International Journal of Biomedicine 14(3) (2024) 371-378
http://dx.doi.org/10.21103/Article14(3)_RA1

REVIEW ARTICLE

INTERNATIONAL JOURNAL OF BIOMEDICINE

Risk of Active Tuberculosis During Anti-TNF-α Inhibitor Use to Treat Rheumatoid Arthritis: A Meta-Analysis of Randomized Controlled Trials

Hanxin Wu[1], Li Peng[1], Weijie Ma[1], Liangyu Zhu[1], Xinya Wu[1], Li Gao[1], Lei Zhong[1], Jieqin Song[1], Bingxue Li[1], Xun Huang[1], Rui Yang[1], Fukai Bao[1,2*], Aihua Liu[1,2*]

[1]*Evidence-Based Medicine Team, The Institute for Tropical Medicine, Faculty of Basic Medical Science, Kunming Medical University, Kunming 650500, Yunnan, China*
[2]*Yunnan Province Key Laboratory of Children's Major Diseases Research, The Affiliated with Children's Hospital, Kunming Medical University, Kunming 650030, Yunnan, China*

Abstract

Background: Given the wide application of TNF-α inhibitors for the treatment of rheumatoid arthritis (RA), more active tuberculosis cases have been reported in patients with RA. This meta-analysis was performed to evaluate the risk of active tuberculosis (TB) in RA patients undergoing treatment with TNF-α inhibitors.

Methods and Results: Thirty randomized controlled trials (RCTs), comprising 18,640 patients, were included in the meta-analysis after searching PubMed, EMBASE, and Web of Science databases. Overall, there was a higher risk of active TB in patients with RA undergoing treatment with TNF-α inhibitors than in the control group (Peto OR, 2.57; 95%CI, 1.42-4.66; *P*=0.002).

Conclusion: Our meta-analysis showed that RA patients treated with TNF-α inhibitors had a higher risk of developing active TB. Tuberculosis screening should be performed before and during the use of TNF-α inhibitors in these patients.(**International Journal of Biomedicine. 2024;14(3):371-378.)**

Keywords: rheumatoid arthritis • tuberculosis • TNF-α inhibitor • meta-analysis

For citation: Wu H, Peng L, Ma W, Zhu L, Wu X, Gao L, Zhong L, Song J, Li B, Huang X, Yang R, Bao F, Liu A. Risk of Active Tuberculosis During Anti-TNF-α Inhibitor Use to Treat Rheumatoid Arthritis: A Meta-Analysis of Randomized Controlled Trials. International Journal of Biomedicine. 2024;14(3):371-378. doi:10.21103/Article14(3)_RA1

Abbreviations

DMARDs, disease-modifying antirheumatic drugs; **csDMARDs**, conventional synthetic DMARDs; **tsDMARDs**, targeted synthetic DMARDs; **bDMARDs**, biological DMARDs; **RA**, rheumatoid arthritis; **RCTs**, randomized controlled trials; **TB**, tuberculosis; **TNF-α**, tumor necrosis factor-alpha.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease with joint damage as its main clinical feature, leading to disability and even death. [1] RA is associated with environmental factors, immune status, and gene mutation.[2] The synovial fluid and tissue of RA patients contain a large number of inflammatory cells and cytokines, which can lead to synovial hyperplasia and destruction of the joints and articular cartilage.[3] Treatment of RA includes immunosuppressive therapy, hormone therapy, and joint surgery. Disease-modifying antirheumatic drugs (DMARDs) are widely used in clinical settings because of their beneficial therapeutic effects.[4] In 2016, the European League Against Rheumatism (EULAR)[5] divided DMARDs into three categories: conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), and biological DMARDs (bDMARDs). Among them, bDMARDs are genetically engineered protein molecules that target host biological factors and delay the development of joint damage caused by RA; hence, they are considered

special treatments.[6] bDMARDs include TNF-α inhibitors (adalimumab, certolizumab pegol, golimumab, infliximab and etanercept),[7] anti-IL-6 receptor antibodies (sarilumab and tocilizumab), and anti-IL-1 receptor antibodies (anakinra). Although bDMARDs can effectively relieve the symptoms of RA, it has been reported that the use of bDMARDs, such as TNF-α inhibitors, can increase the risk of infection and adverse side effects.[8] When RA patients undergo TNF-α inhibitor treatment, it is important to prevent the occurrence of active TB.

