuberculosis. CI: Confidence interval.

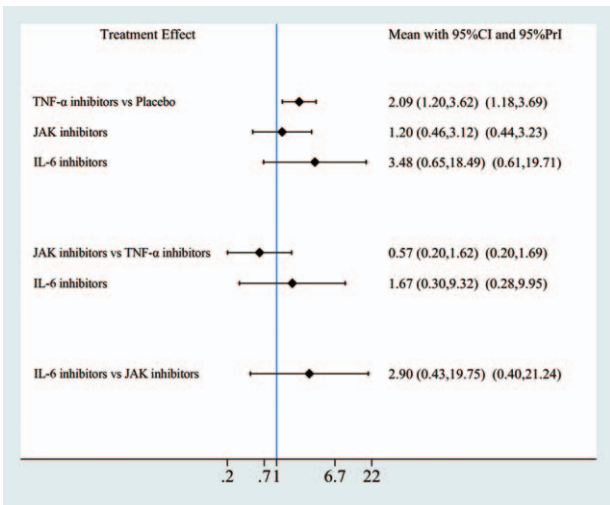

Figure 4: Network meta-analysis comparing different classes of biologics for risk of tuberculosis. CI: Confidence interval; IL-6: Interleukin-6; JAK: Janus kinase; TNF-α: Tumor necrosis factor-α.

10 mg had a higher risk of tuberculosis infection than tofacitinib 5 mg indicated (Peto OR: 7.39, 95% CI: 2.00–27.31, $P = 0.003$; Figure 3).

Indirect comparison of biologics classes against each other

Based on the network meta-analysis, compared with TNF-α inhibitors, JAK inhibitors and IL-6 inhibitors had a higher risk of tuberculosis infection (OR = 1.20 and OR = 3.48); compared with JAK inhibitors, IL-6 inhibitors had a higher risk of tuberculosis infection (OR = 1.67). However, 95% CI for all ORs were wide and crossed one, and the P values were also > 0.05 [Figure 4].

Discussion

Biological agents have been proven to be effective in controlling rheumatic diseases, can have a clinically significant improvement, and ameliorate the natural history of these diseases via targeting the relevant cytokines, such as TNF-α, IL-17, and IL-6, involved in the pathogenesis of inflammatory arthropathy.[14] Despite the significant effectiveness of biologics therapy, they are associated with an increased risk of serious infections, including tuberculosis. This systematic review and meta-analysis aimed to assess the risk of developing tuberculosis in the patients with RA treated with biologics, overall as well as by biologics classes. Our study indicated that there was a significant increase in the risk of tuberculosis infection in RA patients treated with biologics compared with non-biologics, which was supported by traditional meta-analyses and network meta-analyses, while there was no significant difference in tuberculosis incidence between the different classes of biologics.

This study indicated a higher incidence rate of pulmonary tuberculosis in these patients with RA receiving biologics therapy, a finding also previously reported in other studies.[15,16] Besides, extrapulmonary tuberculosis was mainly seen in lymph node tuberculosis. The duration from initiation of biologics therapy to the diagnosis of tuberculosis in this systematic review was 12 to 104 weeks, confirming these previous data on the development of tuberculosis in the first few years of biologics therapy.[17,18] In addition, this study was one of the systematic reviews to estimate the incidence rate of tuberculosis in the different countries and regions of this world, which considered all three biological and targeted drugs available at the time of writing, especially TNF-α inhibitors and JAK inhibitors. The incidence rate of tuberculosis in these patients exposed to biologics was directly linked to the incidence rate of tuberculosis in the general population. Because of the influence of the overall incidence rate of tuberculosis, there was a different incidence rate between classes of these patients on biologics in different countries and regions of this world. This study indicated a high incidence rate of tuberculosis in these patients receiving biologics therapy for RA in regions, such as Asia, Eastern Europe, and South America, and the overall incidence rate of tuberculosis was significantly higher than that in Western Europe and North America.

In our study, the main finding was that TNF-α inhibitors significantly increased the risk of tuberculosis infection in individuals with RA. This result was inconsistent with previous reports that TNF-α inhibitors could increase the risk of tuberculosis.[19] The increasing risk of tuberculosis is the main safety issue for anti-TNF-α therapy, as emphasized by World Health Organization in a "black box" warning because of the risk of developing tuberculosis and other opportunistic infections. The patients with RA have been reported to have an increased risk of tuberculosis while comparing to the general population.[20-22] The patients in endemic areas were expected to have a higher risk of tuberculosis while receiving the treatment of TNF-α inhibitors, which was consistent with our findings in this systematic review. Therefore, the potential for TNF-α inhibitors to further enhance the risk of tuberculosis should not be overlooked. This was enough to suggest that safety researches of TNF-α inhibitors should include the patients from these endemic areas to provide a real overview of the risk of tuberculosis infection.

