Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy: A meta-analysis

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Abstract. Infliximab is a promising drug with good outcomes demonstrated for diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA) and spondyloarthropathy (SpA). However, treatment with this drug may increase the risk of tuberculosis infection. The aim of the present study was to investigate infliximab-associated tuberculosis infection. Literature searches in PubMed, MEDLINE and EMBASE databases were performed. Randomized controlled trials with >95% of the patients >18 years-old were included. Meta-analysis was performed to investigate the incidence of tuberculosis infection after infliximab infusion. A total of 24 RCTs were included in the present meta-analysis. In total, 21 (0.51%) tuberculosis infections were detected among 4,111 patients administered infliximab therapy, compared with 0 (0%) among 2,229 patients assigned to the placebo group. Pooled odds ratio (OR) of developing tuberculosis infection was significantly higher with infliximab therapy than with placebo [2.86; 95% confidence interval (CI), 1.09-7.52]. The OR of tuberculosis infection was 3.93 (95% CI, 0.91-16.91) in RA, 2.46 (95% CI, 0.38-15.92) in SpA and 1.66 (95% CI, 0.26-10.57) in IBD. Rates of tuberculosis infection with infliximab therapy in RA, SpA and IBD were 0.70, 0.22 and 0.52%, respectively. Compared with placebo, infliximab therapy may increase the risk of developing tuberculosis. However, the ORs for the risk of infliximab-associated tuberculosis were not demonstrated to be significant in IBD, RA and SpA; therefore, these findings should be interpreted with caution. The risk of developing tuberculosis demonstrates the importance of the prevention and management of tuberculosis infection with infliximab therapy.

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Introduction

Infliximab is a genetically constructed immunoglobulin (Ig)G1 murine-human chimeric monoclonal antibody that binds the soluble subunit and the membrane-bound precursor of tumor necrosis factor-α (TNF-α). Consequently, it helps to decrease the biological activity of TNF-α (1,2). Neutralization of TNF-α has been suggested as a therapeutic strategy for patients with inflammatory bowel disease (IBD), rheumatoid arthritis (RA), spondyloarthropathy (SpA) and various other chronic inflammatory conditions (3-5). IBD, RA, and SpA are common chronic inflammatory conditions, characterized by episodes of remission and relapse, which have a major impact on the patients' physical, emotional and social well-being. TNF-α cytokine, which is expressed by activated macrophages, has been implicated in the pathogenesis of IBD, RA and SpA (6-8). Infliximab has been widely used to treat patients who failed to respond to other anti-inflammatory agents since FDA approval was attained in 1998. The advent of infliximab has dramatically improved the quality of life and prognosis of these patients.

Multicenter randomized clinical trials (RCTs) have been conducted to evaluate the efficacy and safety of infliximab throughout the past decade. These RCTs demonstrated that infliximab is an effective therapy for the treatment of various inflammatory diseases (9-12). However, the safety of infliximab remains a major concern to physicians and patients, including its short- and long-term side effects, which have limited its clinical use. Although the side effects are uncommon, they may be serious and potentially life-threatening. The most common side effects include infection, infusion reactions, tumor and lupus-like syndrome. Miscellaneous types of infections, such as bacterial, mycobacteria, invasive fungal, viral and parasitic infections have been observed since the approval of infliximab (13).

In animal models, TNF-α has been demonstrated to have a central role in the host response against tuberculosis, including granuloma formation and the containment of disease (14,15). Notably, antibodies against TNF-α induced reactivation of tuberculosis in a mouse model of latent infection (16). The role of TNF-α in the human immune response to tuberculosis remains unclear, and the effect on the tuberculosis infection of infliximab requires clarification. Previous large retrospective reviews of infliximab-induced tuberculosis have shown that the frequency of tuberculosis following infliximab therapy was elevated, as compared with other opportunistic infections (17). In addition, the rate of reported cases of tuberculosis treated with infliximab is higher than the background rate of tuberculosis in patients with rheumatoid arthritis (18-20). However, the findings of previous RCTs that examined the association between infliximab and tuberculosis infection risk were inconsistent. The aim of present study was to analyze the findings of RCTs that investigated infliximab, with an emphasis on tuberculosis infection risk.

Materials and methods

Search strategy and study selection. To perform this review, we conducted a structured search in PubMed (ncbi.nlm.nih.gov/pubmed), MEDLINE (http://webofknowledge.com/medline) and EMBASE (http://www.embase.com) databases up to May 2014 using the following search terms: ('inflammatory bowel disease' or 'Crohn's disease' or 'ulcerative colitis' or 'rheumatoid arthritis' or 'spondyloarthropathy') and ('remicade' or 'infliximab' or 'monoclonal antibody cA2') and ('tuberculosis' or 'mycobacterial infections'). References from the articles that met the eligibility criteria were also examined and evaluated, and were selected for this review if they also met the criteria. Only articles published in English were included. Titles and abstracts of articles identified by the initial search were first evaluated by investigators for appropriateness to the study question, and full papers of potential eligible studies were subsequently obtained and reviewed in detail. The present meta-analysis was designed, analyzed and reported according to the PRISMA statement (21).

Criteria for the inclusion of an article in the present meta-analysis were as follows: (i) Randomized controlled trials; (ii) >95% of the patients are aged >18 years; and (iii) compared infliximab with or without concomitant immunomodulators therapy with placebo. Furthermore, for inclusion, studies were required to be independent from other studies in order to avoid giving double weight to estimates derived from the same trial, and to have sufficient information to allow adequate estimation of the relative risk (RR)/odds ratio (OR) and 95% confidence intervals (CIs).