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis that can cause multiple organ infections.[9] Thousands of people are infected annually with TB bacteria. It has been reported that in RA patients treated with TNF-α inhibitors, the incidence of TB is 18 times higher than that in patients treated with non-biological agents.[10] Therefore, evaluation of active TB risk is essential for the clinical treatment of RA patients. Some studies have indicated that the use of TNF-α inhibitors may increase the likelihood of active TB infection, whereas others have shown that it does not increase the probability of active TB infection. Considering the contradictory results of numerous studies, we conducted a systematic review and meta-analysis of currently published randomized controlled trials (RCTs) to assess the association between the incidence of active TB and the use of TNF-α inhibitors. As a powerful statistical tool, meta-analysis can overcome the limitations of individual studies with different sample sizes and generate better estimations.[11]

This meta-analysis was performed to evaluate the risk of active tuberculosis (TB) in RA patients undergoing treatment with TNF-α inhibitors.

Patients and Methods

Inclusion and eligibility criteria: Studies were eligible for inclusion in the meta-analysis if all the following criteria were met: (1) randomized controlled trials were published up to March 2024; (2) the patients were diagnosed with RA and treated with TNF-α inhibitors according to the 1987 ACR standard or the 2010 ACR/EULAR revised standard;[12,13] and (3) the study design was clinical randomized controlled studies.

Exclusion criteria: (1) Abstract, letter, systematic review, case report, meta-analysis, retrospective studies, and non-clinical studies; (2) studies were not written in English; (3) patients were not treated with TNF-α inhibitors; (4) the control group was not included in the study, the experimental group was not double-blinded, and the statistical methods used were incorrect.

Study Selection and Data Extraction

We included RCTs that used TNF-α inhibitors (adalimumab, certolizumab, etanercept, golimumab, or infliximab) as induction or maintenance therapies for RA patients and reported the occurrence of infectious adverse events. A systematic literature search was performed using PubMed, EMBASE, and Web of Science databases. The search included publications from their inception until March 2024. The eligibility assessment was independently conducted by two investigators. Disagreements were resolved by seeking the opinions of a third investigator. References were managed using NoteExpress (version 3.7.0.9258, Beijing Aegean Software Co. Ltd, Beijing, China, https://www.inoteexpress.com). After a thorough screening of abstracts, irrelevant and duplicate articles were excluded. The remaining full-text articles were retrieved and reviewed to identify the eligible studies. The review was per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14]

Date Extraction Process and Quality Assessment

Two investigators independently retrieved the data from all included articles and compared the results to avoid bias in the data abstraction process. All data were assessed for internal consistency, and disagreements were resolved through discussion. The following items were recorded for each study: first author, year of publication, country, total number of cases, study design, type of TNF-α inhibitor, and number of TB-infected cases. All RCTs were assessed using the Cochrane risk-of-bias tool.

Statistical analysis

In accordance with the Cochrane Handbook, a Chi-squared-based Q-statistic test and I^2 statistical analysis were performed to assess the heterogeneity of the included trials. The assessment of selective outcome reporting or publication bias was conducted using a funnel plot, alongside Begg's and Egger's tests. Inter-study heterogeneity was evaluated using the chi-square-based Q-statistic at a significance level of 0.10. Additionally, the I^2 statistic was computed to quantify the proportion of variation among studies attributable to heterogeneity, rather than to random chance or fixed effects (Mantel-Haenszel method), and was used to calculate the pooled hazard ratios (HRs) and 95% confidence intervals (CI). The negative value of I^2 is equal to zero; hence, I^2 falls within the range of 0%–100%. I^2 values below 40% are considered to indicate "insignificant heterogeneity," while values exceeding 75% are deemed to suggest considerable heterogeneity. When significant heterogeneity was observed, a random-effects model was used; otherwise, a fixed-effects model was adopted.[15]

We used four TNF-α inhibitors for subgroup analysis to analyze the different TB-infected cases among the four types of TNF-αinhibitors.

The statistical methods align with the previously described ones. For statistical analysis, we utilized Review Manager (version 5.3, RevMan Software Co. Ltd, UK), the R software environment, and the meta package for R. All *P*-values were reported as two-tailed, and *P*-values <0.05 were considered statistically significant.

Results

Study Characteristics

Initially, 911 studies were included in the meta-analysis. A total of 605 studies were further analyzed after excluding duplications, reviews, abstracts, cases, meetings, and comments. Finally, 30 RCTs were included in our

meta-analysis by reading the title, abstracts, and full text after excluding studies with no control group, data errors, cohort studies, and case reports. The PRISMA flow diagram of study selection is presented in Figure 1. These 30 RCTs used adalimumab (n=6), golimumab (n=7), infliximab (n=8), certolizumab pegol (n=7), and etanercept (n=2) to treat RA. All RCTs reported the adverse effects of anti-TNF-α therapy, including death and bacterial infection. The mean age of the participants ranged from 30 to 65. The duration of the RCTs ranged from 22 weeks to 193 weeks. The publication dates ranged from 2004 to 2024. The characteristics of the included studies are summarized in Table 1.

