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Risk of tuberculosis in patients treated with TNF-α antagonists: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objectives: An increased risk of tuberculosis (TB) has been reported in patients treated with TNF-α antagonists, an issue that has been highlighted in a WHO black box warning. This review aimed to assess the risk of TB in patients undergoing TNF-α antagonists treatment.

Methods: A systematic literature search for randomised controlled trials (RCTs) was performed in MEDLINE, Embase and Cochrane library and studies selected for inclusion according to predefined criteria. ORs with 95% CIs were calculated using the random-effect model. Subgroup analyses considered the effects of drug type, disease and TB endemicity. The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

Results: 29 RCTs involving 11 879 patients were included (14 for infliximab, 9 for adalimumab, 2 for golimumab, 1 for etanercept and 3 for certolizumab pegol). Of 7912 patients allocated to TNF-α antagonists, 45 (0.57%) developed TB, while only 3 cases occurred in 3967 patients allocated to control groups, resulting in an OR of 1.94 (95% CI 1.10 to 3.44, p=0.02). Subgroup analyses indicated that patients of rheumatoid arthritis (RA) had a higher increased risk of TB when treated with TNF-α antagonists (OR 2.29 (1.09 to 4.78), p=0.03). The level of the evidence was recommended as 'low' by the GRADE system.

Conclusions: Findings from our meta-analysis indicate that the risk of TB may be significantly increased in patients treated with TNF-α antagonists. However, further studies are needed to reveal the biological mechanism of the increased TB risk caused by TNF-α antagonists treatment.

Strengths and limitations of this study

- This meta-analysis evaluated the tuberculosis (TB) risk of all TNF-α antagonists across a variety of conditions in randomised controlled trials (RCTs) with low heterogeneity.
- In addition to the diseases most commonly treated by TNF-α antagonists (rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis), the review included studies that involved patients with asthma, sarcoidosis and graft-versus-host disease.
- The quality of the evidence was assessed using the GRADE approach, which has been recommended for grading evidence by the *British Medical Journal* since 2006.
- The relatively short follow-up period in the RCTs might have caused an underestimation of the TB rates.

ankylosing spondylitis (AS) and other immune-mediated or inflammation-related diseases.[1] Therefore, it is a critical molecular member in targeted biological interventions,[2] and the advent of TNF-α-directed targeted therapies represents a major advance in the treatment and management of conditions such as RA, psoriatic arthritis (PsA) and IBD,[3–5] improving the quality of life for these patients.[6] Increasingly, evidence indicate that TNF-α antagonists may possess promising therapeutic potential in many TNF-α-mediated diseases. Our previous study showed that TNF-α played a critical role in the occurrence and development of inflammation and tumour, and the TNF-α monoclonal antibody which we prepared as a TNF-α antagonist significantly suppressed the growth of breast cancer in an animal model.[7]

To date, five TNF-α antagonists have been used in clinical practice: etanercept, adalimumab, infliximab, golimumab and certolizumab pegol. Although their therapeutic

INTRODUCTION

Tumour necrosis factor-α (TNF-α) is a pleiotropic cytokine that plays a central role in the pathogenesis of rheumatoid arthritis (RA), inflammatory bowel disease (IBD),

efficacy has been confirmed, the side effects of these TNF-α antagonists need to be considered carefully in clinical practice.[8] An increased risk of tuberculosis (TB) among patients receiving TNF-α antagonists has been observed,[9] and several meta-analyses have evaluated the risk of TB in patients treated with TNF-α antagonists or with specific conditions.[10–13] Nevertheless, the association between TNF-α antagonists and an increased risk of TB remains uncertain.

With the aim of further clarifying the issue, this meta-analysis compared the risk of TB between TNF-α antagonists treatment and control groups in randomised controlled trials (RCTs) focusing on any disease condition. A secondary objective was to investigate the association of the rate of active TB with the type of medication, the disease condition and the location of study.

MATERIALS AND METHODS
The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[14]

Inclusion and exclusion criteria
We performed a search for all published RCTs that reported TB risk among patients treated with any of the existing five TNF-α antagonists: etanercept (ETN), adalimumab (ADA), infliximab (IFX), golimumab (GOL) and certolizumab pegol (CZP). Studies were selected for inclusion according to predefined inclusion criteria:
▶ *Participants*: Adults (aged 16 years or older) with any disease included in studies of any of the five TNF-α antagonists.
▶ *Interventions*: TNF-α antagonists ETN, ADA, IFX, GOL or CZP with or without standard-care treatment for any medical condition.
▶ *Comparators*: Placebo with or without standard-care treatment or standard-care treatment alone.
▶ *Outcomes*: Diagnosis of TB, TB reactivation, miliary or cavitary TB of the lung or any other body organ.
▶ *Study design*: RCTs.