Studies were excluded if: (i) They were a review, lecture, comment or research that cannot be extracted with statistical data; or (ii) they included patients that were pregnant, hypersensitive to infliximab, exhibited systemic disease, or were given biological treatment previously.

Outcome assessment. The primary outcome was the occurrence of tuberculosis infection with infliximab, compared with placebo. The secondary outcome was mortality due to tuberculosis infection.

Data extraction. Two investigators individually evaluated all relevant articles identified by the literature search using pre-defined eligibility forms. Any discrepancies were resolved by discussion. The following information was obtained from each study: First author, year of publication, geographical region, disease type, sample size during the study, dosage of infliximab, duration of therapy, combination therapy (if any), number of individuals who experienced tuberculosis infection, tuberculosis manifestation, and prognosis of tuberculosis. Data were extracted as intention-to-treat analyses, wherever trial reporting facilitated this.

Quality evaluation. Jadad scoring was applied to assess the methodological quality of included trials, which judges the descriptions of randomization, double blinding, and subject withdrawal in the included trials (22). The quality scale ranges from 0 to 5 points with a low-quality report scoring ≤2 and a high-quality report scoring ≥3 (23).

Statistical analysis. Statistical heterogeneity between the studies was assessed using χ^2 test and I^2, which assumes the presence of heterogeneity at P<0.10 and/or I^2 >50%. A fixed effects model was used when the heterogeneity test demonstrated a P-value of >0.10 and a I^2 of <50%; otherwise, a random-effects model was used. Subgroup analyses were performed according to disease type, sample size, study quality, duration of therapy, whether patients in both infliximab and placebo arms were exposed to immunosuppressants and whether patients enrolled in infliximab and placebo arms were screened for tuberculosis. We compared individual ORs between these analyses using the Cochran *Q* statistic tool.

Funnel plot graph, and Begg and Egger tests were performed to evaluate publication bias. All analyses were conducted using the Revman 5.0 (Nordic Cochrane Centre, Copenhagen, Denmark) and Stata software (11.0; StataCorp LP, College Station, TX, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

Literature search and characteristics of the included studies. The present search strategy identified 6,892 articles, 6,553 of which were excluded after the title and abstract were reviewed. For the remaining 339 articles, 316 articles were excluded due to duplication (n=54), not being an RCTs (n=127), a lack of placebo (n=67), no outcome of interest (n=49), and no data on tuberculosis (n=19). Finally, 23 articles were included in the present meta-analysis, reporting on 24 respective RCTs. Of these, 8 studies studied infliximab-associated tuberculosis incidence in IBD (24-32), one of which reported two separate trials (29), 7 trials studied infliximab-associated tuberculosis incidence rates in RA (33-39), and 8 trials studied infliximab-associated tuberculosis incidence in SpA (40-47). A flow diagram of the selection process for the inclusion of studies in the present meta-analysis is shown in Fig. 1.

Duration of follow-up ranged between 12 and 54 weeks. The characteristics of the 24 trials are presented in

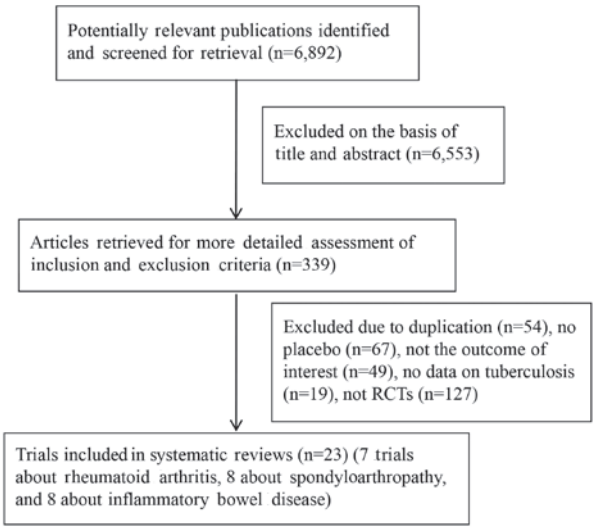

Figure 1. Flowchart of study selection process. RCT, randomized controlled trial.

Tables I and II, including the year the studies were conducted, number of patients treated, dose of infliximab administered, incidence of tuberculosis infection, tuberculosis manifestation, prognosis of tuberculosis and tuberculosis screening test prior to therapy.

Rates of tuberculosis infection in IBD, RA and SpA. Table III presents the rates of tuberculosis infection within each trial arm in each inflammatory disease assessed. Rates of tuberculosis infection with infliximab therapy were 0.70, 0.22 and 0.52%, respectively; whereas the rates of tuberculosis infection with placebo were consistently 0%, in RA, SpA and IBD. The rates of tuberculosis infection with infliximab therapy in IBD, RA and SpA were all higher than the rates with placebo.

Overall risk of tuberculosis infection with infliximab therapy vs. placebo in IBD, RA and SpA. The 24 trials examined in the present meta-analysis contain a total of 6,340 patients with IBD, RA and SpA. Of these, 4,111 (64.8%) patients were randomized to receive infliximab therapy, and 2,229 (35.2%) patients were administered a placebo. In total, there were 21 (0.51%) patients assigned to infliximab therapy who developed tuberculosis infection, as compared with 0 (0%) among patients allocated to placebo therapy. The pooled OR of developing tuberculosis infection was significantly increased with infliximab therapy, as compared with the placebo [2.86; 95% CI, 1.09-7.52] (Fig. 2), with no statistically significant heterogeneity detected between the studies (I^2=0%; P=0.99). However, in each disease subgroup, the trends were not statistically significant. The OR of tuberculosis infection with infliximab therapy was 3.93 (95% CI, 0.91-16.91) in RA, 2.46 (95% CI, 0.38-15.92) in SpA, and 1.66 (95% CI, 0.26-10.57) in IBD. The difference among these subgroups was not statistically significant (Cochran Q=0.53; P=0.77) (Fig. 2). The findings demonstrate that infliximab therapy may increase the risk of developing tuberculosis compared with that for treatment with placebo.

