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The Risk of Tuberculosis in Patients with Rheumatoid Arthritis Treated with Infliximab as Compared to Etanercept: Systematic Review and Metanalysis

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Abstract

Introduction: *Tumor Necrosis Factor-alpha (TNF-α) inhibitors may predispose patients to tuberculosis (TB) infection during the treatment of rheumatoid arthritis (RA). This systematic review analyzes the risk of tuberculosis in RA patients treated with anti-TNF-α antibodies, infliximab compared to etanercept.*

Methods: *A systematic review was conducted using the PubMed, Cochrane, and Embase databases to identify relevant data between 2015 and 2022. Pooled effect estimates of log Risk Ratios were analyzed, bias analysis was conducted, and the potential effects of screening and prophylaxis were reviewed.*

Results: *37 studies identified were screened, and only observational studies met the inclusion criteria. Both infliximab and etanercept patients show the same risk ratio to develop tuberculosis. Bias analysis was performed, and two of four studies showed a moderate risk of bias. Screening and prevention for latent TB infection (LTBI) did not decrease the risk of TB reactivation in two of the three studies referring to these data.*

Discussion: *Infliximab does not pose a higher risk of developing TB than etanercept use in patients with RA. LTBI screening and prophylaxis alone may be insufficient preventive steps for TB development in these patients. Further research in this field is warranted to reduce TB risk, particularly in countries with a high incidence of TB.*

Introduction

Rheumatoid Arthritis (RA) is a chronic rheumatological autoimmune disease with a higher prevalence in industrialized and developed countries (Finckh et al., 2022). Corticosteroids were the initial treatment proposed to relieve the symptoms and reduce the inflammation. Disease-modifying anti-rheumatic drugs (DMARDs) were introduced just for severe cases. With time, a new class of RA drugs was presented as Tumor Necrosis Factor-alpha (TNF-α) inhibitors (Smolen et al. 2007).

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TNF-α is a major cytokine involved in inflammation - essential for the pathogenesis of RA. Two types of TNF-α inhibitors are used for RA treatment: Infliximab and Etanercept. Infliximab is a monoclonal antibody that neutralizes TNF-α by binding and impairing this cytokine. On the other hand, Etanercept is a biological TNF inhibitor that competes with soluble TNF-α, binding to TNF-α receptors (Ehlers. 2005). Usually, these drugs are recommended for refractory cases of unresponsive treatment with the traditional DMARDS (Hyndman, I. 2016).

The use of TNF-α inhibitors is associated with a higher risk of infections, particularly tuberculosis (TB), compared to synthetic DMARDs (Zhang et al., 2017) due to the protection TNF plays against the Mycobacterium tuberculosis (Scrivo et al., 2014). TB is the ninth leading cause of death worldwide, according to the World Health Organization (WHO, 2021).