The exclusion criteria included: (1) duplicated studies or studies based on unoriginal data, (2) studies that did not report TB incidence, (3) studies that did not observe TB events and (4) articles not published in English.

Data sources and search strategies
We systematically searched for reports of trials and systematic reviews up to December 2015 from the following online databases: MEDLINE, Embase and Cochrane Library. No restrictions were imposed with regard to region and time. To identify all RCTs, a highly sensitive search strategy developed on the basis of Cochrane Handbook for Systematic Reviews of Interventions was applied, which combined with the following key terms: 'etanercept', 'adalimumab', 'infliximab', 'golimumab',

'certolizumab' and 'TNF-α antagonist' (The MEDLINE search strategy is provided in online supplementary appendix 1). In addition, the reference lists of all topic-related review articles, reports or meta-analyses were searched for potentially relevant studies.

Selection of studies
Two reviewers independently screened the titles and abstracts of all records retrieved by the searches and identified studies that were potentially eligible for inclusion. Full-text versions were obtained, and these were independently assessed for eligibility by two reviewers according to inclusion and exclusion criteria. Disagreements between reviewers at both stages of screening were resolved by discussion and consensus.

Data extraction and methodological quality assessment
Data extraction was conducted independently by two investigators, and discrepancies were resolved through discussion. For each included study, we extracted essential information, including publication details, sample size, characteristics of trial participants, timing of assessment, interventions/comparisons, incidence cases of TB, performance of TB screening prior to therapy and geographic location of the study classified according to the incidence rate (IR) of TB (WHO, incidence TB estimation, 2014). Countries with an IR ≥40/100 000 are considered as high-incidence TB areas. The methodological quality of all included RCTs was assessed using the Cochrane collaboration's tool. The tool contains seven dimensions: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Studies were considered as low risk of bias when all these key aspects were assessed to be at low risk.

Statistical analysis
Principal statistical analyses were performed using Review Manager 5.2 software according to the Cochrane handbook. On the basis of events reported by included studies, the number of patients developing TB was compared between the placebo-controlled or standard-care populations and patients receiving at least one dose of TNF-α antagonists. Statistical heterogeneity among results was evaluated by using the I^2 statistic with the significance level set at 0.1. Meta-analyses were performed using the random-effects model. Results were presented as OR and its 95% CI. An OR >1 suggests a higher risk of TB than the control. Publication bias was tested by funnel plots, Egger's regression method and Begg's rank correlation method, using Stata software (V.11.0, College Station, Texas, USA). To evaluate the influence of all single studies on the pooled outcome, we also performed sensitivity analysis through the leave-one-out approach. Stratified analyses were performed by type of medication, disease being treated and estimated TB rates of studies' geographic locations.

Quality of evidence

We assessed the quality of evidence using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methods.[15] GRADEprofiler 3.6 software was applied to create the evidence profile. The GRADE approach categorises the quality of evidence as follows: (1) high quality (further research is extremely unlikely to change the credibility of the pooled results); (2) moderate quality (further research is likely to influence the credibility of pooled results and may change the estimate); (3) low quality (further research is extremely likely to influence the credibility of pooled results and is likely to change the estimate) and (4) very low quality (the pooled results have extreme uncertainty).

RESULTS
Search results

A total of 6843 study records were identified following the search strategy; 2773 references were left after removing duplicates. After title and abstract screening, 187 references progressed to the next stage, in which articles were re-evaluated based on full texts. Ultimately, 27 RCTs met the inclusion criteria and were included in our meta-analysis. In addition, two records were added after checking the references of previous systematic reviews.[16 17] The PRISMA flow diagram of study selection is presented in figure 1.