Meta-analysis of tuberculosis infection with infliximab therapy vs. placebo in each subgroup. Subgroup analyses were performed (Table IV). The OR of tuberculosis infection with infliximab therapy was elevated in trials with ≥50 weeks of treatment (3.00; 95% CI, 0.97-9.29), as compared with those with a duration of <50 weeks (2.46; 95% CI, 0.38-15.92); however, there was no statistically significance (Cochran Q=0.03; P=0.86). Furthermore, the OR was also increased in the larger sample studies (2.94; 95% CI, 0.87-9.94), as compared with the smaller sample studies (2.71; 95% CI, 0.55-13.26); however, again there was no significant differences detected (Cochran Q=0.01; P=0.93). There were also no significant differences in the OR of tuberculosis infection with infliximab therapy accompanied with or without immunosuppressor (2.96; 95% CI, 0.94-9.29; and 2.59; 95% CI, 0.42-15.92; respectively, Cochran Q=0.02, P=0.90). When screening for tuberculosis prior to the examination of therapy according to the study design, the OR was also increased in trials that screened for tuberculosis (3.10; 95% CI, 1.04-9.21), as compared with those without screening (2.09; 95% CI, 0.26-17.13) (Cochran Q=0.11, P=0.74). Finally, risk of bias was judged in the RCTs (Fig. 3), the OR was elevated in trials with high or unclear risk (3.14; 95% CI, 0.93-10.54), as compared with those at low risk (2.35; 95% CI, 0.47-11.77); however, there was also no significant differences detected (Cochran Q=0.08; P=0.78). The results showed that subgroup differences did not increase the risk of tuberculosis infection with infliximab therapy compared with placebo.

Publication bias. Funnel plot analysis was performed, as demonstrated in Fig. 4. Funnel plot asymmetry was detected in the present meta-analysis (Egger test, P=0.002 and Begger test, P=0.004). These results provide some evidence of publication bias in the present study.

Discussion

TNF-α is required for granuloma formation and maintenance, and has an important role in host defense against diseases caused by intracellular pathogens, such as *Mycobacterium tuberculosis*, *Histoplasma capsulatum* and *Listeria monocytogenes* (48-50). The increased clinical use of TNF-α antagonists has markedly improved the management of immunomediated diseases; however, it may have led to an increase in the incidence of infections with intracellular agents. To the best of our knowledge, the present meta-analysis was the first to evaluate the potential risk of tuberculosis infection with infliximab therapy in the management of RA, SpA and IBD, by collating all obtainable data from 24 individual RCTs. The present meta-analysis demonstrated that the OR of tuberculosis infection with infliximab therapy was 2.86-fold greater than when using the placebo. However, the ORs in all three disease subgroups were not demonstrated to be statistically significant.

The role of TNF-α in the human immune response to *M. tuberculosis* is yet to be fully elucidated. An *in vitro* study has proposed that TNF-α has a significant role in the regulation of granuloma formation, which limits microbial growth (51). TNF-α, which is a pleiotropic cytokine produced by infected and activated macrophages/proinflammatory T cells, enhances

Table I. RCTs evaluating the incidence of infliximab-associated tuberculosis in patients with RA, SpA and IBD.

A, Rheumatoid arthritis

Author, year	Country	Study design	Disease	Treatment (number of patients)	Duration (wks)	Ref.
Maini *et al*, 1998	Netherlands, Germany, Austria, UK	MC, DB, PC, phase 3 RCT; MTX allowed	Active RA	Grp 1: Placebo plus MTX (n=14) Grp 2: Placebo plus 1 mg/kg infliximab q4wks (n=14) Grp 3: MTX plus 1 mg/kg infliximab q4wks (n=15) Grp 4: Placebo plus 3 mg/kg infliximab q4wks (n=15) Grp 5: MTX plus 3 mg/kg infliximab q4wks (n=14) Grp 6: Placebo plus 10 mg/kg infliximab q4wks (n=14) Grp 7: MTX plus 10 mg/kg infliximab q4wks (n=15)	26	(33)
Lipsky *et al*, 2000	USA, Netherlands, Germany, Austria, UK	MC, DB, PC, phase 3 RCT (ATTRACT); corticosteroids and NSAIDs allowed	Active RA	Grp 1: MTX plus placebo at wks 0, 2, 6 and q4kws (n=88) Grp 2: MTX plus infliximab 3 mg/kg at wks 0, 2, 6 and every 8 wk (n=86) Grp 3: MTX plus infliximab 3 mg/kg at wks 0, 2, 6 and every 4 wk (n=86) Grp 4: MTX plus infliximab 10 mg/kg at wks 0, 2, 6 and every 8 wk (n=87) Grp 5: MTX plus infliximab 10 mg/kg at wks 0, 2, 6 and every 4 wk (n=81)	54/104	(34)
St Clair *et al*, 2004	North America, and Europe	MC, PC, phase 3 RCT (ASPIRE); corticosteroids and NSAIDs allowed	Early RA (≤3 years)	All patients: MTX 7.5 mg/week, which increased to 15 mg/week by wk 4 and 20 mg/week by wk 8 (n=1,004) Grp 1: Placebo at wks 0, 2, 6 and q8kws through wk 46 (n=282) Grp 2: Infliximab 3 mg/kg at wks 0, 2, 6 and q8kws through wk 46 (n=359) Grp 3: Infliximab 6 mg/kg at wks 0, 2, 6 and q8kws through wk 46 (n=363)	54	(35)
Quinn *et al*, 2005	UK	DB, PC RCT; MTX allowed	Early poor prognosis RA	Grp 1: Placebo plus MTX (n=10) Grp 2: 3 mg/kg infliximab at wks 0, 2, 6 and q8wks plus MTX (n=10)	48	(36)
Westhovens *et al*, 2006	Belgium, US, Netherlands	MC, DB, PC, phase 3 RCT (START); AZA, 6-MP MTX, DMARDs and corticosteroids allowed	Active RA	Grp 1: Placebo at wks 0, 2, 6 and 14, and infliximab 3 mg/kg at wks 22, 26, and 30, and q8wks through wk 46 (n=363) Grp 2: Infliximab 3 mg/kg at wks 0, 2, 6, 14 and at least 3mg/kg q8wks through wk 46 (n=360) Grp 3: Infliximab 10 mg/kg at 0, 2, 6, 14 and q8wks through wk 46 (n=361)	54	(37)
Abe *et al*, 2006	Japan	MC, DB, PC RCT; corticosteroids and NSAIDs allowed	RA	Grp 1: Placebo plus MTX (n=47) Grp 2: 3 mg/kg infliximab at wks 0, 2, 6 plus MTX (n=49) Grp 3: 10 mg/kg infliximab at wks 0, 2 and 6 wk plus MTX (n=51) Most of Grp 1, 2 and 3: 3 mg/kg infliximab q8wks plus MTX thereafter	36	(38)
Schiff *et al*, 2008	Brazil, America, Argentina, France, Mexico	DB, PC phase 3 RCT (ATTRACT)	RA	Grp 1: Placebo plus MTX (n=110) Grp 2: 3 mg/kg infliximab plus MTX at wks 0, 2, 6, 14, every 8 wk (n=165)	52	(39)