Table 1.

The characteristics of the included studies.

Study	Biologic agent		Study duration	Patients	Patients with TB
Kavanaugh et al., 2013 [31]	ADA+MTX	PBO+MTX	26 weeks	1032	1
Bingham et al., 2015 [32]	GLM+MTX	PBO+MTX	112 weeks	592	3
Yonekura et al., 2017 [33]	ETN	CON	132 weeks	698	1
Chen et al., 2008 [34]	ADA+MTX	MTX	12 weeks	47	1
St Clair et al., 2004 [35]	IFX+MTX	PBO+MTX	54 weeks	1040	4
Keystone et al., 2008 [36]	CZP+MTX	PBO+MTX	52 weeks	982	5
Keystone et al., 2010 [37]	GLM+MTX	PBO+MTX	52 weeks	345	1
Hsia et al., 2013 [38]	GLM+MTX	PBO+MTX	52 weeks	2210	5
Breedveld et al., 2006 [39]	ADA+MTX	MTX	104 weeks	525	1
Huang et al., 2009 [40]	ADA+MTX	MTX	24 weeks	302	3
Kim et al., 2013 [41]	IFX	PBO	30 weeks	138	0
Kremer et al., 2010 [42]	GLM+MTX	PBO+MTX	48 weeks	643	2
Kay et al., 2008 [43]	GLM+MTX	PBO+MTX	52 weeks	172	0
Kay et al., 2015 [44]	GLM	PBO	160 weeks	2292	15
Smolen et al., 2012 [45]	GLM	PBO	160 weeks	236	1
Smolen et al., 2015[46]	CZP+MTX	PBO+MTX	24 weeks	619	6
Bi et al., 2018 [47]	CZP+MTX	PBO+MTX	24 weeks	429	8
Klareskog et al., 2011[48]	ETN	CON	260 weeks	549	0
Schiff et al., 2008 [49]	IFX+MTX	PBO+MTX	52 weeks	275	2
Husni et al., 2022 [50]	GLM	PBO	112 weeks	584	3
Nam et al., 2014 [51]	IFX+MTX	MTX	78 weeks	112	1
Ruperto et al., 2007 [52]	IFX+MTX	PBO+MTX	52 weeks	112	1
Emery et al., 2017 [53]	CZP+MTX	PBO+MTX	52 weeks	876	1
Taylor et al., 2017 [54]	ADA	PBO	24 weeks	818	1
Fleischmann et al., 2019 [55]	ADA+MTX	PBO+MTX	26 weeks	978	0
Westhovens et al., 2006 [56]	IFX+MTX	MTX	22 weeks	1084	4
Smolen et al., 2009 [57]	CZP+MTX	PBO+MTX	24 weeks	619	5
Abe et al., 2006 [58]	IFX+MTX	PBO	36 weeks	147	0
van Vollenhoven, et al., 2011[59]	ADA	PBO	38 weeks	155	1
Kang et al., 2018 [60]	CZP+MTX	PBO+MTX	24 weeks	127	2

CZP: Certolizumab pegol; GLM: Golimumab; ADA: Adalimumab; GLM: Golimumab; IFX: Infliximab; ETN: Etanercept; PBO: placebo; MTX: methotrexate.

