The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor-α Antagonist: A Metaanalysis of Both Randomized Controlled Trials and Registry/Cohort Studies

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ABSTRACT. ***Objective.*** Tumor necrosis factor-α (TNF-α) antagonists have significantly improved treatment results in rheumatoid arthritis (RA), but have also increased the risk of tuberculosis (TB). Etanercept (ETN), adalimumab (ADA), infliximab (IFX), golimumab, and certolizumab pegol are the 5 drugs currently available on the market. This article aimed to evaluate the risk of TB infection from these 5 drugs for patients with RA.

Methods. We searched PubMed, EMBASE, COCHRANE library, OVID, and EBSCO for randomized controlled trials (RCT) of TNF-α antagonist versus control and registry/longitudinal cohort studies of 1 TNF-α antagonist versus another. The Mantel-Haenszel test was adopted to analyze risk ratio (RR) in this metaanalysis.

Results. Fifty RCT and 13 non-RCT were included in this study. No significant difference in TB risk was found in the RCT because of the short observational periods. In the non-RCT, TNF-α antagonist was associated with a higher TB risk in patients with RA (RR 4.03, 95% CI 2.36-6.88), and the TB incidence rates of IFX and ADA were 2.78 and 3.88 times, respectively, higher than that of ETN. Further, preventive treatment for latent TB infection (LTBI) was shown to reduce the TB risk by 65% (RR 0.35, 95% CI 0.15–0.82).

Conclusion. This study demonstrated a significant increase in TB risk in patients with RA treated with TNF-α antagonists; among them, ETN is least likely to cause active TB. The study also proposes the necessity of LTBI prophylaxis in patients with RA. (J Rheumatol First Release October 15 2015; doi:10.3899/jrheum.150057)

Key Indexing Terms:
TUBERCULOSIS RHEUMATOID ARTHRITIS
TUMOR NECROSIS FACTOR-α ANTAGONISTS

Rheumatoid arthritis (RA) is a systemic autoimmune disease often presented with chronic joint inflammation. Clinical pathology usually involves joint synovitis and systemic vasculitis[1]. In recent years, the treatment of RA has reached a breakthrough because of the use of tumor necrosis factor-α (TNF-α) antagonists, a new disease-modifying antirheumatic drug (DMARD). TNF-α is involved in the body's inflammatory responses in RA. It participates in the inflammatory cells infiltration, the production of inflammatory cytokines, and the formation of the synovial pannus[2]. Therefore, the use of TNF-α antagonists can relieve the clinical symptoms of patients and prevent joint destruction[3,4]. There are 5 TNF-α antagonists currently used in the clinical fields: etanercept (ETN), adalimumab (ADA), infliximab (IFX), golimumab (GOL), and certolizumab pegol[5].

Although TNF-α antagonists have shown promising effect in the treatment of patients with RA, the researchers have found that the patients receiving such therapy have a significantly increased incidence rate of active tuberculosis (TB). TB is an infectious disease caused by mycobacterium TB (Mtb), and the World Health Organization reported an average TB incidence rate of around 5–91.8 per 100,000 patient-years (PY)[6]. The randomized controlled trials (RCT) of IFX first reported a 4-fold increase in the risk of TB infection[7,8], and soon more RCT focusing on different TNF-α

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antagonists have reported higher risks of TB compared with placebo groups. Registry and longitudinal cohort studies have directly compared the different TB risks between ETN, ADA, and IFX, and suggested that the TB risk caused by the monoclonal antibody was generally higher than the receptor antibody[9,10], but comprehensive review of TB incidence rates among different drugs is still required.

Metaanalysis is a quantitative evaluation method in evidence-based medicine and has been widely accepted as one of the most effective and reliable tools. Our study evaluated all published RCT and registry/longitudinal cohort studies for the risk of TB in different TNF-α antagonist treatments.

MATERIALS AND METHODS

Selection criteria. The eligible criteria of this meta search were the following: (1) we included all RCT, registry studies, and longitudinal cohort studies in which TNF-α antagonists were used to treat patients with RA who were ≥ 18 years old; (2) all studies had an evaluation of the TB incidence rate; (3) RCT had one of the TNF-α antagonists as intervention and placebo or placebo plus methotrexate (MTX) as an arm of control; (4) if there had been both a primary study and extended study in an RCT, only the extended study was considered for inclusion; (5) in registry studies and longitudinal cohort studies, we included studies that had at least 2 cohorts receiving different TNF-α antagonists; and (6) all articles were in English.