Table I. Continued.

B, Spondyloarthropathy

Author, year	Country	Study design	Disease	Treatment (number of patients)	Duration (wks)	Ref.
Braun *et al*, 2002	Germany	MC, DB, PC, phase 2 RCT; NSAIDs allowed	Severe AS	Grp 1: Placebo at wks 0, 2, 6 (n=35) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6 (n=35)	12	(40)
Van der Heijde *et al*, 2005	Europe, US, Canada	MC, DB, PC, phase 3 RCT (ASSERT); NSAIDs allowed	Active AS	Grp 1: Placebo at wks 0, 2, 6, 12 and 18 (n=78) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6, 12 and 18 (n=201)	24	(41)
Marzo-Ortega *et al*, 2005	UK	DB, PC, phase 2 RCT; NSAIDS and corticosteroids allowed	Active AS	Grp 1: Infliximab 5 mg/kg at wks 0, 2, 6 14, 22 + MTX 7.5 mg/week (n=28) Grp 2: Placebo+MTX 7.5 mg/sem (n=14)	30	(42)
Inman *et al*, 2010	Canada	MC, DB, PC, phase 3b RCT; NSAIDS and corticosteroids allowed	Active AS	Grp 1: Placebo (n=37) Grp 2: Infliximab 3 mg/kg at wks 0, 2, 6 and q8wks through wk 52 (n=39) All patients: Infliximab 5 mg/kg at wks 22 or 38 if BASDAI>3 and a relative decrease of <50% in BASDAI	52	(43)
Van den Bosch *et al*, 2002	Belgium	DB, PC, phase 2 RCT; corticosteroids and NSAIDs allowed	Active SpA	Grp 1: Placebo at wks 0, 2, 6 (n=20) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6 (n=20)	12	(44)
Antoni *et al*, 2002	Europe, US, Canada	MC, DB, PC, phase 3 RCT (IMPACT); one of MDARDs allowed	Active SpA	Grp 1: Placebo at wks 0, 2, 6, and 14 (n=52) then infliximab 5 mg/kg at wks 16, 18, 22, 30,38 and 46 (n=50) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6, and 14 (n=52), placebo at wks 16, 18 and infliximab 5 mg/kg at wks 22, 30, 38 and 46 (n=49)	50	(45)
Kavanaugh *et al*, 2005	Europe, US, Canada	MC, DB, PC, phase 3 RCT (IMPACT II); MTX and corticosteroids allowed	Active SpA	Grp 1: Placebo at wks 0, 2, 6, and q8wks through wk 22 (n=100) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6, and q8wks to wk 22 (n=100)	24	(46)
Sieper *et al*, 2007	Austria, Europe, South Korea	MC, DB, PC Phase 3b RCT (INFAST)	MTS active axial SpA	Grp 1: Placebo+ naproxen 1000 mg/d at wks 0, 2, 6, 12, 18, 24 wks (n=52) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6, 12, 18, 24 wks (n=105)	24	(47)

C, Inflammatory bowel disease

Author, year	Country	Study design	Disease	Treatment (number of patients)	Duration (wks)	Ref
Present *et al*, 1999	North America and Europe	MC, DB, PC phase 3 RCT	Fistulizing CD	Grp 1: Infliximab 10 mg/kg at wks 0, 2, 6 (n=32) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6 (n=31) Grp 3: Placebo at wks 0, 2, 6 (n=31)	52	(25)

Table I. Continued.

