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## Systematic review and meta-analysis on the association of tuberculosis in Crohn's disease patients treated with tumor necrosis factor- $\alpha$ inhibitors (Anti-TNF $\alpha$ )

Brent L Cao, Ahmad Qasem, Robert C Sharp, Latifa S Abdelli, Saleh A Naser

Brent L Cao, Ahmad Qasem, Robert C Sharp, Latifa S Abdelli, Saleh A Naser, Division of Molecular Microbiology, Burnett School of Biomedical Sciences, College of Medicine, University of Central Florida, Orlando, FL 32816, United States

ORCID number: Brent L Cao (0000-0002-6148-6409); Ahmad Qasem (0000-0003-3740-6963); Robert C Sharp (0000-0002-5167-8941); Latifa S Abdelli (0000-0001-6216-3241); Saleh A Naser (0000-0001-9222-4527).

**Author contributions:** Cao BL and Qasem A are Co-first authors; Cao BL designed the study, acquired the data, analyzed and interpreted the data, and participating in writing the manuscript; Qasem A, Sharp RC, and Abdelli LS interpreted the data and participated in revisions of the manuscript; Naser SA is the group leader who supervised all aspects of the data collection/analyses and manuscript writing.

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Correspondence to: Saleh A Naser, PhD, Professor, Associate Director, Burnett School of Biomedical Sciences, Division of Molecular Microbiology, College of Medicine, University of Central Florida, 4110 Libra Drive, Orlando, FL 32816, United States. [saleh.naser@ucf.edu](mailto:saleh.naser@ucf.edu)  
Telephone: +1-407-8230955

Fax: +1-407-8230955

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### Abstract

#### AIM

To perform a meta-analysis on the risk of developing *Mycobacterium tuberculosis* (TB) infection in Crohn's disease (CD) patients treated with tumor necrosis factor-alpha (TNF $\alpha$ ) inhibitors.

#### METHODS

A meta-analysis of randomized, double-blind, placebo-controlled trials of TNF $\alpha$  inhibitors for treatment of CD in adults was conducted. Arcsine transformation of TB incidence was performed to estimate risk difference. A novel epidemiologically-based correction (EBC) enabling inclusions of studies reporting no TB infection cases in placebo and treatment groups was developed to estimate relative odds.

#### RESULTS

Twenty-three clinical trial studies were identified, including 5669 patients. Six TB infection cases were reported across 5 studies, all from patients receiving TNF $\alpha$  inhibitors. Eighteen studies reported no TB infection cases in placebo and TNF $\alpha$  inhibitor treatment arms. TB infection risk was significantly increased among patients receiving TNF $\alpha$  inhibitors, with a risk difference of 0.028 (95%CI: 0.0011-0.055). The odds ratio was 4.85 (95%CI: 1.02-22.99) with EBC and 5.85 (95%CI: 1.13-30.38) without EBC.

## CONCLUSION

The risk of TB infection is higher among CD patients receiving TNF $\alpha$  inhibitors. Understanding the immunopathogenesis of CD is crucial, since using TNF $\alpha$  inhibitors in these patients could favor mycobacterial infections, particularly *Mycobacterium avium* subspecies *paratuberculosis*, which ultimately could worsen their clinical condition.

**Key words:** Tuberculosis; Tumor necrosis factor-alpha inhibitors; Crohn's Disease; Meta-analysis; Systematic review

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**Core tip:** The increased risk of *Mycobacterium tuberculosis* (TB) and other *Mycobacterium* species when on tumor necrosis factor-alpha (TNF $\alpha$ ) inhibitor treatments has been a problem in patients with autoimmune disorders, such as Crohn's disease (CD). This meta-analysis examines in detail the clinical trials that involve CD patients on TNF $\alpha$  inhibitors and their risk of developing TB infections. Our data concludes that, out of twenty-three studies examined, TNF $\alpha$  inhibitors are indeed associated with an increased risk of TB infection in CD patients. Knowledge of this data could help re-analyze what medications autoimmune patients should be prescribed to and evaluate possible linkages to *Mycobacterium avium* subspecies *paratuberculosis* infection. Thus, this information should be used to further inform clinical decision making and research.