The exclusion criteria included the following: (1) studies that did not include an RA cohort, (2) registry or cohort studies with only 1 TNF-α antagonist cohort, (3) studies that had crossed data with other published articles, and (4) studies that had no analysis of TB incidence.

Search strategy. Databases search was based on the MeSH and keywords: IFX, ETN, ADA, GOL, certolizumab pegol, TNF-α antagonist, RA, and the combination of them. The major medical databases were covered: PubMed, EMBASE, COCHRANE library, OVID, and EBSCO. We did not set a start time.

Study evaluation and data extraction. Two investigators evaluated the references individually and full texts were obtained for relevant articles. Studies were excluded when we failed to acquire the full texts through online methods. As instructed in the *Cochrane Handbook for Systematic Reviews of Interventions*, we performed an evaluation of bias rather than the quality evaluation, and all published RCT included were evaluated using the assessment tool described in the Cochrane handbook. A study was to be considered "possibly biased" when a "high risk" was found in any of the 7 dimensions evaluated. The following dimensions were considered: allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The quality of the nonrandomized studies was assessed using the Newcastle-Ottawa Scale with some modifications to match the needs of our study. Three items were examined: patient selection, comparability, and assessment of outcome. For the comparability between the 2 groups, we focused on the following variables: age, sex, diabetes, purified protein derivative test positivity, and prophylaxis. Studies were graded on a star scoring scale with higher scores representing studies of higher quality, and a maximum of 9 stars can be given for each study (Supplementary Table 1 available online at jrheum.org).

After we acquired all the articles that met our inclusion criteria, we obtained the following information: the name of author, published date, country of origin, study duration, number of patients included in each cohort or registry study, the TB incidence (for RCT, data were analyzed using the intention-to-treat results), whether latent TB infection (LTBI) screening or treatment was administered, and specific therapy regimen for each cohort.

Statistical analysis. Metaanalysis of registry and cohort studies was conducted using Review Manager 5.0 software according to the Cochrane handbook[11] while R Project 3.1.1. was used to analyze RCT. This was because 80% of RCT reported 0 TB events in both arms of our study, making the risk ratio (RR) unable to be defined using Review Manager. To overcome this problem, we used R Project and the library package "meta" to add a continuity correction factor of 1/2 to each arm, allowing the log RR to be estimated. For registry and longitudinal cohort studies, because the TB risk was often reported as the incidence rate, we calculated the incidence rate ratios (IRR) rather than RR. When we compared the TB risk of a specific group with the local TB incidence rates, which were presented as incidence per 100,000 PY, we recalculated the incidence rate of each specific group to present them as incidence per 100,000 PY as well.

Two researchers conducted metaanalysis independently and 1 researcher executed the final data. We used the chi-square test and I^2 index for the heterogeneity evaluation[12]. In the chi-square test, $p > 0.1$ showed homogeneity, and in the I^2 index, > 50 showed heterogeneity. For the homogeneity studies, we adopted the fixed effects Mantel-Haenszel model, and used RR and 95% CI to show the results. For the heterogeneity studies, we adopted the random effects model.

RESULTS

Search results. There were 8750 articles identified by a systematic literature research, and 3756 references were further selected by eliminating duplicate articles. Later, 278 articles were selected by reading the title and article. After a thorough reading of these articles, 216 articles were excluded. The reasons are shown in Figure 1.

Finally, 50 published RCT were included for the final analysis: 9 for ETN, 18 for ADA, 9 for IFX, 8 for GOL, and 6 for certolizumab pegol. Thirteen registry and longitudinal cohort studies were included[13-23,24,25], all including at least 2 TNF-α antagonists cohorts. The detailed characteristics of the RCT and registry/cohort studies are shown in Supplementary Tables 2 and 3 (available online at jrheum.org). We evaluated the bias for RCT as previously stated, with the bias graph shown in Figure 2 and the detailed evaluation results listed in Supplementary Table 4 (available online at jrheum.org). For the registry and longitudinal cohort studies, all 13 articles had scored at least 5 stars, showing satisfying quality (Figure 2). However, we should note that 3 non-RCT included rheumatoid diseases other than RA[15,19,23], such as spondyloarthritides, psoriasis, and Behçet disease. However, because the majority of the diseases reported in the 2 articles were still RA[15,23] (590 out of 788 patients; 1 article did not present the percentage of each disease), we included these studies for first-step analysis and evaluated the possible bias in the later discussion.