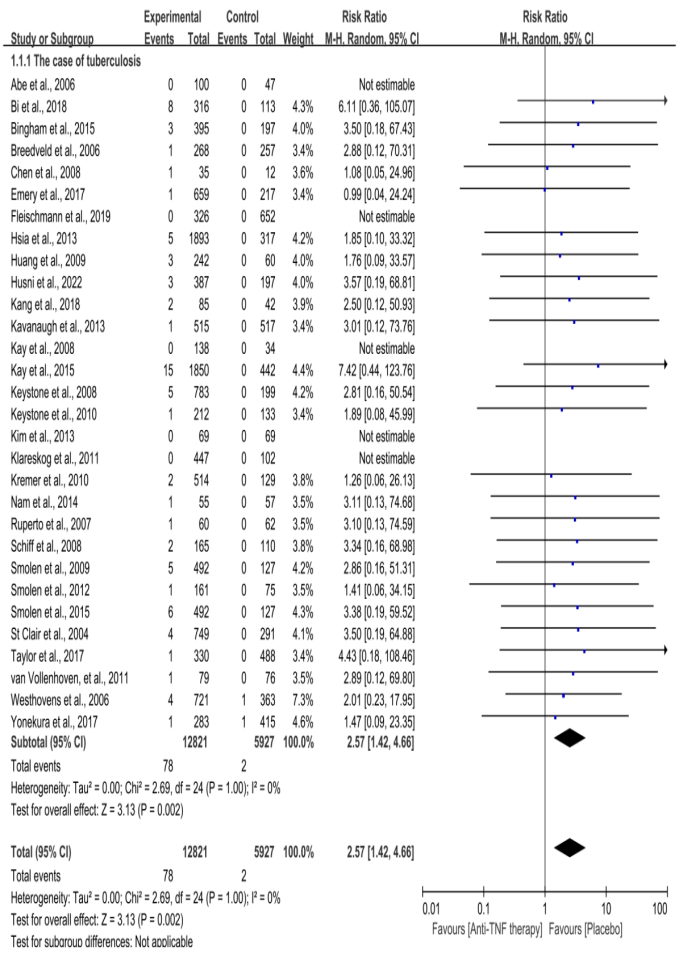

Fig.2. *Meta-analysis results of published RCTs on the risk of developing active TB during treatment with TNF-α inhibitors.*

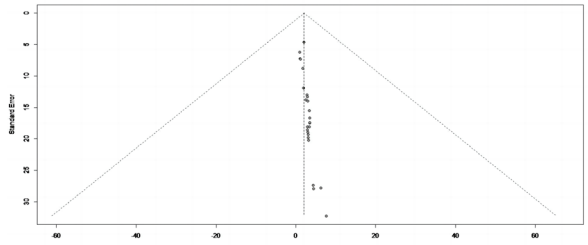

Fig.3. *Funnel plot of TB infection.*

The Risk of Active TB during Treatment with TNF-α Inhibitors

Patients with RA undergoing anti-TNF-α therapy had a higher risk of active TB than those in the control group (Peto OR, 2.57; 95%CI, 1.42-4.66; *P*=0.002; Figure 2). I^2 of 0% was detected. A funnel plot was used to assess the potential publication bias, and the results showed no significant risk of publication bias (Figure 3). Sensitivity analysis was used to assess the risk of TB; the results did not materially change (fixed-effects, OR: 2.84, 95% CI: 1.57–5.13 ; Random-effects, OR 2.85, 95% CI: 1.56–5.20) (Table 2).

Nevertheless, the statistical power of this analysis is often limited, and as a result, we cannot rule out clinically significant differences in the progression of tuberculosis under anti-TNF-α therapy.

Table 2.

Meta-analysis results.

Study	n	Fixed-effects model		Random-effects mode		Tests of homogeneity		
		OR	95%CI	OR	95%CI	Q	I^2	P
RCTs	30	3.07	1.69-5.59	2.85	1.56-5.20	2.37	0	1
Adalimumab	6	2.46	0.67-9.04	2.44	0.67-8.93	0.46	0	0.99
Certolizumab pegol	7	3.31	0.95-10.34	2.86	0.85-9.57	0.75	0	0.98
Golimumab	7	3.51	1.13-10.89	3.08	0.98-9.67	0.90	0	0.99
Infliximab	8	2.84	0.80-10.07	2.80	0.79-9.93	0.13	0	1
Etanercept	2	4.38	0.18-107.92	4.38	0.18-107.92	/	/	/

RCTs: randomized controlled trials; OLE: open-label extension; OR: odds ratio; CI: confidence interval.

Discussion

Recently, TNF-α inhibitors have been proven to offer significant benefits to RA patients in relieving symptoms and improving the quality of life.[16] However, adverse effects of anti-TNF-α therapy are common.[17] Some studies reported only a few cases or one case and, thus, were not representative. Currently, studies have reported conflicting results. Some studies have indicated that the use of TNF-α inhibitors does not lead to tuberculosis, while others have reported cases of tuberculosis associated with their use. Hence, it remains unclear whether treatment with TNF-α inhibitors increases the risk of active tuberculosis. Further clarification is needed regarding whether the use of TNF-α inhibitors in treating RA leads to an increased incidence of tuberculosis.