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## INTRODUCTION

The prevalence of Crohn's disease (CD) is growing globally, especially in places adapting western lifestyles<sup>[1]</sup>. The most accepted hypothesis for CD pathogenesis is that a dysregulated immune response to opportunistic intestinal pathogens leads to persistent inflammation<sup>[2]</sup>. Studies have shown that the levels of circulating pro-inflammatory cytokines are highly elevated in CD patients, including tumor necrosis factor-alpha (TNF $\alpha$ )<sup>[3]</sup>. Therefore, there is an increase in the development and use of TNF $\alpha$  inhibitors, which are monoclonal antibodies designed to antagonize this specific cytokine in order to reduce the symptoms of CD<sup>[4]</sup>. Currently, there are three European Medicines Agency and United States Food and Drug Association approved TNF $\alpha$  inhibitors indicated for CD treatment:

Adalimumab, certolizumab pegol, and infliximab.

Although these medications have shown efficacy in alleviating CD symptoms in some patients, 10%-30% of CD patients had no initial response to TNF $\alpha$  inhibitors, and about 50% of the initial responders have lost their response over time<sup>[5]</sup>. TNF $\alpha$  inhibitor treatment for other inflammatory autoimmune disorders, such as rheumatoid arthritis (RA), show similar effects, where roughly 30%-40% of RA patients have a poor response to the medications<sup>[6,7]</sup>. Moreover, about 40% of CD patients are at high risk of disease relapse after discontinuing TNF $\alpha$  inhibitor treatment<sup>[8]</sup>.

Additionally, inhibiting TNF $\alpha$  increased risk of infections as an adverse effect, especially opportunistic infections<sup>[9]</sup>. However, it is uncertain whether there is sufficient evidence indicating an increase in risk of developing *Mycobacterium tuberculosis* (TB) infection from using TNF $\alpha$  inhibitors among CD patients. A 2016 meta-analysis reported a significant increase in opportunistic infections overall and a moderate increase in other types of infections; however, that study did not find a significant increase in the risk of TB infection development among CD patients who received TNF $\alpha$  inhibitors<sup>[10]</sup>.

Our primary focus on TB infection is pertinent, since there is an irrefutable growing evidence relating CD to *Mycobacterium avium* subspecies *paratuberculosis* (MAP), an intracellular TB-like bacterium<sup>[11]</sup>. More importantly, TNF $\alpha$  is necessary for formation and maintenance of granuloma in order to limit mycobacterial infections like MAP<sup>[12]</sup>. Thus, targeting TNF $\alpha$  can not only disrupt the body's ability to contain and respond to TB but also to MAP, which could further increase the patient's susceptibility to MAP or worsen their disease condition<sup>[2]</sup>. Therefore, the effect of TNF $\alpha$  inhibitors on CD patients-associated with MAP infection requires further investigation.

Other meta-analyses of TB infection risk potentially associated with anti-TNF $\alpha$  therapy excluded trials reporting zero-event data from both anti-TNF $\alpha$  treatment and placebo groups ("double-zero studies")<sup>[13,14]</sup>. The number of such "double-zero studies" was high as the incidence of TB infection was very low. Additionally, data from trials reporting zero-event data from one group ("single-zero studies") were subject to modification ("continuity correction") that lacks biological basis. These analytical approaches cast uncertainty about whether there is sufficient evidence indicating an increase in risk of developing TB infection from using TNF $\alpha$  inhibitors. Numerous double-blind, randomized, placebo-controlled trials (RCTs) of TNF $\alpha$  inhibitor use in CD patients provide data to estimate the risk of TB development in CD patients receiving those medications. This will open more insights into selecting the most appropriate treatment plan and antibiotics for CD patients<sup>[15]</sup>. Thus, we conducted a meta-analysis of randomized controlled trials to quantitatively analyze the altered risk for developing TB in CD patients treated with TNF $\alpha$  inhibitors.

## MATERIALS AND METHODS

This systematic review and meta-analysis was registered in the prospective register of systematic reviews (PROSPERO) international database on February 8<sup>th</sup>, 2018 (ID: CRD42018087548)<sup>[16]</sup>. The work followed the preferred reporting items for the systematic reviews and meta-analyses (PRISMA) checklist<sup>[17]</sup>.

### Data source and search strategy

A search in the PubMed database up to January 21, 2018 was conducted. The following search terms were used: Tuberculosis, biologic(s), adalimumab, certolizumab, infliximab, anti-TNF $\alpha$ , TNF $\alpha$  inhibitors, or TNF $\alpha$  in conjunction with Crohn's disease. The search results were further restricted to double-masked, randomized, placebo-controlled trials. ClinicalTrials.gov supplemented the searches, in the event of clinical trials that did not yet have published data in PubMed. Irrelevant studies were screened out after title and abstract review. Full text and abstracts of studies that made it past the initial screening were evaluated more closely.