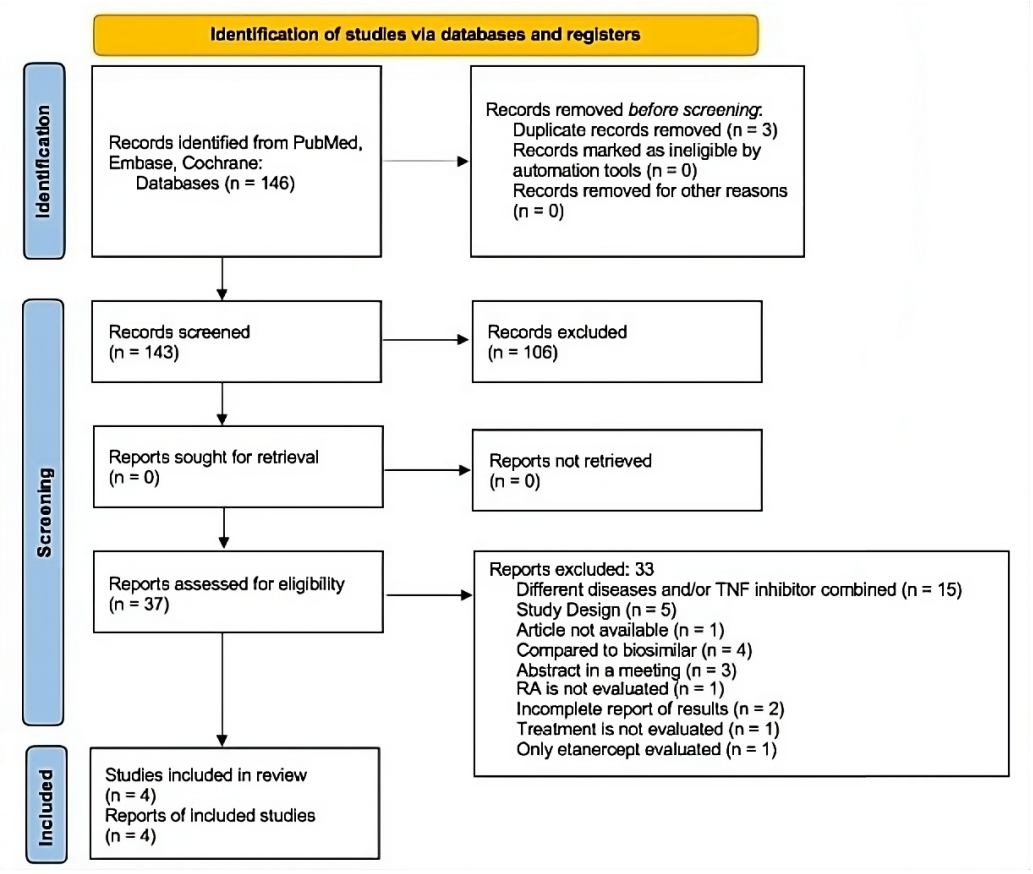

Figure 1: *PRISMA flow diagram for study identification, screening, and inclusion process.*

Indeed, the high incidence of TB poses a relevant health problem for the use of TNF-α inhibitors. The medication may cause the maintenance of Mycobacterium tuberculosis besides the progression of active TB infection. Whereas Infliximab and Etanercept have distinct mechanisms of action, it is plausible that these drugs mediate different effects on the activation of latent or active TB.

Ai et al. (2015) and Minozzi et al. (2016) reviewed the association between TNF-α inhibitors and TB incidence in publications until 2014. Therefore, this review aims to evaluate the risk of TB acquisition or reactivation in patients with RA who underwent treatment with infliximab or etanercept from studies published between 2015-2022.

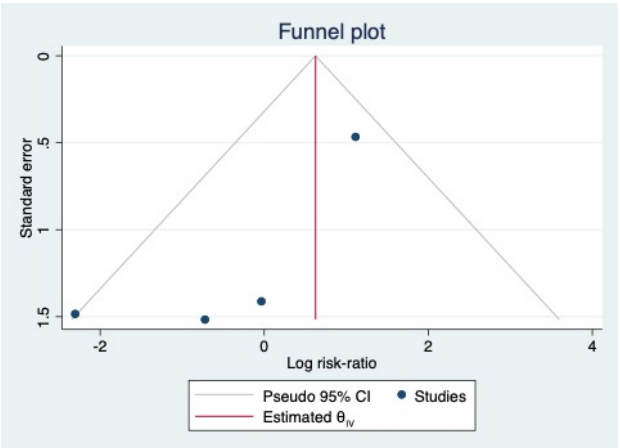

Figure 2: *Assessment of publication bias with funnel plot.*

Materials and Methods

Study Design and Eligibility Criteria

This review was conducted according to the PRISMA 2020 guideline (Page et al., 2021). We included studies that evaluated patients with RA treated with infliximab (intervention) or etanercept (control) and had an outcome of TB acquisition or reactivation. Observational and randomized clinical trials were included.

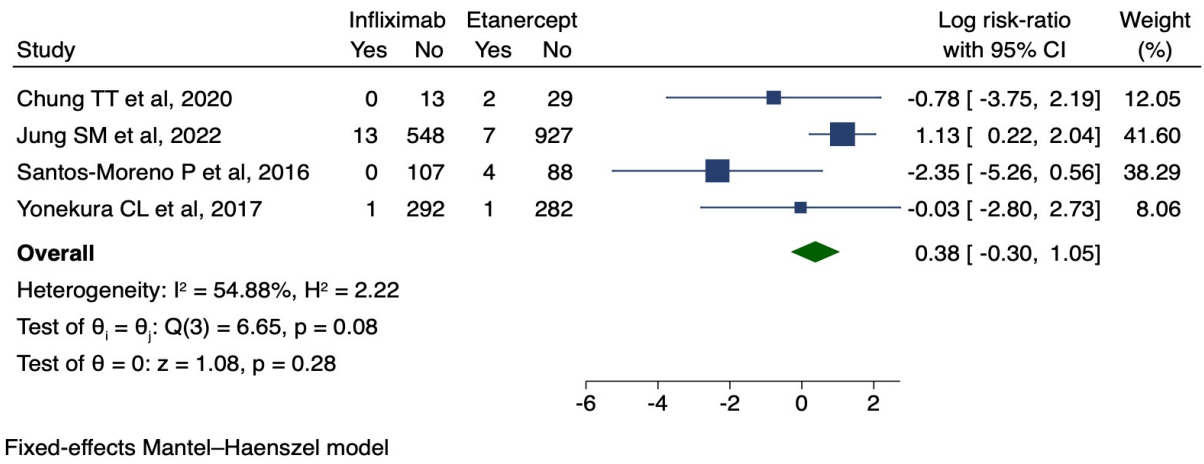

Figure 3: *Forest plot of the Relative Risk of TB (Yes/No) in patients treated with infliximab (treatment) compared to those treated with etanercept (control).*

Information Sources

PubMed, Cochrane, and Embase were the databases queried until September 2022.