Randomized controlled trials have a superior ability for causal inference compared to observational studies, enabling more accurate identification of the impact of interventions on outcomes.[18] We searched the databases and included 30 RCTs, including 18,640 cases. A network meta-analysis was conducted to assess the risk of tuberculosis among RA patients treated with five different types of TNF-α inhibitors. We found that the possibility of active TB in RA patients treated with TNF-α inhibitors was higher than that in the control group (OR 2.85, 95% CI: 1.56–5.20). The lack of significant heterogeneity among studies and the stability of results from sensitivity analyses led us to consider the results of this meta-analysis reliable.

The meta-analysis results were contingent on factors such as the quality of the included studies and the presence of study heterogeneity.[19] The variability in treatment duration with TNF-α inhibitors, differences in individual immune status, and the potential for patients to receive additional therapies during the treatment period could lead to inconsistencies in the results of randomized controlled trials. The incidence of tuberculosis has been declining over the years, which is attributed in part to latent tuberculosis screening and treatment protocols implemented before the initiation of TNF-α inhibitors. However, regardless of whether a TNF-α inhibitor was used, there appeared to be an increased risk of TB development. Therefore, the use of TNF-α inhibitors may be a risk factor. A meta-analysis by Minozzi et al. included 71 RCTs involving 22,760 participants taking TNF-α inhibitors and found that there was a statistically significant increase in active TB in these patients.[20]

TNF-α stimulates fibroblast growth and induces the release of collagenase and prostaglandin from adherent synovial cells and fibroblasts.[17] In RA patients, a high level of TNF-α destroys the bone and cartilage. Our meta-analysis showed that the risk of active TB in patients with RA treated with TNF-α inhibitors was higher than that in the controls. Pro-inflammatory cytokines such as TNF-α can stimulate osteoclastogenesis and bone erosion.[21] The increase of TNF-α can lead to the expression of receptor activator of nuclear factor kappa-B ligand (RANKL), which could promote osteoclast differentiation.[22] TNF-α inhibitors can inhibit the production of pro-inflammatory factors, reduce the production of osteoclasts, and reduce bone erosion to relieve the symptoms of RA.[23] It has been reported that in patients with RA using TNF-α inhibitors, TB-causing bacteria cannot be controlled in macrophages, and granulomas cannot be maintained for a long time.[24] Therefore, RA patients with long-term use of TNF-α inhibitors should be regularly tested for TB, and prophylactic anti-TB drugs should be administered. TNF-α inhibitors can affect T cell function and increase the risk of viral diseases.[20] TNF-α inhibitors can also affect the ability of macrophages to phagocytose and clear pathogens, change the expression of chemokine receptors, and affect the deformation and movement of macrophages.[25]

Recently, with the widespread use of TNF-α inhibitors, more related adverse events have been reported, such as TB, other bacterial infections, and cancer.[26] The different infection rates caused by other types of TNF-α inhibitors should also be considered. TNF-α is an important cytokine that mediates the immune response. Previously, both anti-infection immunity and immunopathological damage in TB immunity.[27] TNF-α inhibitors would translate latent TB infections into active TB.[28] To decrease the rate of active TB, it is necessary to test for TB using the tuberculin skin test and IFN-γ release assay, both before and during the use of TNF-α inhibitors.[29,30]

Although our meta-analysis found a higher risk of active TB in patients with RA undergoing anti-TNF-α therapy, our study has some limitations. Because only a few RCTs were included, some important data was inevitably missed. Furthermore, we should distinguish between the epidemic and non-epidemic areas of TB and analyze the respective incidence rates of TB separately to provide a reference for the prevention of TB in different areas. Future studies should consider these aspects to strengthen our results further.

This study was registered with PROSPERO (No. CRD42022377240)

Competing Interests

The authors declare that they have no competing interests.

Sources of Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 82160304, 81860644, and 81560596) and the Natural Foundation of Yunnan Province [No. 2019FE001 (-002) and 2017FE467 (-001)].

Acknowledgments

The research project was conducted under the supervision of Professor Fukai Bao, MD, PhD, and Professor Aihua Liu, MD. The funding institutions (the National Natural Science Foundation of China and the Natural Foundation of Yunnan Province) had no role in the study design or implementation of the manuscript.

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Correspondence:

Professor Aihua Liu, Evidence-Based Medicine Team, Institute for Tropical Medicine, Faculty of Basic Medical Science, Kunming Medical University, Kunming 650500, Yunnan, China, liuaihua@kmmu.edu.cn (Aihua Liu),

Professor Fukai Bao, Evidence-Based Medicine Team, Institute for Tropical Medicine, Faculty of Basic Medical Science, Kunming 650500, Yunnan, China, baofukai@kmmu.edu.cn (Fukai Bao)