### Selection

Only studies and sources in English were considered. Studies were included if they were randomized, placebo-controlled, double-masked trials with appropriate exposure in adult populations. Exposure was defined as the patient receiving treatment of TNF $\alpha$  inhibitors (adalimumab, certolizumab pegol, and infliximab), which were approved for the treatment of CD in adult patients (18 years or older) by the EMA and the FDA. Non-approved drugs and biosimilars of TNF $\alpha$  inhibitors were excluded from the study. All doses of drugs were included. Observational studies and duplicates were screened out. Single studies that had both an induction and maintenance phase but reported distinct patient groups were analyzed as two separate trials.

### Data extraction

Data was extracted onto a Microsoft Excel spreadsheet. First author, year of publication, study duration, number of participants in treatment and control groups, patient characteristics, treatment parameters (*i.e.*, TNF $\alpha$  inhibitor and placebo), events in treatment and control groups, and screening method were obtained from each study. Studies found from ClinicalTrials.gov were also analyzed for the aforementioned criteria. Cases of TB infection were the primary outcome assessed in this analysis. TB infection was defined as diagnosis of active TB by the clinician or other medical professional.

### Risk difference

Arcsine differences (ASD) were used as the measure of risk differences. For a trial with  $N_T$  subjects in the anti-TNF $\alpha$  treatment group,  $N_C$  subjects in the control group, and  $a$  and  $b$  being the number of reported TB cases, respectively, the ASD can be calculated with Equation 1

below:

$$\widehat{ASD} = \arcsin \sqrt{\frac{a}{N_T}} - \arcsin \sqrt{\frac{b}{N_C}} \quad (\text{Equation 1})$$

The use of arcsine transformation can be dated back to the 1940s<sup>[18,19]</sup>. The main advantages of using ASD are that the variance of the point estimate (*i.e.*, ASD) is determined solely by the sample size and that it handles occurrences of 0 counts, allowing for incorporation of trials with 0 events in both control and treatment groups into meta-analyses<sup>[20]</sup>.

### Relative odds

Odds ratio (ORs) were calculated using the Yusuf-Peto method<sup>[21]</sup>. Although widely used, the Mantel-Haenszel method cannot include trials with zero events from either one or both groups without substituting zero with a non-zero number. The Yusuf-Peto method can include single-zero studies; thus, the Yusuf-Peto odds ratio ( $OR_{\text{peto}}$ ) has been recognized as a relatively efficient estimator, especially when treatment effects from trials are not large or the sample size is similar between two groups<sup>[22]</sup>. The  $OR_{\text{peto}}$  can be calculated with Equation 2:

$$\text{Log} \widehat{OR}_{\text{peto}} = \left( a - \frac{a+b}{n_T+n_C} * n_T \right) * \frac{(n_T+n_C)^2 / (n_T+n_C-1)}{(a+b)(n_T-a+n_C-b)n_Tn_C} \quad (\text{Equation 2})$$

Where  $n_T$ ,  $n_C$ ,  $a$  and  $b$  denote the same as in Equation 1.

However, the Yusuf-Peto method cannot include double-zero studies. Existing approaches that have been used for meta-analysis on TNF $\alpha$  inhibitors are to exclude double-zero studies and, for single-zero studies, to change zero counts by adding either 0.5 or a similar number that is inversely proportional to the relative size of the opposite group<sup>[9,10,23]</sup>. These analytical treatments are not biologically supported. In the case of excluding double-zero studies, the results will bias away from the null hypothesis. Thus, we proposed an epidemiologically-based background correction (EBC). Our approach was to estimate the expected number of incidence cases (*e.g.*, if 0.01 TB cases were expected from an experimental arm, such TB cases could not be "observed" but using 0.01 to replace 0 would reflect the underlying epidemiology). Our correction assumed that the incidence of TB infection was 20 cases/100000 person-years as reported for patients with inflammatory bowel disease (IBD) in the United Kingdom<sup>[24]</sup>. EBC was then calculated according to Equation 3 below.

$$\text{EBC} = n \times \text{Follow up duration (years)} \times \frac{20 \text{ cases}}{100,000 \text{ person-years}} \quad (\text{Equation 3})$$

Where  $n$  is the number of subjects in either the treatment or the placebo group. The EBC was added into counts for both TB and non-TB for any trials reporting zero occurrences.