Research Strategy

Two independent teams searched the databases using MESH terms "infliximab," "etanercept," "rheumatoid arthritis," and "tuberculosis," along with their synonyms. The complete search strategy is described in Appendix 1 (supplementary material). Only studies published in English between 2015 and 2022 were included. Ongoing and unpublished studies were also excluded.

Selection Process

The studies were selected according to the PRISMA guidelines. The articles obtained using the search strategy were uploaded to Rayyan (http://rayyan.qcri.org), a free web tool for initial screening (Ouzzani et al., 2016).

Researchers were divided into two teams, with two people on each team. They screened all the references and excluded duplicates using Rayyan. During the selection process, each team was blinded to the selection of the other team. The initial screening strategy reviewed titles and abstracts. Then, an assessment of the full text allowed the close examination and determination of whether the contents of each study met the predefined inclusion criteria for review. Two researchers resolved disagreements between the teams regarding a study's inclusion by discussing the rationale behind the decision-making process and reaching a consensus.

Data Collection Process

All the authors collected data independently using an online spreadsheet specially designed for this review. All authors reviewed the spreadsheet to guarantee adequate data collection for each article. A web meeting with all the authors discussed the final data collection.

Data Items

The data included the following: first author, publication year, country, study design, number of patients in the study, number of participants receiving infliximab and etanercept, number of TB cases in each group, relative risk for TB acquisition or reactivation, frequency of TB screening tests, and frequency of participants receiving TB prophylaxis.

Study Risk of Bias Assessment

Two researchers independently assessed the risk of bias for observational studies using the tool proposed by Hoy et al. (2012). The tool evaluates nine aspects of the study, shown in Appendix 2 (supplementary material).

Results

Study Selection

After duplicate exclusion, the initial search identified 143 studies from PubMed, Embase, and Cochrane databases. After screening the titles and abstracts, 106 studies were excluded, and the remaining 37 studies were evaluated according to the eligibility criteria. Four studies were included after full-text

Articles			Infliximab		Etanercept	
Study	Country	Type of Study	Total (n)	TB cases (n)	Total (n)	TB cases (n)
Santos-Moreno, P. et al, 2016	Colombia	Observational retrospective	107	0	92	4
Yonekura CL et al, 2017	Brazil	Observational retrospective	293	1	283	1
Chung TT et al, 2020	Hong Jong	Observational retrospective	13	0	31	2
Jung SM et al, 2022	South Korea	Observational retrospective	561	13	934	7

n: number, **TB:** Tuberculosis, **IFX:** Infliximab, **ETN:** Etanercept.

Table 1: *Study characteristics. n= number; TB= tuberculosis; IFX= infliximab; ETN = etanercept.*

assessment. The screening process is illustrated in Figure 1.

Study Characteristics

Four studies were included after full-text assessment. The four studies were observational (Santos-Moreno et al., 2016; Yonekura et al., 2017; Chung et al., 2020; Jung et al., 2022). The study's characteristics are presented in Table 1.

Risk of Bias in Studies

Two studies showed a score corresponding to a low risk of bias, and two had a moderate risk of bias, as shown in Table 2. Bias assessment was also performed by funnel plot analysis, as shown in Figure 2.

Risk for Tuberculosis in Patients Treated with Infliximab or Etanercept

Of the 37 included studies, only four observational studies reported information directly between TB incidence in patients treated with infliximab and etanercept. The total number of participants from all four observational studies was 974 in the infliximab group and 1,246 in the etanercept group. The combined reported active TB incidences in the infliximab and etanercept groups were 14 in both groups. A forest plot was created using the Stata software.

Fixed effects model using the Mantel-Haenszel method was used to analyze the log Risk Ratio of the included studies (Figure 3). The risk ratio of developing TB for infliximab compared to the etanercept group was 1.08, and there was no difference in either group (p=0.28) (Figure 3). Based on this analysis, infliximab-treated RA patients present the same Risk Ratio of developing TB as compared to etanercept-treated patients. The results differ from those from the literature (Ai et al., 2015; Minozzi et al., 2016), probably due to the small number of publications that fulfill the inclusion criteria.