Study characteristics and methodological quality

The 29 included studies involved a total of 11 879 patients.[16–44] The duration of outcome assessment in included studies ranged from 8 weeks to 3 years.
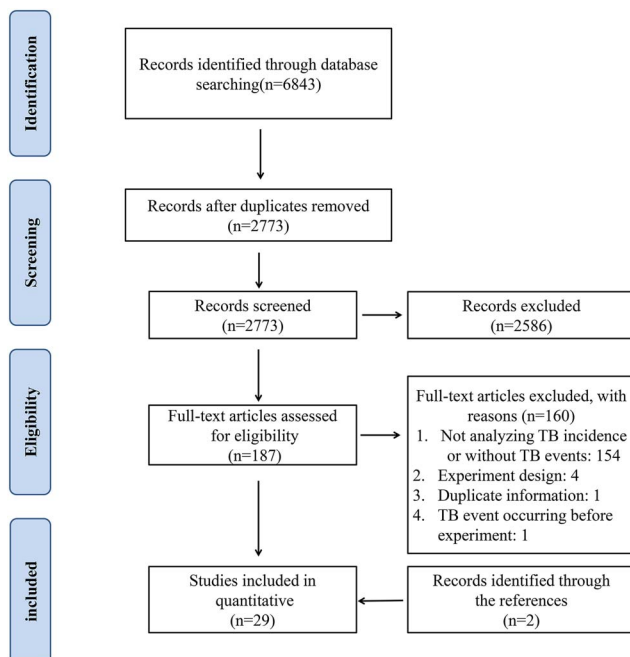

Figure 1 PRISMA flow diagram of study selection.

Fourteen trials assessed infliximab, two trials assessed golimumab, nine trials assessed adalimumab, one trial assessed etanercept and three trials assessed certolizumab pegol. Thirteen RCTs were in areas with a low IR of TB and eleven in areas with a high incidence; this information was unavailable in the remaining five RCTs (table 1). TB screening was reported in 26 RCTs but was not carried out in 3 trials. A total of 45 TB cases occurred among 7912 patients treated with TNF-α antagonists and only 3 cases developed in 3967 patients in the control groups (see online supplementary appendix 2). The methodological quality assessments of included studies are summarised in online supplementary appendix 3.

TB risk and TNF-α antagonists

Pooled analysis determined that treatment with TNF-α antagonists was associated with an increased occurrence of TB compared with control groups (OR 1.94 (1.10, 3.44), p=0.02; figure 2). No significant heterogeneity was detected (I^2=0%). The funnel plot revealed no obvious asymmetry in distribution, suggesting a low likelihood of publication bias (see online supplementary appendix 4), and this was statistically confirmed by Begg's test (p=0.348) and Egger's regression asymmetry test (p=0.321). Sensitivity analysis using random-effects model suggested that pooled result was not affected substantially by any of the included studies (see online supplementary appendix 5).

We performed subgroup analyses based on type of medication, disease under treatment and TB rate of the geographic location. In these analyses, the type of drugs was not associated with statistically significant differences in the risk of TB between patients treated with TNF-α antagonists and control groups (IFX: 1.82 (0.82–4.06), ADA: 2.11 (0.73–6.12), CZP: 2.38 (0.42–13.42)) (see online supplementary appendix 6). When grouped for disease, a significantly increased TB risk was associated with anti-TNF-α drugs in RA patients (OR 2.29 (1.09 to 4.78), p=0.03) (figure 3). When analysed according to estimated TB rates of studies' geographic locations, ORs for studies in high or low TB rate areas were 2.39 (95% CI 0.97 to 5.90, p=0.06) and 1.64 (95% CI 0.70 to 3.88, p=0.26), respectively (figure 4).

GRADE profile evidence

The results of assessing the quality of evidence are shown in online supplementary appendix 7. The quality for the main result was recommended as 'low' by the GRADE system.

DISCUSSION

TNF-α antagonists have been widely used in many rheumatic diseases due to their considerable therapeutic effects and are promising candidates for future clinical applications in many other relevant diseases.[7 24] However, an increased risk of TB has been observed