### Statistical analysis

Statistical analysis followed the intent-to-treat principle. R version 3.4.3<sup>[25]</sup> with the "meta" package was used to

make plots and calculate the Yusuf-Peto odds ratio and ASD along with the corresponding confidence intervals (calculation accuracy was verified through manual calculation on a Microsoft Excel spreadsheet). Weight of contribution from individual studies to the pooled estimate was based on the inverse variance of the point estimate for individual studies. Inter-study variance was estimated using the DerSimonian-Laird method<sup>[26]</sup>. Two-sided *P* values of less than 0.05 and the 95% confidence interval (95%CI) excluding the null indicated statistical significance.

## RESULTS

### Search results

The selection process was summarized in Figure 1. A total of 748 articles were located from PubMed. Based on the review of titles and abstracts, 706 studies were not relevant or were duplicates, and they were subsequently excluded. The remaining 42 articles were more closely examined to determine inclusion in the analysis. Six studies were excluded because they were head-to-head, 3 were not placebo-controlled, 5 did not study EMA and FDA approved drugs, and 3 studies were duplicates (measured the same sample). Two trials were located through clinicaltrials.gov; of which, one (NCT00291668) did not post the results and was excluded. Thus, a total of 23 studies were included in the meta-analysis<sup>[27-48]</sup>.

The 23 studies (Table 1) has evaluated adalimumab (7 studies; 1726 patients), certolizumab pegol (6 studies; 2,008 patients), and infliximab (10 studies; 1935 patients). Both induction and maintenance studies were included (5 induction; 18 maintenance). A total of 5669 patients underwent the clinical trials, with 3275 patients in the treatment group and 2394 patients in the control group. Follow-up duration ranged from 4 to 104 wk (mean follow-up duration = 32 wk). A total of about 3558 person-years were exposed to TNF $\alpha$  inhibitors or placebo (2033 person-years in the treatment, 1525 in person-years in the control). Publication dates ranged from 1997 to 2016. A total of 6 cases of TB were reported; all were from the anti-TNF $\alpha$  treatment groups. Two cases of TB were reported with adalimumab (one study), 1 with certolizumab pegol, and 3 with infliximab (three studies).

### Risk difference

The risk difference between TNF $\alpha$  inhibitors and placebo was 0.028 (95%CI: 0.0011-0.055; *P* < 0.05) (Table 2). Random model results are presented, although the inter-study variance did not additionally contribute to the total variance of the pooled ASD (*i.e.*, the DerSimonian-Laird estimate of inter-study variance was zero). The weights for each drug - adalimumab, certolizumab pegol, and infliximab - were 28.9%, 36.9%, and 34.2% respectively. The respective risk differences were 0.028, 0.015, and 0.042 (Figure 2).

The funnel plot of the ASDs (Figure 3) indicates that trials showing no difference were apparently more likely published. This did not suggest publication bias, since risk of TB infection was neither the reason for publishing those trials nor the primary objective of those studies. In fact, the funnel plot reflects the fact that larger studies provided better chance to detect rare risks than smaller ones.

### Relative odds

The sizes of the treatment arms were mostly similar to the sizes of the control arms, with the median ratio being 1.03. However, particular studies had very unbalanced arm sizes (maximum ratio = 3.32:1, average ratio = 1.64:1). The odds ratio was 4.85 (95%CI: 1.02-22.99; *P* < 0.05) with EBC and 5.85 (95%CI: 1.13-30.38; *P* < 0.05) without EBC (Table 2). The random effects model was not used because the Yusuf-Peto odds ratio was calculated under the assumption of a fixed effects model<sup>[21]</sup>. Weights for adalimumab, certolizumab pegol, and infliximab were 31.1%, 18.2%, and 50.7%, respectively, in the analysis with EBC (Figure 4). Without EBC, only 5 studies could be included (with the weight of 31.5% for adalimumab, 17.7% for certolizumab pegol, and 50.8% for infliximab).

### Expected number of anti-TNF $\alpha$ treated cases to observe a tuberculosis case

If the background TB infection incidence in patients was 20 cases/100000 person-years, one TB case might be expected from a community of 5000 CD patients within a year. An ASD of 0.028 would be translated into a TB incidence of 177 cases/100000 person-years; thus, 1 TB case may be expected when treating 565 patients with TNF $\alpha$  inhibitors for one year (Table 3). If the harm effect of TNF $\alpha$  inhibitors can be described on a multiplicative scale as shown from the pooled Yusuf-Peto odds ratio, the numbers of patients to be treated to expect 1 TB case might be around 855 to 1031 (Table 3).