IFX/ETN/ADA/GOL/certolizumab pegol versus placebo in RCT. There were 0 cases of TB confirmed in either the intervention or placebo group in ETN RCT, so metaanalysis was conducted on the other 4 drugs. The RR for IFX, ADA, GOL, and certolizumab pegol were 1.65, 1.01, 1.18, and 1.02, respectively. However, no significant TB risk difference was observed between each TNF-α antagonist and the control group (Supplementary Figure 1, available online at jrheum.org). To reduce the bias, metaanalysis was again performed with RCT considered "possibly biased" excluded,

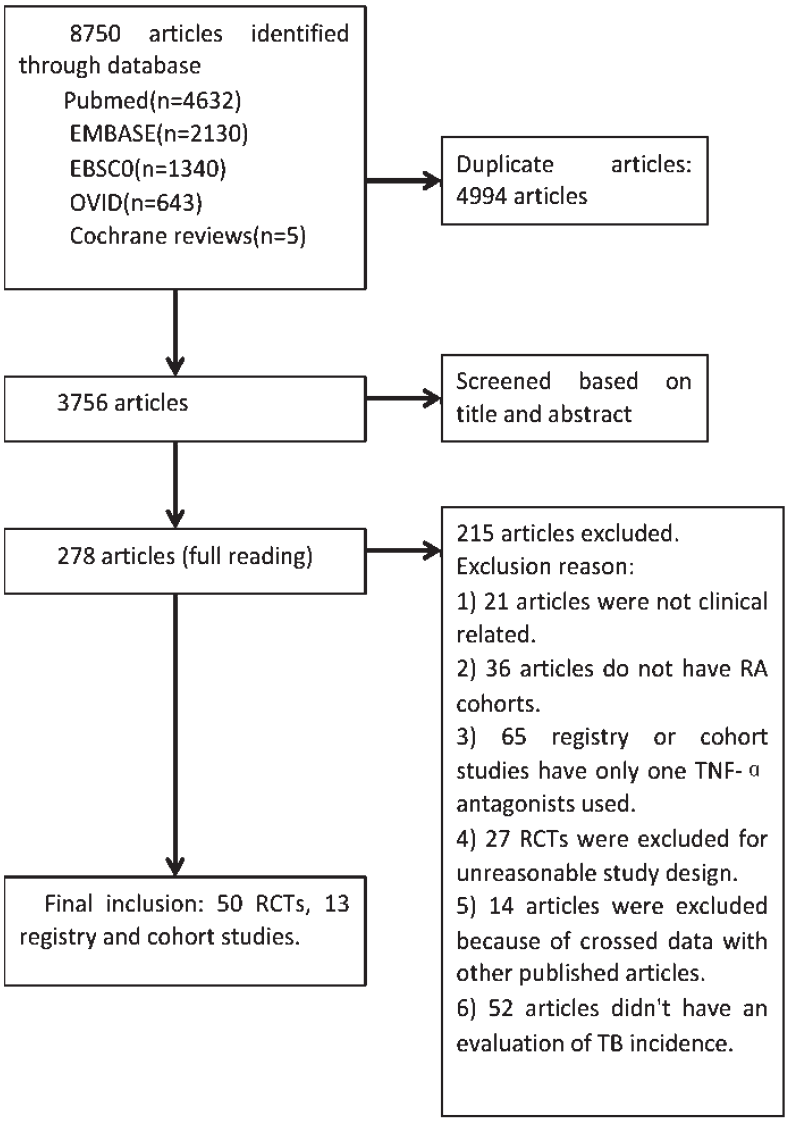


Figure 1. Selection process of the metaanalysis. RA: rheumatoid arthritis; TNF-α: tumor necrosis factor-α; RCT: randomized controlled trials; TB: tuberculosis.

and no significant difference was found between the 2 analyses (Supplementary Figure 2, available online at jrheum.org).