Table 1 Characteristics of randomised controlled trials included

First author	Year	Disease	Timing of assessment	Comparison	EA
Kim[16]	2007	RA	Week 24	PBO vs ADA	No
Rutgeerts[17]	2005	UC	Week 54	PBO vs IFX	Yes
Baranauskaite[18]	2012	PsA	Week 16	MTX vs IFX+MTX	Yes
Barker[19]	2011	Ps	Week 24	MTX vs IFX	–
Braun[20]	2002	AS	Week 12	PBO vs IFX	No
Breedveld[21]	2006	RA	Year 2	MTX vs ADA/ADA+MTX	–
Chen[22]	2009	RA	Week 12	MTX vs ADA+MTX	No
Colombel[23]	2010	CD	Week 20	AZA vs IFX/IFX+AZA	–
Couriel[24]	2009	GvH	Month 6	MP vs IFX+MP	No
Judson[25]	2014	Sarcoidosis	Week 44	PBO vs GOL	–
Kavanaugh[26]	2013	RA	Week 26	PBO+MTX vs ADA+MTX	Yes
Kennedy[27]	2014	RA	Week 12	PBO vs ADA	No
Keystone[28]	2004	RA	Week 52	PBO+MTX vs ADA+MTX	No
Keystone[29]	2008	RA	Week 52	PBO+MTX vs CZP+MTX	Yes
Maini[30]	1999	RA	Week 102	DMARDs vs IFX+DMARDs	No
Nam[31]	2014	RA	Week 78	PBO+MTX vs IFX+MTX	No
Reich[32]	2012	Ps	Week 12	PBO vs CZP	No
Schiff[33]	2014	RA	Year 2	ABA+MTX vs ADA+MTX	No
Schiff[34]	2008	RA	Year 1	PBO+MTX vs IFX+MTX	Yes
Sieper[35]	2014	AS	Week 28	PBO+NPX vs IFX+NPX	Yes
Smolen[36]	2009	RA	Week 24	PBO+MTX vs CZP+MTX	Yes
St Clair[37]	2004	RA	Week 54	PBO+MTX vs IFX+MTX	No
Suzuki[38]	2014	UC	Week 8	PBO vs ADA	No
Tam[39]	2012	RA	Month 6	MTX vs IFX+MTX	Yes
Van Den Bosch[40]	2002	AS	Week 12	PBO vs IFX	-
van der Heijde[41]	2007	RA	Year 3	MTX vs ETN/ETN+MTX	Yes
van Vollenhoven[42]	2011	RA	Week 24	PBO+MTX vs ADA+MTX	Yes
Wenzel[43]	2009	Asthma	Week 76	PBO vs GOL	No
Westhovens[44]	2006	RA	Week 22	PBO+MTX vs IFX+MTX	Yes

ABA, abatacept; ADA, adalimumab; AS, ankylosing spondylitis; AZA, azathioprine; CD, Crohn's disease; CZP, certolizumab pegol; DMARDs, disease-modifying anti-rheumatic drugs; EA, endemic area of TB; ETN, etanercept; GOL, golimumab; GvH, graft-versus-host disease; IFX, infliximab; MP, methylprednisolone; MTX, methotrexate; NPX, naproxen; PBO, placebo; Ps, plaque psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis.

among patients receiving anti-TNF treatments,[9] an issue that has been highlighted by WHO in a black box warning for TB and other opportunistic infections.

This meta-analysis aimed to consider TB risk in any patient treated with TNF-α antagonists, with the premise that the adverse event profile of TNF-α antagonists would be similar irrespective of the condition being treated. Twenty-nine published RCTs involving 11 879 patients were eventually included. In addition to the diseases most commonly treated with TNF-α antagonists (RA, UC, AS and PsA), this review also included studies that involved patients with asthma, sarcoidosis and Graft-versus-Host disease (GvH). We found that the risk of TB was statistically significantly increased in patients treated with TNF-α antagonists. With patients being treated with any TNF-α antagonist for any disease included, the risk of TB was almost doubled compared with those in normal care or placebo comparator arms. This result is in accordance with previously reported suspicions that TNF-α antagonists could increase TB risk, but differs from the findings of two previous meta-analyses on this topic, which found no significantly increased TB risk among patients with chronic immune-

mediated inflammatory diseases or RA treated with different TNF-α antagonists.[10 11] One possible reason for this discrepancy may be the relatively small number of patients included in those meta-analyses.