Tuberculosis Screening and Prophylaxis

Three studies in our analysis (Yonekura et al., 2017; Chung et al., 2020; Jung et al., 2022) described screening for latent TB infection (LTBI) in almost 100% of the patients. All patients who tested positive for LTBI were prophylactically treated with isoniazid and/or rifampin. Patients received treatment for TB before or concomitantly with biological therapy. Yonekura et al. (2017) showed that the incidence of TB after infliximab or etanercept treatment decreased in patients with LTBI who received prophylactic therapy. Jung et al., 2022 showed that the incidence rate of TB in patients undergoing biological treatment with prophylaxis tended to be lower (but with no statistical difference) than in patients without evidence of LTBI. Chung et al. (2020) identified etanercept and previous TB infection as independent risk factors, especially in RA cases treated with anti-TNF-α.

Discussion

Infliximab and Etanercept are part of the anti-TNF drugs used in the treatment regimen for patients with RA. Previous studies found that anti-TNF drugs were associated with TB infection in patients with RA. Thus, it is crucial to study the association between infliximab and etanercept with the risk of TB infection in RA patients. Our review aimed to investigate the risk of TB infection in RA patients receiving infliximab compared to those receiving etanercept. Four observational studies involving 974 in the infliximab group and 1,246 in the etanercept group meet the inclusion criteria. This review showed no difference in developing TB infection in patients with RA treated with infliximab compared to etanercept.

The last two reviews and meta-analyses included studies published until 2014 (Ai et al., 2015; Minozzi

et al., 2016). For instance, Minozzi et al. (2016) reviewed 71 RCTs that used any of the five anti-TNF-α inhibitors (adalimumab, golimumab, infliximab, certolizumab, or etanercept) in rheumatological disorders - specifically for the treatment of RA, psoriatic arthritis, and ankylosing spondylitis. They found a significant association between drug use and TB occurrence. Ai et al. (2015) also reviewed 50 RCTs and 13 non-RCTs using the same five drugs and concluded that the incidence rate in the infliximab group was 2.78 times higher than in the etanercept group.

Contrary to these studies, our study narrows the scope of the review by comparing the risk of TB infection, specifically in patients with RA using infliximab versus etanercept, and includes studies from 2015 to 2022. In our examination, patients in the infliximab group showed the same Relative Risk of developing TB infection as those in the etanercept group.

Funnel plot analysis was used to assess the publication bias of the studies included in this review. The results showed a moderate publication bias, considered a disadvantage of the present work. The initial search strategy designed yielded no RCTs that met the inclusion criteria for the study. Hence, only observational studies were within the scope, another limitation of this review.

The screening and prophylaxis of LTBI and treatment of active TB are in the guidelines of the American College of Rheumatology (Singh et al., 2016) and the WHO (WHO, 2021). In the last decade, several studies have demonstrated that screening strategies can decrease the risk of TB in patients treated with biologic drugs (Gómez-Reino et al., 2007; Singh et al., 2012; Solovic et al., 2010). However, the studies evaluated here showed only a slight decrease in the incidence of TB, even when screening and prophylaxis are performed with almost 100 % penetration (Chung et al., 2020; Jung et al., 2022).

The results of LTBI screening and prophylactics for the prevention of TB show the importance of their indication for all patients with RA before treatment with biological therapy. However, many years after implementation, the studies in large populations presented here indicate that these approaches may need to be revised. Indeed, the sensitivity and specificity of screening tests, resistance to therapy against TB, and new biological drugs for RA and other rheumatic diseases that pose no risk of TB must be addressed. These results are of great importance, and other studies need to be conducted mainly in countries with a high incidence of TB. In addition, due to the difference in costs of these drugs, each cost-benefit should be considered.

Author	Total Score	Risk of Bias
Yonekura 2017	2	Low
Jung SM 2022	1	Low
Santos-Moreno 2016	4	Moderate
Chung tt 2020	4	Moderate

Table 2: *Bias assessment of the studies.*

Conclusion

Infliximab and etanercept resulted in the same Relative Risk of developing TB in patients with RA. Thus, the choice of treatments should be considered in terms of cost-benefit. LTBI screening and prophylaxis alone may be insufficient preventive steps for TB development in these patients.

Supplementary materials

The following supporting information can be downloaded at:
journal.ppcr.org/index.php/ppcrjournal/article/view/240
Appendix 1: Definition of search strategy;
Appendix 2: Risk of Bias Tool for Observational Studies.

Author Contributions

K.H.M, V.R.M., A.S.L., N.V., S.K., M.C., A.L.C., S.F.; methodology, K.H.M, A.S.L., N.V., S.K., V.R.M; formal analysis, K.H.M, N.V., S.K., M.C., S.F., A.S.L; data curation, S.K, N.V., A.S.L., K.H.M., V.R.M.; writing-original draft preparation, K.H.M., V.R.M., S.K., S.F.; writing—review and editing, V.R.M., K.H.M., S.F.; supervision, V.R.M and K.H.M. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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