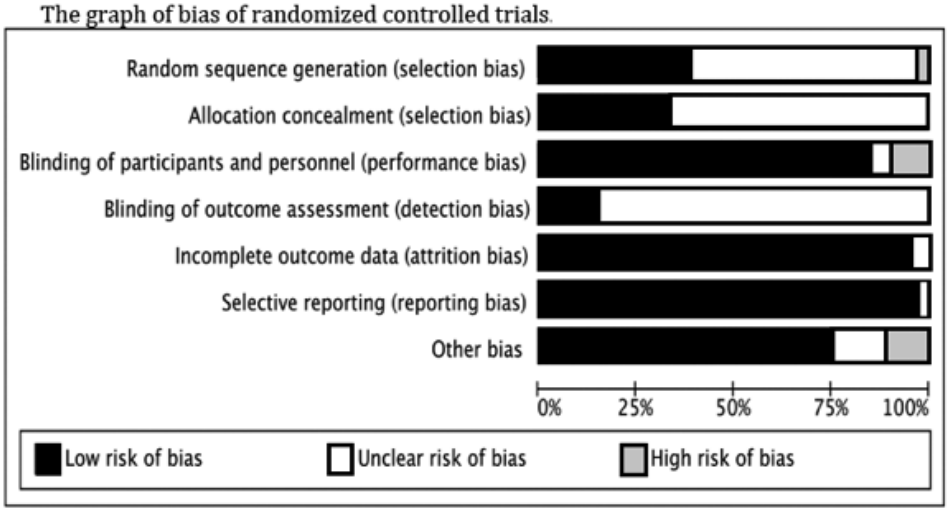
RA versus general population in non-RCT. Of the 13 non-RCT included, 11 noted the local TB incidence rate reported by either the local institution or the study itself[13,15,16,21,24,26,27,28,29,30,31]. The TB risk of patients with RA who were not treated with biologic DMARD (RA/nonbiologic DMARD cohorts) was increased 3.17 times (95% CI 2.12–4.73) when compared with the general population (Figure 3), and the TB incidence rate of patients with RA who received biologic DMARD (RA/biologic DMARD cohorts) showed an increase of 17.07 times (95% CI 13.85–21.04) compared with the general population (Figure 3).

RA/biologic DMARD cohorts versus RA/nonbiologic DMARD cohorts in non-RCT. About 323,709 PY were analyzed to compare the TB risk between the patients with RA who received TNF-α antagonists and the patients with RA who did not. The results of the metaanalysis showed a 4.03 times (95% CI 2.36–6.88) increase of the TB incidence rate in the former group (Figure 3).

IFX versus ETN, ADA versus ETN, and IFX versus ADA cohorts in non-RCT. We further compared the TB risk between the IFX versus ETN, ADA versus ETN, and IFX versus ADA cohorts. Metaanalysis showed that the TB risk of IFX was 2.78 times higher than ETN, while the TB risk of ADA was 3.88 times of ETN, both with statistical significance. The TB risk of IFX was 1.28 times higher than ADA, without statistical significance (Figure 4).

Treated LTBI/RA cohorts versus untreated LTBI/RA cohorts

The graph of bias of randomized controlled trials.



Assessment of Quality of registry and cohort studies

		Selection			Comparability		Outcome Assessment		
Authors	Year	1	2	3	4	5	6	7	Score (out of 9)
Askling (13)	2005	*	*	**			*	*	6
Wallis (14)	2004	*	*		**		*	*	6
Sichletidis (15)	2006	*	*	*			*	*	6
Seong (16)	2007	*	*	*	*	*	*	*	7
Gomez-Reino (17)	2007	*	*	*			*	*	5
Favalli (25)	2009	*	*	*	**	*	*	*	7
Tubach (19)	2009	*	*		*		*	*	5
Dixon (18)	2010	*	*		**		*	*	6
Tam (20)	2010	*	*	*	**		*	*	7
Winthrop (21)	2013	*	*			*	*	*	5
Atzeni (22)	2012	*	*		*		*	*	5
Yoo (23)	2014	*	*	*		*	*	*	6
Arkema (24)	2015	*	*		*		*	*	5

Figure 2. The bias graph of randomized controlled trials, and the quality assessment of the registry and cohort studies. In the bias graph, high risk is graded in the dimension of other bias when the sponsors of the research evolved in the data collection of adverse events. Explanation of asterisks is given in Supplementary Table 1, available online at jrheum.org.

and non-LTBI/RA cohorts. To evaluate the efficacy of LTBI chemoprophylaxis, we analyzed 4 studies in which patients with RA were screened and treated for LTBI before the TNF-α antagonist treatment[15,16,17,20]. We compared the TB risk between patients with LTBI who received chemoprophylaxis and patients with LTBI who did not, and the result showed that the TB risk of the treated LTBI cohorts was 0.35 times (95% CI 0.15–0.82) the untreated LTBI cohorts (Figure 5). Finally, we compared the TB risk between patients with LTBI who received chemoprophylaxis and patients without LTBI, and no significant difference was found (Figure 5).