## DISCUSSION

One of the most common complications following the use of TNF $\alpha$  inhibitors is increasing frequency of opportunistic infections<sup>[49]</sup>. Particularly, there is strong evidence linking mycobacterial infection to TNF $\alpha$  inhibitors, and TB infection risk is higher among patients receiving infliximab in comparison to controls<sup>[50]</sup>. Interestingly, TNF $\alpha$ -deficient animal models were more susceptible to mycobacterial infections compared to wild-type controls, although there was no survival rate difference in a healthy environment<sup>[51]</sup>. This indicates that TNF $\alpha$  plays a critical role in the immune response against mycobacterial infections.

Several studies have shown that there is a microbial factor affecting CD patients, and MAP was isolated from intestinal tissues, blood, and milk samples of not

**Table 1 Summary of randomized, placebo-controlled, double-masked trials included**

Study	Follow-up duration (wk)	Anti-TNF $\alpha$ treatment		Placebo	
		N <sup>1</sup>	N <sup>2</sup>	N <sup>1</sup>	N <sup>2</sup>
<b>Adalimumab</b>					
Hanauer <i>et al</i> <sup>[44]</sup> , 2006	4	0	225	0	74
Colombel <i>et al</i> <sup>[47]</sup> , 2007	52	2	517	0	261
Sandborn <i>et al</i> <sup>[35]</sup> , 2007a	52	0	37	0	18
Sandborn <i>et al</i> <sup>[34]</sup> , 2007b	4	0	159	0	166
Rutgeerts <i>et al</i> <sup>[37]</sup> , 2012	48	0	64	0	65
Watanabe <i>et al</i> <sup>[28]</sup> , 2012	52	0	25	0	25
Watanabe <i>et al</i> <sup>[28]</sup> , 2012	4	0	67	0	23
		Total	1094		632
<b>Certolizumab pegol</b>					
Winter <i>et al</i> <sup>[27]</sup> , 2004	12	0	66	0	24
Schreiber <i>et al</i> <sup>[30]</sup> , 2005	20	0	145	0	73
Sandborn <i>et al</i> <sup>[36]</sup> , 2007c	26	0	331	0	329
Schreiber <i>et al</i> <sup>[31]</sup> , 2007	20	1	216	0	212
Sandborn <i>et al</i> <sup>[33]</sup> , 2011	6	0	223	0	215
UCB Pharma <sup>[42]</sup> , 2014	36	0	87	0	87
		Total	1068		940
<b>Infliximab</b>					
Targan <i>et al</i> <sup>[29]</sup> , 1997	12	0	83	0	25
D'Haens <i>et al</i> <sup>[46]</sup> , 1999	4	0	22	0	8
Present <i>et al</i> <sup>[41]</sup> , 1999	18	0	63	0	31
Rutgeerts <i>et al</i> <sup>[38]</sup> , 1999	36	0	37	0	36
Hanauer <i>et al</i> <sup>[45]</sup> , 2002	44	1	385	0	188
Sands <i>et al</i> <sup>[32]</sup> , 2004	40	0	139	0	143
Lémann <i>et al</i> <sup>[43]</sup> , 2006	52	0	57	0	58
Colombel <i>et al</i> <sup>[48]</sup> , 2010	30	1	169	0	170
Regueiro <i>et al</i> <sup>[40]</sup> , 2011	52	0	11	0	13
Regueiro <i>et al</i> <sup>[39]</sup> , 2016	104	1	147	0	150
		Total	1113		822

<sup>1</sup>Number of TB cases; <sup>2</sup>Number of total subjects.

**Table 2 Risk of *Mycobacterium tuberculosis* infection associated with the use of tumor necrosis factor-alpha inhibitors in patients with Crohn's disease**

	<i>n</i>	Risk estimate	95%CI	<i>P</i> value
Risk difference odds ratio	23	0.028	(0.0011, 0.055)	0.042
Including Double-Zero Studies	23	4.85	(1.02, 22.99)	0.047
Excluding Double-Zero Studies	5	5.85	(1.13, 30.38)	0.036

*n*: Number of individual clinical studies pooled together.

only CD patients but also patients with RA and type 1 diabetes<sup>[52-58]</sup>. Since MAP shares molecular homology and activity similar to TB, inducing TB infection susceptibility is an alarming sign for the immune response against MAP infection<sup>[58-60]</sup>.