Author, year	Country	Study design	Disease	Treatment (number of patients)	Duration (wks)	Ref.
Sands *et al*, 2001	US	MC, DB, PC phase 2, RCT	Active UC (MT&W score >10)	Grp 1: Single dose of placebo (n =3) Grp 2: Single dose of infliximab 5 mg/kg (n=3) Grp 3: Single dose of infliximab 10 mg/kg (n=3) Grp 4: Single dose of infliximab 20 mg/kg (n=2)	12	(26)
Hanauer *et al*, 2002	North America, Europe, Israel	MC, DB, PC, phase 3 RCT (ACCENT I); AZA 6-MP, MTX and cortico-steroids allowed	MTS CD	All patients: Infliximab 5 mg/kg at wk 0 (n=573) Grp 1: Placebo at wks 2, 6 and q8wks to wk 46 (n=188) Grp 2: Infliximab 5 mg/kg at wks 2, 6 and q8wks to wk 46 (n=192) Grp 3: Infliximab 5 mg/kg at wks 2 and 6 and 10 mg/kg q8wks to wk 46 (n=193)	54	(27)
Sands *et al*, 2004	North America, Europe, Israel	MC, DB, PC, phase 3 RCT (ACCENT II); AZA, 6-MP, MTX and corticosteroids allowed	Fistulizing CD	All patients: Infliximab 5mg/kg at wks 0, 2, 6 (n=306) Grp 1: Placebo at wk 14 and q8wks through wk 46 (n=144) Grp 2: Infliximab 5 mg/kg at wk14 and q8wks to wk 46 (n=138)	54	(28)
Rutgeerts *et al*, 2005	Belgium, Canada, Israel, America, France	MC, DB, PC, phase 3 RCT (ACT I); AZA, 6-MP and corticoster-oids allowed	Active UC	Grp 1: Placebo at wks 0, 2, 6 and q8wks to wk 46 (n=121) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6 and q8wks to wk 46 (n=121) Grp 3: Infliximab 10 mg/kg at wks 0, 2, 6 and q8wks to wk 46 (n=122)	54	(29)
Rutgeerts *et al*, 2005	Belgium, Canada, Israel, America, France	MC, DB, PC, phase 3 RCT (ACT II); AZA, 6-MP and corticoster-oids allowed	Active UC	Grp 1: Placebo at wks 0, 2, 6 and q8wks through wk 22 (n=123) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6 and q8wks to wk 22 (n=121) Grp 3: Infliximab 10 mg/kg at wks 0, 2, 6 and 10 mg/kg q8wks to wk 22 (n=120)	54	(29)
Lemann *et al*, 2006	France	MC, DB, PC, phase 2 RCT; AZA and 6-MP allowed	Luminal steroid-dependent CD	Grp 1: Placebo (n=58) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6 (n=57)	52	(30)
Colombel *et al*, 2010	Netherlands, Belgium, France	MC, DB, phase 3 RCT (SONIC); AZA, 6-MP and corticosteroids allowed	MTS CD	Grp 1: AZA 2.5 mg/kg capsules/placebo infusion (n=161) Grp 2: Placebo capsules/infliximab 5 mg/kg infusions (n=63) Grp 3: AZA 2.5 mg/kg capsules/infliximab 5 mg/kg infusions (n=179) Capsules (daily)/infusions (wks 0, 2, 6, q8wks to wk 22)	50	(31)
Ochsenkuhn *et al*, 2004	Germany	SC, OL, PC phase 2 RCT; AZA and 6-MP allowed	Active UC	Grp 1: Prednisolone 1.5 mg/kg qd for 2 wks, followed by a tapering regimen with a weekly reduction of 5 mg (n=7) Grp 2: Infliximab 5 mg/kg at wks 0, 2, 6 (n=6)	14	(32)

RCT, randomized controlled trial; RA, rheumatoid arthritis; SpA, spondyloarthropathy; IBD, inflammatory bowel disease; wks, weeks; Grp, group; q8wks, every 8 weeks; MC, multicenter; DB, double-blind; PC, placebo-controlled; AS, anylosing spondylitis; DMARDS, disease-modifying antirheumatic drugs; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; AZA, azathioprine; 6-MP, 6-mercaptopurine; CD, Crohn's disease; UC, ulcerative colitis; OL, open label; SC, single center; MTS, moderate-to-severe; MT&W. modified Truelove and Witts.

Table II. Characteristics of the included randomized clinical trials.

Author, year	Patients treated with infliximab	Patients that developed TB with infliximab	Patients treated with placebo	Patients that developed TB with placebo	TB manifestation	Prognosis	Screened	Ref.
Inflammatory bowel disease								
Present *et al*, 1999	63	0	31	0	NS	NS	NS	(25)
Sands *et al*, 2001	8	0	3	0	NS	NS	NS	(26)
Hanauer *et al*, 2002	385	1	188	0	NS	Recovered	PPD and CXR	(27)
Sands *et al*, 2004	6	0	7	0	NS	NS	NS	(28)
Rutgeerts *et al*, 2005	241	1	123	0	NS	NS	PPD and CXR	(29)
Rutgeerts *et al*, 2005	243	0	212	0	NS	NS	PPD and CXR	(29)
Lemann *et al*, 2006	57	0	58	0	NS	NS	PPD and CXR	(30)
Colombel *et al*, 2010	242	1	161	0	NS	Recovered	PPD and CXR	(31)
Ochsenkuhn *et al*, 2004	138	0	144	0	NS	NS	NS	(32)
Rheumatoid arthritis								
Maini *et al*, 1998	87	0	14	0	NS	NS	No	(33)
Lipsky *et al*, 2000	340	1	88	0	Disseminated TB	DNS (resistant TB)	No	(34)
St Clair *et al*, 2004	722	4 (US, 1; Europe, 3)	282	0	4 Pulmonary	Recovered	No	(35)
Quinn *et al*, 2005	10	0	10	0	NS	NS	CXR	(36)
Westovens *et al*, 2006	724	8	363	0	2 Pulmonary, 5 extrapulmonary (not disseminated)	1 DNS	CXR	(37)
Abe *et al*, 2006	100	0	47	0	NS	NS	CXR	(38)
Schiff *et al*, 2008	165	2	110	0	1 Pulmonary, 1 extrapulmonary	Recovered	Yes	(39)
Spondyloarthropathy								
Braun *et al*, 2002	35	1	35	0	Disseminated TB	Recovered	CXR, not PPD	(40)
van der Heijde *et al*, 2005	201	0	78	0	NS	NS	CXR or PPD	(41)
Marzo-Ortega *et al*, 2005	28	0	14	0	NS	NS	Yes	(42)
Inman *et al*, 2010	39	0	37	0	NS	NS	NS	(43)
Van den Bosch *et al*, 2002	20	1	20	0	Disseminated TB	Recovered	Yes	(44)
Antoni *et al*, 2005	100	0	100	0	NS	NS	NS	(45)
Kavanaugh *et al*, 2007	52	0	52	0	NS	NS	CXR, PPD	(46)
Sieper *et al*, 2014	105	1	52	0	NS	Recovered	CXR, PPD	(47)