DISCUSSION

Our metaanalysis included 50 published RCT and 13 registry or longitudinal cohort studies. In the 50 RCT, all 9 ETN RCT reported 0 cases of TB in either the intervention or placebo group, thus no analysis was done on ETN. In 1 IFX RCT[32], a dosage higher than that of common practice was adminis-

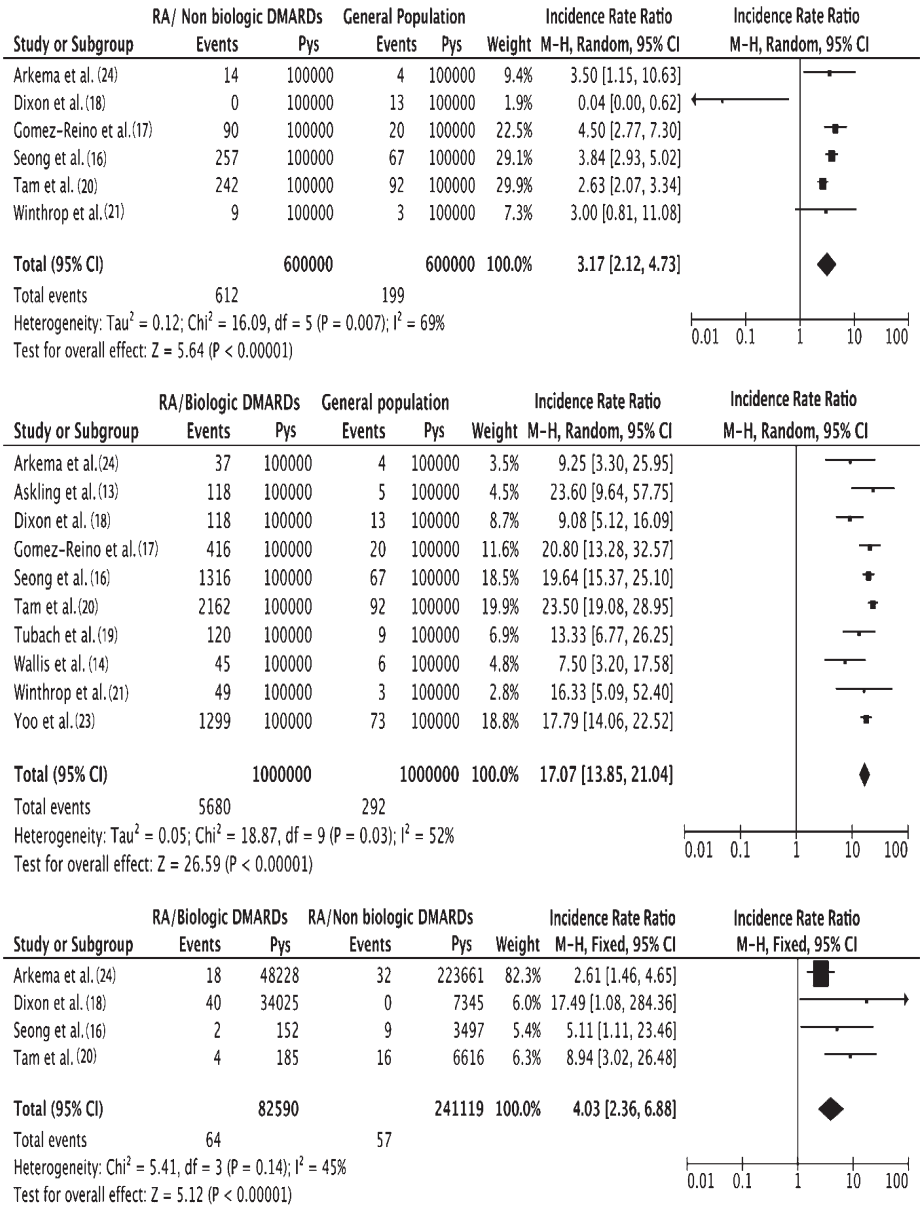


Figure 3. Forest plot of the TB risk ratio of (1) patients with RA not receiving biologic DMARD versus general population, (2) patients with RA receiving biologic DMARD versus general population, and (3) patients with RA receiving biologic DMARD versus patients with RA not receiving biologic DMARD. The TB incidence rates of the general population are cited from the following references: Arkema, *et al*[24], UK Health Protection Agency[26], Cabases, *et al*[27], Seong, *et al*[16], Hong Kong Department of Health[28], Winthrop, *et al*[21], Askling, *et al*[13], Antoine, *et al*[29], US Centers for Disease Control and Prevention[30], and the Korean National Tuberculosis Association[31]. TB: tuberculosis; RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drugs; Pys: patient-years; M-H: Mantel-Haenszel test.

tered and therefore this RCT was excluded to avoid bias in evaluating TB risks. In the 13 non-RCT studies included, there was no GOL or certolizumab pegol cohort. This is likely because these 2 biologics are relatively new, and therefore lack large-scaled registry or cohort studies to compare with other biologics.