In order to take into account the effects of disease condition and the rate of TB in the background population on the pooled results, subgroup analyses were performed. When patients with RA were considered alone, the level of increased risk of TB in RA patients receiving TNF-α antagonists, compared with placebo or normal care groups, was higher than the increased risk among patients in any disease condition. Although it has been reported that RA patients showed an increased risk of TB when compared with the general population,[45–47] the potential for anti-TNF drugs to increase this risk further should not be ignored. It was also expected that patients in endemic areas would have a higher risk of TB after treatment with anti-TNF agents. While the difference in TB incidence between anti-TNF treated patients and control groups was not statistically significant (p=0.06), the trend towards higher incidence was enough to suggest the likelihood of a repeatable difference, which indicates that safety studies should include
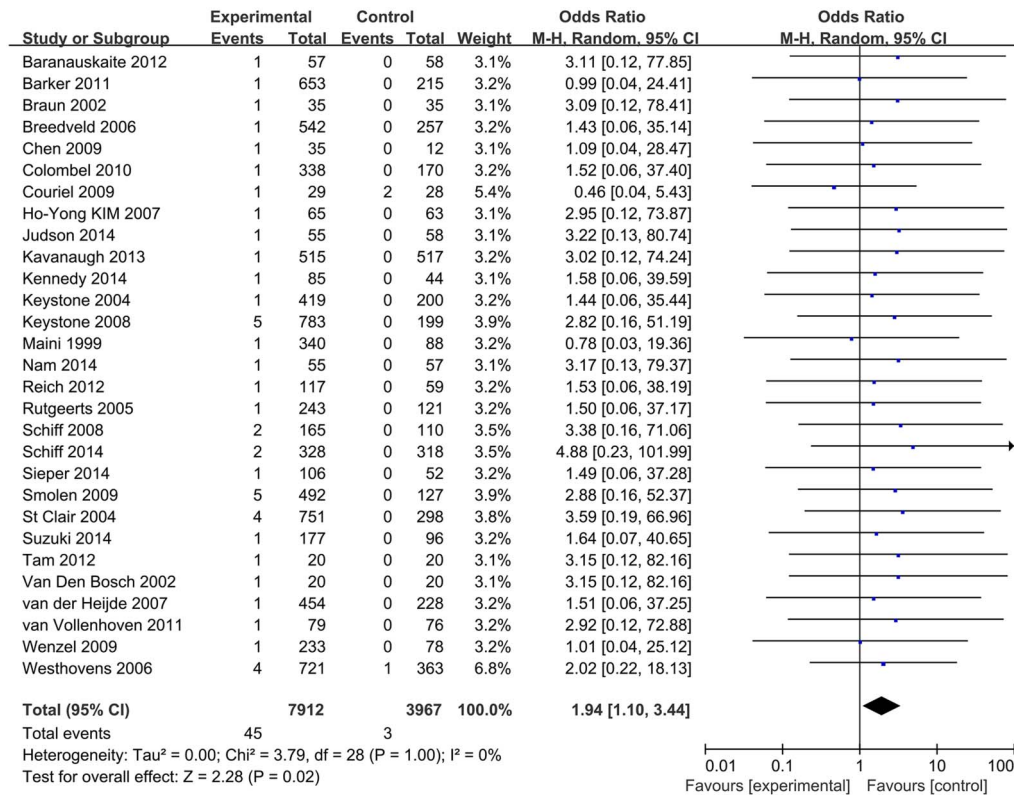
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Baranauskaite 2012	1	57	0	58	3.1%	3.11 [0.12, 77.85]	
Barker 2011	1	653	0	215	3.2%	0.99 [0.04, 24.41]	
Braun 2002	1	35	0	35	3.1%	3.09 [0.12, 78.41]	
Breedveld 2006	1	542	0	257	3.2%	1.43 [0.06, 35.14]	
Chen 2009	1	35	0	12	3.1%	1.09 [0.04, 28.47]	
Colombel 2010	1	338	0	170	3.2%	1.52 [0.06, 37.40]	
Couriel 2009	1	29	2	28	5.4%	0.46 [0.04, 5.43]	
Ho-Yong KIM 2007	1	65	0	63	3.1%	2.95 [0.12, 73.87]	
Judson 2014	1	55	0	58	3.1%	3.22 [0.13, 80.74]	
Kavanaugh 2013	1	515	0	517	3.2%	3.02 [0.12, 74.24]	
Kennedy 2014	1	85	0	44	3.1%	1.58 [0.06, 39.59]	
Keystone 2004	1	419	0	200	3.2%	1.44 [0.06, 35.44]	
Keystone 2008	5	783	0	199	3.9%	2.82 [0.16, 51.19]	
Maini 1999	1	340	0	88	3.2%	0.78 [0.03, 19.36]	
Nam 2014	1	55	0	57	3.1%	3.17 [0.13, 79.37]	
Reich 2012	1	117	0	59	3.2%	1.53 [0.06, 38.19]	
Rutgeerts 2005	1	243	0	121	3.2%	1.50 [0.06, 37.17]	
Schiff 2008	2	165	0	110	3.5%	3.38 [0.16, 71.06]	
Schiff 2014	2	328	0	318	3.5%	4.88 [0.23, 101.99]	
Sieper 2014	1	106	0	52	3.2%	1.49 [0.06, 37.28]	
Smolen 2009	5	492	0	127	3.9%	2.88 [0.16, 52.37]	
St Clair 2004	4	751	0	298	3.8%	3.59 [0.19, 66.96]	
Suzuki 2014	1	177	0	96	3.2%	1.64 [0.07, 40.65]	
Tam 2012	1	20	0	20	3.1%	3.15 [0.12, 82.16]	
Van Den Bosch 2002	1	20	0	20	3.1%	3.15 [0.12, 82.16]	
van der Heijde 2007	1	454	0	228	3.2%	1.51 [0.06, 37.25]	
van Vollenhoven 2011	1	79	0	76	3.2%	2.92 [0.12, 72.88]	
Wenzel 2009	1	233	0	78	3.2%	1.01 [0.04, 25.12]	
Westhovens 2006	4	721	1	363	6.8%	2.02 [0.22, 18.13]	
Total (95% CI)		**7912**		**3967**	**100.0%**	**1.94 [1.10, 3.44]**	
Total events	45		3				