TB, tuberculosis; PPD, purified protein derivative; CXR, chest X-ray; NS, not stated; DNS, did not survive.

Table III. Rates of tuberculosis infection following infliximab therapy versus placebo in patients with RA, IBD and SpA.

Disease	Number of trials	Total number of infliximab patients	Number of infliximab patients infected with tuberculosis (%)	Total number of placebo patients	Number of placebo patients infected with tuberculosis (%)
RA	7	2,148	15 (0.70)	914	0 (0)
IBD	8	580	3 (0.52)	388	0 (0)
SpA	9	1,383	3 (0.22)	927	0 (0)
Total	24	4,111	21 (0.51)	2,229	0 (0)

RA, rheumatoid arthritis; IBD, inflammatory bowel disease; SpA, spondyloarthropathy.

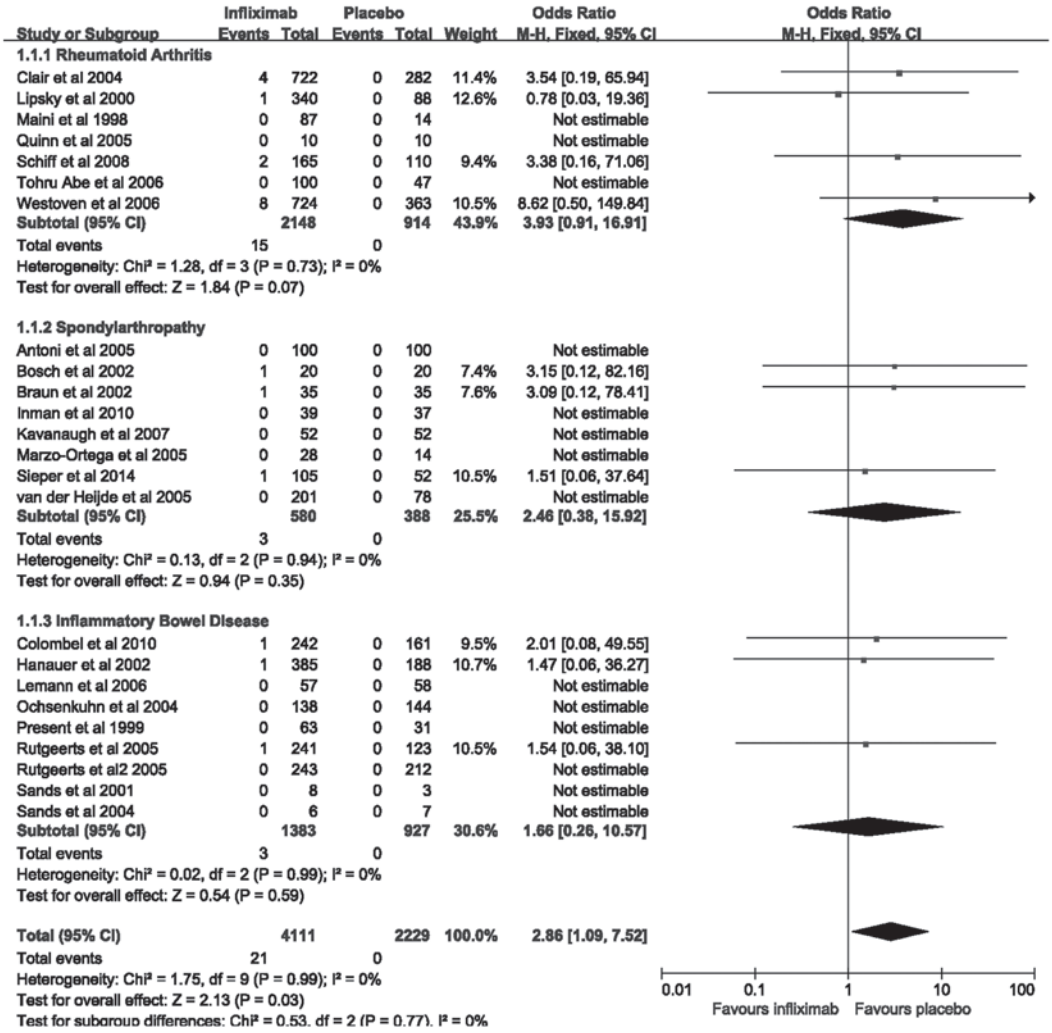

Figure 2. Forest plot of tuberculosis infection in randomized controlled trials of infliximab therapy vs. placebo in rheumatoid arthritis, spondyloarthropathy and inflammatory bowel disease. M-H, Mantel-Haenszel; CI, confidence interval.

macrophage activation, chemokine production by macrophages, and immune cell recruitment during tuberculosis infection (51). Anti-TNF-α monoclonal antibody administration may subsequently increase the risk of the dissolution of intact granulomas, the production of viable mycobacteria, and disease reactivation. This may clarify the increased likelihood of tuberculosis that was observed in patients receiving infliximab therapy.