We first analyzed the TB risk of each biologic (except ETN) compared with a placebo group in RCT studies. For 4 TNF-α antagonists, TB risk was found to increase only slightly when compared with the placebo group, but all without statistical significance. This result contradicted our prior knowledge that TNF-α antagonists can increase TB risk, but recently another metaanalysis has found no significant difference of TB risk in patients with chronic

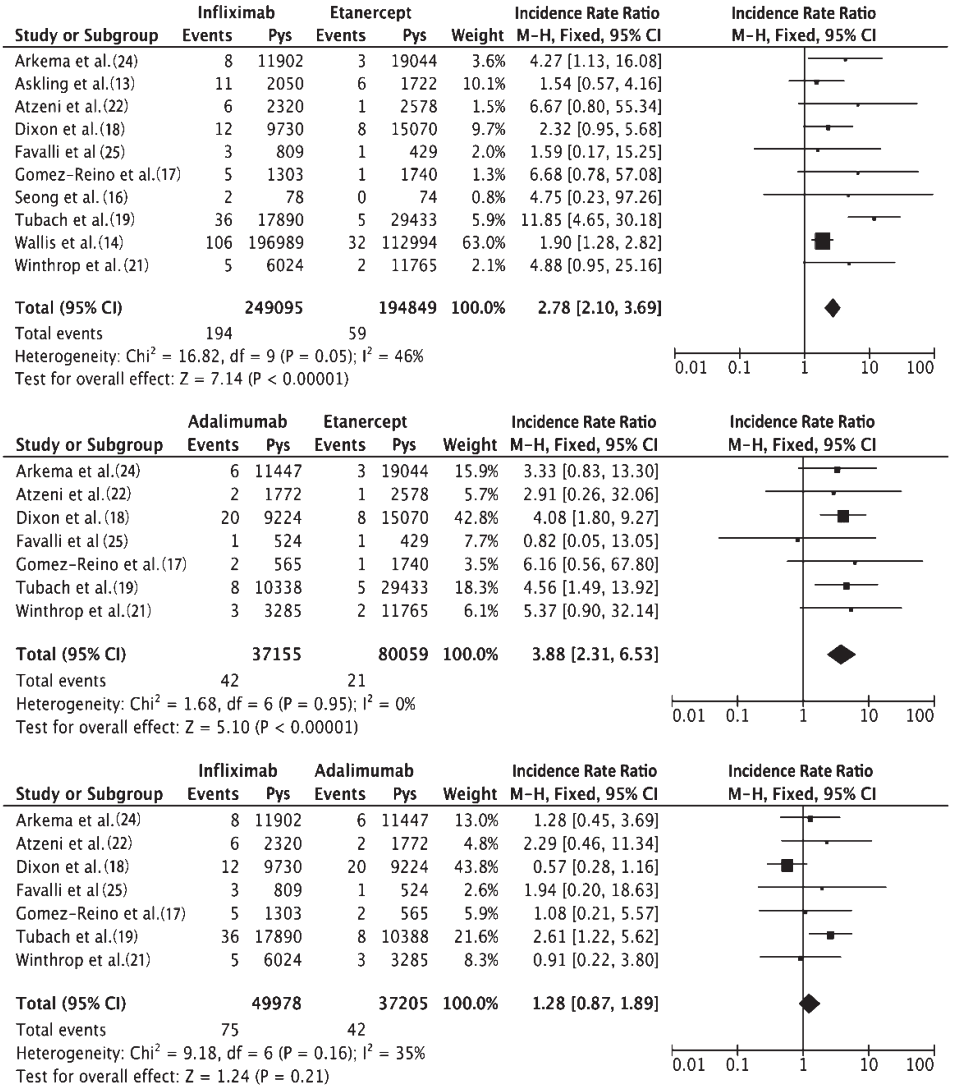


Figure 4. Forest plot of the TB risk ratio of (1) IFX versus ETN, (2) ADA versus ETN, and (3) IFX versus ADA. TB: tuberculosis; IFX: infliximab; ETN: etanercept; ADA: adalimumab; Pys: patient-years; M-H: Mantel-Haenszel test.