Heterogeneity: Tau² = 0.00; Chi² = 3.79, df = 28 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.28 (P = 0.02)

Figure 2 Meta-analysis of TB risk associated with TNF-α antagonists. TNF-α, tumour necrosis factor-α; TB, tuberculosis.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
1.1.1 RA							
Breedveld 2006	1	542	0	257	5.3%	1.43 [0.06, 35.14]	
Chen 2009	1	35	0	12	5.1%	1.09 [0.04, 28.47]	
Ho-Youn KIM 2007	1	65	0	63	5.2%	2.95 [0.12, 73.87]	
Kavanaugh 2013	1	515	0	517	5.3%	3.02 [0.12, 74.24]	
Kennedy 2014	1	85	0	44	5.2%	1.58 [0.06, 39.59]	
Keystone 2004	1	419	0	200	5.3%	1.44 [0.06, 35.44]	
Keystone 2008	5	783	0	199	6.5%	2.82 [0.16, 51.19]	
Maini 1999	1	340	0	88	5.3%	0.78 [0.03, 19.36]	
Nam 2014	1	55	0	57	5.2%	3.17 [0.13, 79.37]	
Schiff 2008	2	165	0	110	5.9%	3.38 [0.16, 71.06]	
Schiff 2014	2	328	0	318	5.9%	4.88 [0.23, 101.99]	
Smolen 2009	5	492	0	127	6.5%	2.88 [0.16, 52.37]	
St Clair 2004	4	751	0	298	6.4%	3.59 [0.19, 66.96]	
Tam 2012	1	20	0	20	5.1%	3.15 [0.12, 82.16]	
van der Heijde 2007	1	454	0	228	5.3%	1.51 [0.06, 37.25]	
van Vollenhoven 2011	1	79	0	76	5.3%	2.92 [0.12, 72.88]	
Westhovens 2006	4	721	1	363	11.3%	2.02 [0.22, 18.13]	
Subtotal (95% CI)		**5849**		**2977**	**100.0%**	**2.29 [1.09, 4.78]**	
Total events	33		1				

Heterogeneity: Tau² = 0.00; Chi² = 1.52, df = 16 (P = 1.00); I² = 0%
Test for overall effect: Z = 2.20 (P = 0.03)

1.1.2 AS							
Braun 2002	1	35	0	35	33.4%	3.09 [0.12, 78.41]	
Sieper 2014	1	106	0	52	33.7%	1.49 [0.06, 37.28]	
Van Den Bosch 2002	1	20	0	20	32.9%	3.15 [0.12, 82.16]	
Subtotal (95% CI)		**161**		**107**	**100.0%**	**2.43 [0.38, 15.77]**	
Total events	3		0				

Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%
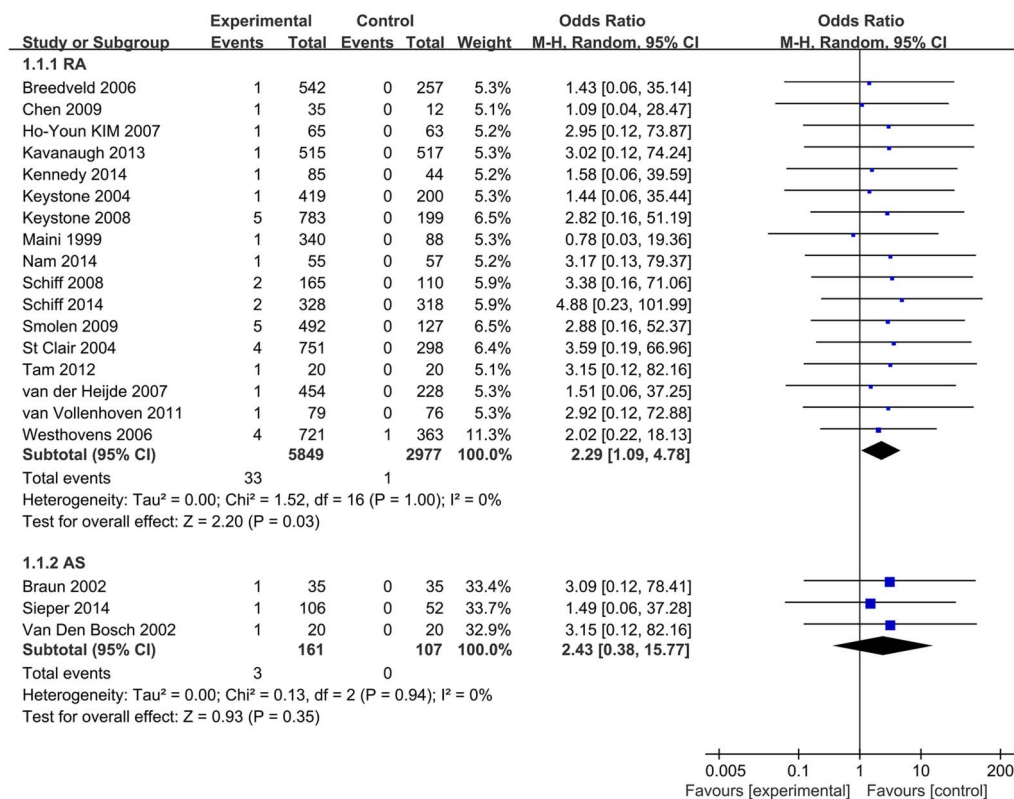Test for overall effect: Z = 0.93 (P = 0.35)

Figure 3 Subgroup analysis of TB risk in RA and AS patients. AS, ankylosing spondylitis; RA, rheumatoid arthritis; TB, tuberculosis.
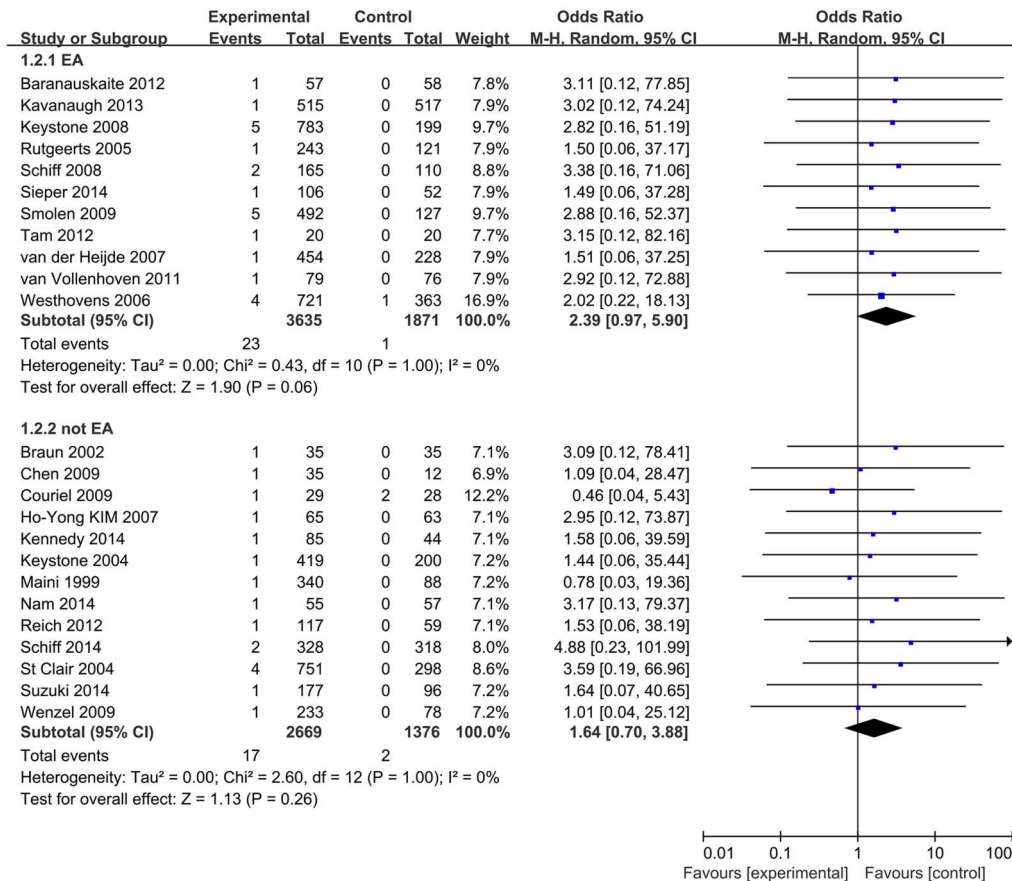
Figure 4 Subgroup analysis of TB risk in high or low TB rate areas. TB, tuberculosis.