In the present meta-analysis, 21 cases of tuberculosis, including 15 patients with RA, 3 patients with SpA and 3 patients with IBD, were evaluated. There were some limitations to the present study, even though the probability in each disease subgroup was not statistically significant. Firstly, as a consequence of latent tuberculosis infection (LTBI) screening, a relatively low number of cases of TB activation were recorded in clinical trials of infliximab in IBD, RA and

Table IV. Subgroup analyses of the odds ratio of TB infection with infliximab therapy vs. placebo in IBD, RA and SpA.

Variable	Number of trials	Number of infliximab patients	Number of placebo patients	OR of TB infection	95% CI	I^2 value (%)
All trials	24	4,111	2,229	2.86	1.09-7.52	0
Disease						
RA	7	2,148	914	3.93	0.91-16.91	0
SpA	8	580	388	2.46	0.38-15.92	0
IBD	9	1,383	927	1.66	0.26-10.57	0
Duration of therapy						
≥50 weeks	13	3,327	1,760	3.00	0.97-9.29	0
<50 weeks	11	784	469	2.46	0.38-15.92	0
Immunosuppressor use						
Yes	17	3,390	1,771	2.96	0.94-9.29	0
No	7	721	458	2.59	0.42-15.92	0
Screened for TB						
Yes	16	2,556	1,471	3.10	1.04-9.21	0
No	5	1,149	384	2.09	0.26-17.13	0
Sample size[a]						
Large	8	3,098	1,495	2.94	0.87-9.94	0
Small	16	1,013	734	2.71	0.55-13.26	0
Risk of bias						
Low risk	7	896	579	2.35	0.47-11.77	0
High or unclear	17	3,215	1,650	3.14	0.93-10.54	0

[a]Large samples sizes were ≥200 participants, whereas small sample sizes were <200 participants. TB, tuberculosis; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; SpA, spondyloarthropathy; OR, odds ratio; CI, confidence interval.

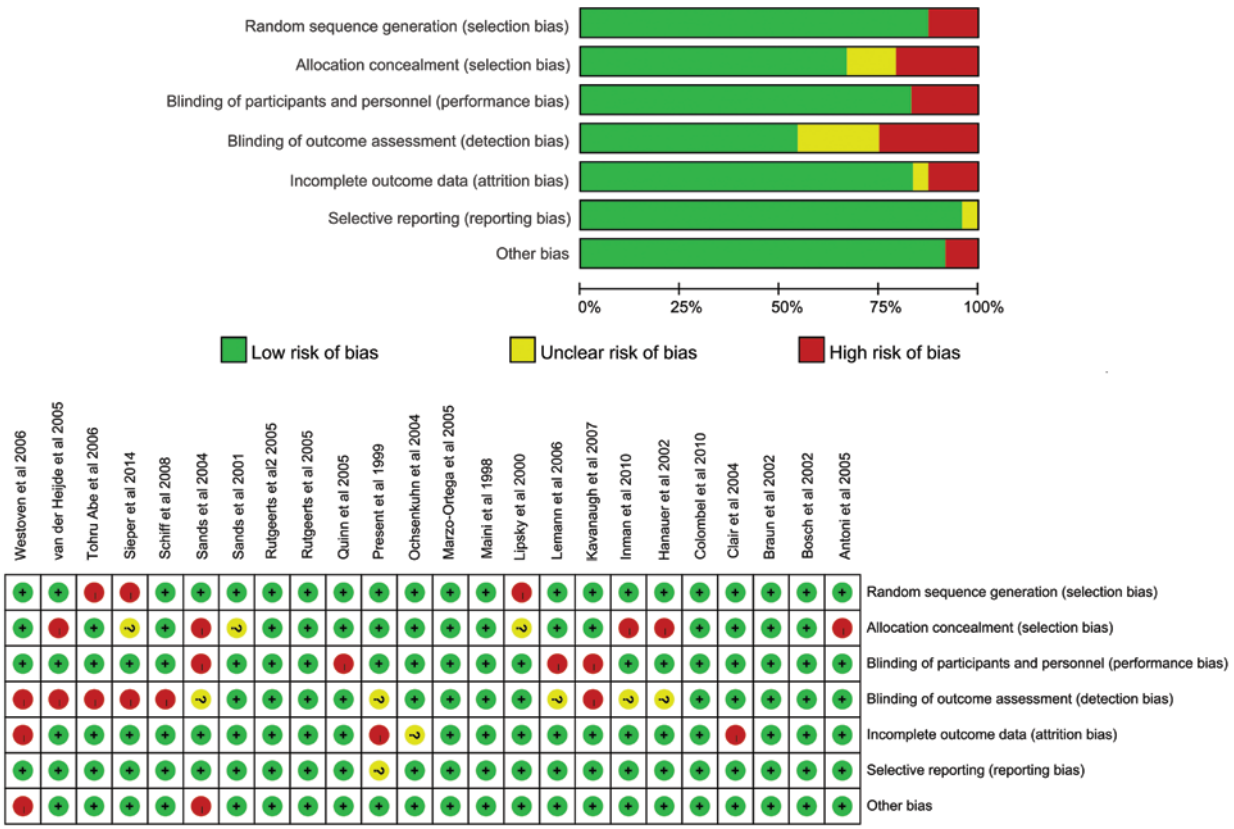

Figure 3. Risk of bias in 24 randomized controlled trials of tuberculosis infection with infliximab therapy.