immune-mediated inflammatory diseases treated with different TNF-α antagonists as well[33]. One explanation may be the relatively short observed PY in the RCT (21–1081 PY), especially since crossover from placebo to anti-TNF-α treatment at 12 or 14 weeks became common in the recent clinical studies. Because the incidence of TB infection is low overall[6] (5–91.8/100,000 PY), a short followup period makes it hard for RCT to analyze the safety of a drug (80% of the RCT included in our study reported 0 TB cases). Large-scaled registry or longitudinal cohort studies, on the other hand, mostly have a longer observed period (230–506,972 PY), and therefore may be more suitable for the safety analysis of anti-TNF-α drugs.

In registry and cohort studies, RA is shown to increase the risk of TB 3.17 times, and the use of TNF-α antagonists would further increase the TB risk about 4 times in patients with RA. Such results can be explained by the involvement of TNF-α in Mtb infection. Mtb infection may lead to 3 outcomes: (1) TB bacilli cleared, (2) LTBI status, and (3) active TB status. About 30% of patients infected with Mtb will end up in LTBI status, of which 5–10% will eventually develop active TB[34]. TNF-α is a key cytokine in the body's immune response to Mtb infection. It can both enhance the phagocytosis activity of macrophages and assist interferon-γ (IFN-γ)-induced cell apoptosis, eventually clearing the Mtb and forming calcification[35,36]. Another role of TNF-α involves the pathological changes of LTBI, in which the Mtb is restrained inside the granuloma and thus prevented from

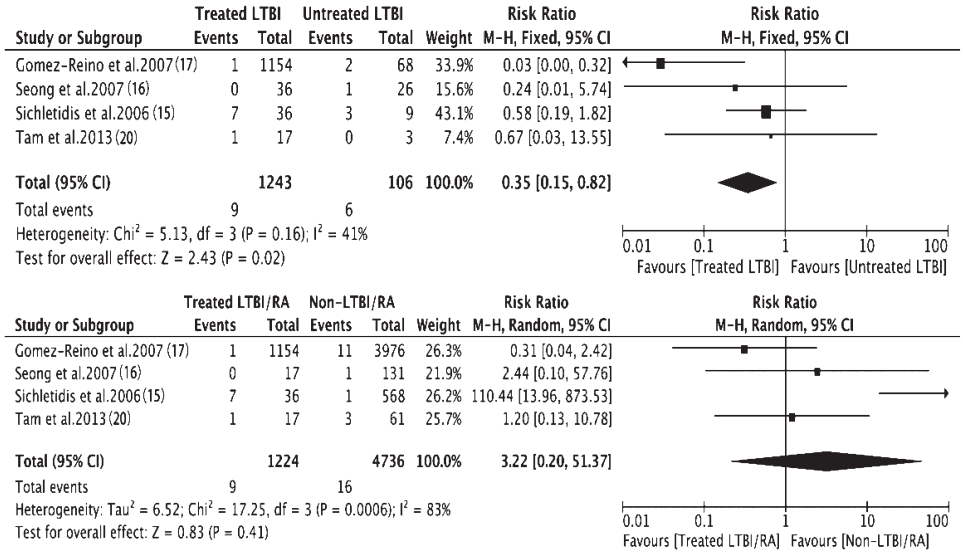


Figure 5. Forest plot of the TB risk ratio of (1) patients with RA/LTBI who received prophylaxis versus patients with RA/LTBI who did not, and (2) patients with RA/LTBI who received prophylaxis versus patients without RA/LTBI. TB: tuberculosis; RA: rheumatoid arthritis; LTBI: latent TB infection; M-H: Mantel-Haenszel test.

disseminating into the blood[36]. Because the stimulation of the macrophages and the IFN-γ are closely related to the integrity of the TB granuloma, TNF-α can enhance this activity and reduce the occurrence of active TB. When a patient is receiving TNF-α antagonist treatment, the TNF-α pathway is inhibited[37] and therefore TB risk elevates.