patients from these areas to provide a true profile of the risk of infection. No differences in TB incidence were identified between anti-TNF-treated patients and controls when subgroup analyses were conducted by single drug types. However, it is likely that this is a result of the small number of included patients.

TNF-α is an immune mediator that plays a critical role in protective mechanism against infections, especially TB. TNF increases the phagocytic capacity of macrophages and enhances intracellular killing of mycobacterium via the generation of reactive nitrogen and oxygen intermediates, effectively synergising with interferon (IFN)-γ.[48] TNF-α is also involved in the pathological changes of latent tuberculous infection (LTBI), especially in maintaining the formation and function of granuloma which prevents mycobacterium from disseminating into the blood.[49] These TNF-mediated immune mechanisms may explain the reason for the increased risk of TB in patients receiving anti-TNF agents' treatment.

The results of this review may have direct implications in the management of a large number of patients treated currently with biologics. Therapeutic approaches that include intensive screening and surveillance seem to be advisable when TNF-α antagonists are used. One review of infection risk associated with anti-TNF-α agents suggested that a patient eligible for such treatment should undergo a careful medical history and tests such

as the TB skin test (TST) or chest X-ray to assess the risk of TB re-activation.[50] Interferon-γ release assay (IGRA) is also established as an alternative to the TST in TB infection diagnosis, especially in the diagnosis of LTBI due to the higher specificity.[51]

Previous studies have shown that prophylaxis in patients before or during anti-TNF-α therapy with standard anti-TB regimen prevented reactivation effectively.[52 53] One study estimated that preventive treatment in patients with LTBI can reduce the risk of reactivation by 65%.[10] Some countries have formulated national guidelines to deal with LTBI before anti-TNF agents treatment.[54] During the anti-TNF therapy, the patients should also be closely monitored at least once a year to identify reactivation of latent TB or new TB infection. Patients' adherence to isoniazid (INH) treatment is important for preventing the reactivation of latent TB. Screening and surveillance may be of particular importance when TNF-α antagonists are used as part of combined therapies. A previously published systematic review[55] reported that, compared with monotherapy, the risk of TB was increased 13-fold when anti-TNF agents were combined with immunosuppressant agents such as methotrexate or azathioprine. Additionally, a recent network meta-analysis and Cochrane overview highlighted the association between different biologics including TNF-α antagonists and higher rates of adverse effects in several diseases.

These adverse events included TB reactivation, although the roles of other factors potentially associated with TB reactivation were not fully illuminated.[13]

Several limitations in this study should be addressed. First, the review identified only a limited number of RCTs, with only two studies about golimumab and one about etanercept. Second, the relatively short follow-up period in the RCTs might have caused an underestimation of TB incidence rates. Third, the meta-analysis was limited to published scientific publications, and the omission of unpublished data from pharmaceutical trials may affect the pooled results.

In summary, our results suggest that the risk of TB is doubled when patients with any condition are treated with anti-TNF-α drugs. When anti-TNF-α treatments are considered, the increased risk of TB should be part of the treatment decision-making process. Patients should be screened for LTBI and anti-TB prophylaxis or concomitant treatment should be considered. Further high-quality research regarding the long-term safety of biologics is needed to improve the safety of biological treatment in clinical use.

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