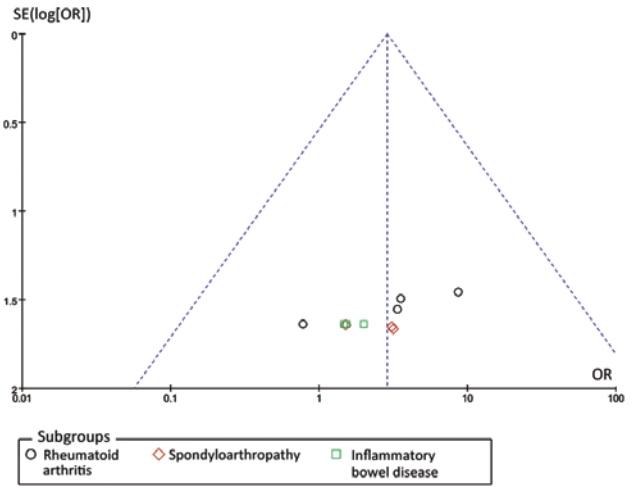

Figure 4. Funnel plot of studies that evaluated the association between infliximab therapy and the risk of tuberculosis infection, vs. placebo.

SpA. Overall, there were 0.51% cases of tuberculosis, 0.70% of which were in patients with RA, and 0.52 and 0.22% cases were in those with IBD and SpA, respectively. Compared with the tuberculosis incidence (38-300/100,000) in the general population based on data from the WHO in 2013, infliximab infusion appears to increase the occurrence of tuberculosis (52). However, a major limitation of the present meta-analysis is that there were only 21 tuberculosis cases included; thus the small sample size may account for why the ORs for the risk of infliximab-associated tuberculosis were consistently demonstrated to lack significance in IBD, RA and SpA. Therefore, the results of the present meta-analysis should be interpreted with caution. Secondly, besides a single trial performed in Japan, the remaining studies were conducted in Europe and the USA, with apparent variations in tuberculosis risk among the different countries. Due to the low incidence of tuberculosis in the Western countries, the incidence of tuberculosis infection in patients treated with inflaximab may be underestimated. Thirdly, the majority of tuberculosis cases were in RA trials, suggesting that the underlying disease and previous immunosuppressive treatment may constitute adjunctive risk factors for tuberculosis activation. Indeed, patients with SpA and IBD predominantly have limited background of immunosuppressive therapies when compared with sufferers of RA. However, not all trials included in the present study constrained the immunosuppressive therapies prior to enrollment, which may have impacted the precision of assessing the risk of infliximab therapy without or with immunosuppressors. The screening procedure for LTBI was reported in 14 trials, whereas it was not documented in the others. Conversely, despite the elevated risk that was demonstrated in the trials after the introduction of procedures to identify LTBI, screening procedures for LTBI prior to treatment are still required due to the limited sample size, relatively low incidence of tuberculosis infection and publication bias. For that reason, screening and management for latent tuberculosis is essential prior to the administration of anti-TNF-α treatments.

It has been demonstrated that infliximab infusion raises the tuberculosis incidence rate (35,38,39). The incidence rate of tuberculosis within this critique may be an underestimation, as the majority of the data that was analyzed originated from Western countries, whereas tuberculosis infection has a higher prevalence in developing countries. As is the situation in China, with the evolution of diagnostic techniques and medical treatment, RA, SpA and IBD incidence increased due to an increase in diagnosis. Despite the cost of infliximab, some patients are able to afford the cost and they are now at an increased risk for tuberculosis infection with a high latent infection rate among the population. It may be interesting to undertake multi-center clinical trials in East Asia in order to avoid inclusion bias.

By comparison, a significant proportion of extra-pulmonary and disseminated forms of tuberculosis were recognized, regardless of the preceding latent tuberculosis screening and treatment (38,39). The frame from the initial infusion to the incidence of tuberculosis varies and no obvious dose dependent effect was observed. These findings suggest that merely screening for TB and treating it prior to infliximab is not sufficient. Additional follow-up is required in order to carefully assess the potential of extra-pulmonary tuberculosis occurring at any dosage, months or years after infusion. The present meta-analysis established that infliximab therapy induced tuberculosis. This indicated that the overall likelihood of TB infection in patients receiving infliximab infusion is sufficient to justify the overall screening, prophylaxis treatment, and close observation of this potentially fatal side effect. Therefore, we consider a PPD test or tuberculin skin test and chest X-ray to be essential prior to treatment, particularly in developing countries.

The present research exhibited numerous positive aspects. Firstly, demanding and conventional methodologies were applied to conduct the present meta-analysis, including the reporting of our search strategy, inclusion criteria, and data extraction process. Moreover, data extraction was conducted by two independent reviewers. Secondly, all trials enrolled in the meta-analysis were high quality RCTs. Finally, no significant heterogeneity was detected between the studies when data were pooled to estimate the OR of tuberculosis infection with infliximab therapy vs. placebo.

The present meta-analysis has several limitations, as a result of the qualities of the published literature that is readily available for analysis. Firstly, only seven of the RCTs were at a low risk of bias, and the quantity of subjects incorporated into the present meta-analysis was limited. Secondly, with the exception of one RCT, all included trials were from developed countries with low tuberculosis incidence rates, and studies from developing countries with a high incidence of tuberculosis were not available, which resulted in a publication bias. Finally, other concerns regarding potential biases remain. In particular, the included trials did not provide any information regarding host-related risk factors, including ethnicity, malnutrition, drug abuse, comorbidity, and contact with infected persons.

In conclusion, the present meta-analysis of 24 RCTs, comprising details from >6,340 patients with RA, SpA and IBD, demonstrated that the OR of tuberculosis infection was markedly increased with infliximab therapy, as compared with placebo therapy. The overall rates of tuberculosis infection were low (0.51%).

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