We further compared the TB risk directly between each biologic. The TB incidence rates of IFX and ADA were 2.78 and 3.88 times, respectively, higher than that of ETN, while the ADA and IFX cohorts showed no statistical difference. This conclusion is in accordance with the previously reported fact that TB incidence rate caused by receptor antibody is generally lower than the monoclonal antibody. The reason may be based on different mechanism of TNF-α antagonists. Monoclonal antibody can inhibit the activation of T cells, thus suppressing sensitization of immune T cells and the release of IFN-γ[38,39], increasing the risk of TB. Another possible reason is that ETN has showed considerably lower complement-dependent cytotoxicity activities compared with IFX and ADA[40], which means that ADA and IFX are more likely to induce apoptosis and cell cycle arrest, resulting in the susceptibility to TB. However, the treatment efficacy is not considered in our study. There has been a study reporting that GOL appears to be inferior in efficacy to ETN, ADA, and certolizumab pegol in treating RA, but no significant difference has been found[41]. How to balance between the treatment efficiency and the risk of TB requires further research.

In 4 of the observational studies, patients were screened and treated for LTBI, though the regimen of the prophylaxis differs among the studies. The result showed that if a person was diagnosed with LTBI and received preventive treatment, the risk of TB would decrease by 65% compared with those who refused the treatment. Further, when compared with patients with RA without LTBI, patients with LTBI receiving the prophylaxis did not have an increased TB risk. The results again pointed out the necessity of LTBI screening and prophylaxis before treatment with TNF-α antagonists. However, this result raised an important question: because some studies recruited patients without LTBI screening or treatment, especially studies initiated before October 2001 (before the US Food and Drug Administration warning and recommendation to screen for LTBI before treatment), could this cause bias to the result? To evaluate this factor, we repeated the metaanalysis in RCT excluding all studies without LTBI screening/treatment and the result showed no significant difference from the previous analysis, suggesting that the unscreened patients with LTBI have limited bias effect on the result (Supplementary Figure 3, Supplementary Table 5, available online at jrheum.org). One probable reason may be that in the RCT, both the intervention and the placebo groups included unscreened patients with LTBI, reducing the bias when evaluating the TB risk of the specific DMARD between the 2 groups. Also, the relatively short observational period may be another reason why the bias is not significant in our metaanalysis. For non-RCT, metaanalysis could not be conducted because only a few studies reported TB incidence rates after LTBI screening and prophylaxis.

Strengths and limitations. Our study distinguishes itself from previous metaanalysis by including both RCT and registry and cohort studies. However, only registry and longitudinal cohort studies are proven suitable for such analysis because

RCT report only limited TB cases. We revealed that TNF-α antagonists increased TB risk by 4 times in patients with RA, and for the first time, to our knowledge, directly compared the TB risks between each TNF-α antagonist in a meta-analysis. We reported that the TB risk of IFX and ADA were 2.78 and 3.88 times, respectively, higher than that of ETN. Another metaanalysis has also reported a lower TB incidence rate of ETN than other drugs, but the study only displayed the incidence rate without directly comparing the drugs[33]. Our study, however, focused on the TB risk comparison between each TNF-α antagonist and reached a result of significant value. Another strength of our article is that this is the first metaanalysis proving that LTBI prophylaxis is indeed effective in reducing the TB risk to that of patients without LTBI.

Our metaanalysis has some limitations. First, many of the included RCT have a relatively short observed PY, which may be the reason that no significant result has been reached. However, we can conclude that the TB risk can be better evaluated in longer observational periods; that is why we chose large-scaled registry and cohort studies for further analysis. Another problem is that 3 articles included in the non-RCT group contained rheumatoid diseases other than RA, but because almost 80% of the overall cases were RA, we consider this a bias that will not influence the result significantly. To further prove our point, we repeated metaanalysis with the excluded 3 articles and the result showed no significant difference from our previous study (Supplementary Figure 4, available online at jrheum.org). Finally, we used crude incidence rates rather than adjusted IRR in our study because only a few studies had reported the adjusted estimates (Supplementary Table 6, available online at jrheum.org). Thus, reporting only adjusted IRR would result in limited data, so metaanalysis of the crude IRR was used in our study instead.

We report a 3.6 times increase of TB risk in patients with RA, and a further 4-fold risk increase in patients with RA using TNF-α antagonists. Also, patients with RA receiving ETN are the least likely to be infected with active TB than those receiving IFX and ADA. Finally, preventive treatment for LTBI is shown to decrease the TB risk by 65%. Our study directly compared the different TB risks among TNF-α antagonists and proved the necessity of prophylaxis use. However, treatment efficacy is not considered in our study, and further research is needed to find the best balance between the risk and efficacy in clinical practice.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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