TNF-α, as an immune mediator, played an important role in the protective mechanism from infections, particularly tuberculosis. TNF-α could increase the phagocytic capacity of macrophages, and enhance the intracellular killing of *Mycobacterium* by generating oxygen intermediates and reactive nitrogen, which had a synergistic effect with interferon-γ (IFN-γ). Besides, TNF-α was also involved in the pathological progress of the latent tuberculous infection, particularly in maintaining the formation and function of granulomas, which could prevent the dissemination of *Mycobacterium*. Therefore, these mechanisms of TNF-α-mediated immune might explain the reason why the increased risk of developing tuberculosis in these patients treated with TNF-α inhibitors.

For patients with RA treated with JAK inhibitors, the risk of tuberculosis is higher than placebo, but this difference is not statistically significant in this meta-analysis. However, we found in a subgroup analysis that tofacitinib 10 mg had a higher risk of tuberculosis infection than tofacitinib 5 mg indicated. In the management of patients with RA recommended by the European League Against Rheumatism, JAK inhibitors were recommended for these patients who failed to initial treatment with methotrexate or other csDMARDs with poor prognostic factors in the EULAR.[4] However, its safety issue has always been controversial. Recently, Pfizer had already pointed out the safety issues of tofacitinib and switched patients in a post-marketing study to the 5 mg dose from 10 mg dose, but the Food and Drug Administration was concerned enough to slap the dreaded "black box" warning on this drug.[23] Among 5671 patients participating in phase II, phase III, and long-term extension trials of tofacitinib, 26 cases of tuberculosis were reported only in the patients treated with tofacitinib in phase III and long-term extension trials, and the crude incidence rate (95% CI) was 0.21 per 100 patient-years (PY) (0.14–0.30). Few studies were culture-confirmed, and 77% of cases of tuberculosis occurred in those treated with tofacitinib 10 mg twice a day.[24] Maiga *et al*[25] have shown that tofacitinib administration led to increased bacterial replication through using the paucibacillary chronic mouse model of latent tuberculous infection, indicating a risk of tuberculosis reactivation, and promoted *M. tuberculosis* replication in a dose-dependent manner. In addition, the incidence rate of tuberculosis was significantly correlated with a background country's incidence rates of tuberculosis. The crude incidence rates of tuberculosis in high, medium, and low endemic countries and regions were 0.75 (0.49, 1.15), 0.08 (0.03, 0.21), and 0.02 (0.003, 0.15) per 100 PY, respectively.[26] Besides, screening and treatment of latent tuberculosis infection were effectively carried out in phase III clinical trial of tofacitinib. In 286 patients with untreated latent tuberculosis infection upon screening, there was none developing tuberculosis after receiving accompanying treatment with tofacitinib and isoniazid (INH), and also none developing severe hepatitis by INH.[26] A real-world cohort comparing the incidence rates of tuberculosis between the patients treated with JAK inhibitors and TNF-α inhibitors in clinical practice remains to be established in some regions. Currently, it is strongly recommended that a screening and treatment strategy for tuberculosis infection is referenced to that for TNF-α inhibitors.[27]

The findings from this systematic review and meta-analysis might have a direct implication for the management of many patients with RA receiving currently biologics therapy. A management strategy that includes rigorous screening and monitoring seems to be desirable while receiving TNF-α inhibitors and JAK inhibitors therapy. Some national clinical guidelines for the management of latent tuberculous infection before TNF-α inhibitors treatment have been formulated in several countries and regions.[28] These patients should also be closely monitored at least once a year during the TNF-α inhibitors and JAK inhibitors therapy to identify new tuberculosis infection or reactivation of latent tuberculosis. One systematic review regarding the infection risk related to TNF-α inhibitors treatment demonstrated that a patient who was available for such therapy should receive detailed medical history consultations and tests, such as the tuberculosis skin test (TST) or chest X-ray, to evaluate the risk of tuberculosis reactivation.[29] IFN-γ release assay could be also used as an alternative to the TST for the diagnosis of tuberculosis infection, particularly in the diagnosis of latent tuberculous infection because of the higher specificity.

Several limitations in this systematic review and meta-analysis should be addressed. First, a slightly short follow-up period in RCTs might lead to an underestimation of the risk of tuberculosis. Those long-term observational studies, including population-based registration studies, could provide longer-term safety assessments of biologics, but they had some significant limitations in terms of the risk of bias and confounding factors. These evidences from RCTs should preferably be supplemented with the data from long-term follow-up, particularly the data on long-term safety issues. Second, the systematic review and meta-analysis were limited to published literature, and the data omissions due to unpublished pharmaceutical trials might affect the reliability of pooled results to a certain extent.

Conclusions

This meta-analysis demonstrated the evidence of an elevated risk of tuberculosis in patients with RA treated with TNF-α inhibitors, and a dose-dependent elevated risk of tuberculosis in patients treated with tofacitinib. Therefore, when TNF-α inhibitors and JAK inhibitors treatment are considered in the patients with RA, the increased risk of developing tuberculosis should be a carefully considered part of the decision-making process, and these patients must be screened for tuberculosis, and anti-tuberculosis prophylaxis or concomitant treatments should be considered.

Conflicts of interest

None.

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