This study advances knowledge and awareness of the association between TNF $\alpha$  inhibitors and TB among CD patients. First, a non-biased estimation of TB infection risk associated with TNF $\alpha$  inhibitors for CD treatment was performed through arcsine transformation of TB incidence, which enabled the inclusion of all qualified studies including double-zero studies in the analysis. Second, a novel, epidemiologically-based background correction to adjust for zero counts was developed to enable the inclusion of double-zero studies into the estimation of the relative effect (odds ratio in this study). Lastly, with the use of these analytical approaches, a

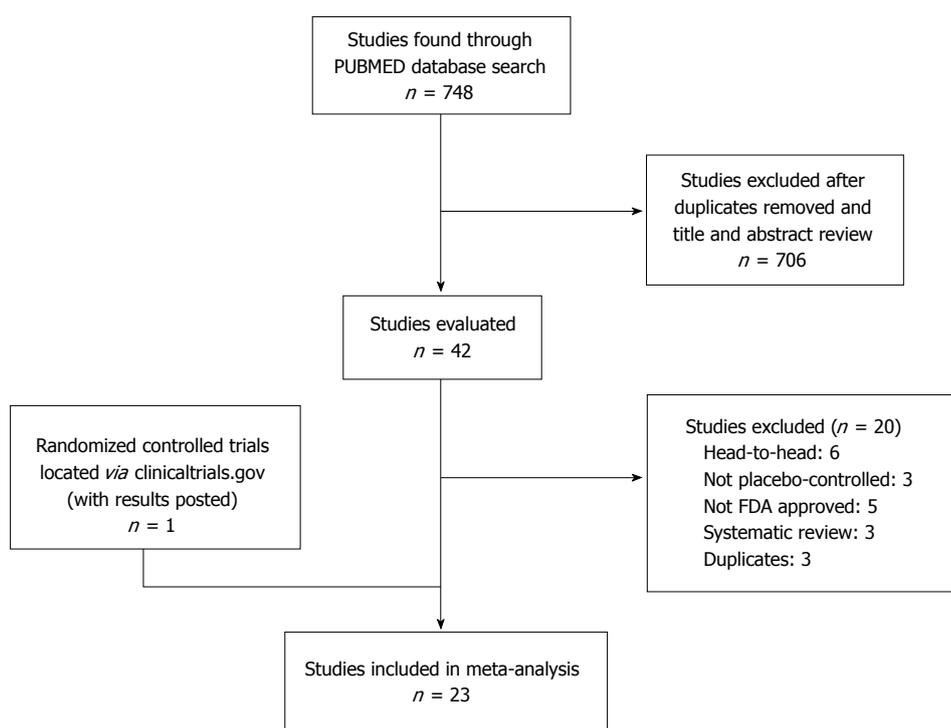
significant increase of TB infection risk associated with using TNF $\alpha$  inhibitors to treat CD was shown from existing evidence, challenging findings of previous studies.

In our study, all 23 qualified trials were included. Among these 23 studies, 18 (78%) did not report TB cases from either the anti-TNF $\alpha$  treatment or the control group; these double-zero studies would have been excluded if we had followed the methods that previous meta-analyses in this area took. The double-zero observation was not a surprise. TB infection was rare in the Americas, Europe, Japan, Austria, and South Africa, where these RCTs were conducted. The median sample size of the control group across these 23 studies was 73 people; the median follow-up duration was 30 wk. Mathematically, only about 0.0084 TB cases would be expected in these control patients if the background TB

**Table 3** Estimated absolute incidence of *Mycobacterium tuberculosis* infection in patients with Crohn's disease treated with tumor necrosis factor-alpha inhibitors and the number of patients with Crohn's disease who need to be treated with tumor necrosis factor-alpha inhibitors to expect one *Mycobacterium tuberculosis* case

	Incidence of TB with TNF $\alpha$ treatment (cases/person-years) <sup>1</sup>	Number of patients treated to see one TB Case in one year
Based on risk difference	177/100000	565
Based on relative odds estimated with background correction	97/100000	1031
Based on relative odds estimated without background correction	117/100000	855

<sup>1</sup>The background incidence was assumed to be 20 cases/100000 person-years as reported by Aberra *et al*<sup>[24]</sup>. TB: *Mycobacterium tuberculosis*.



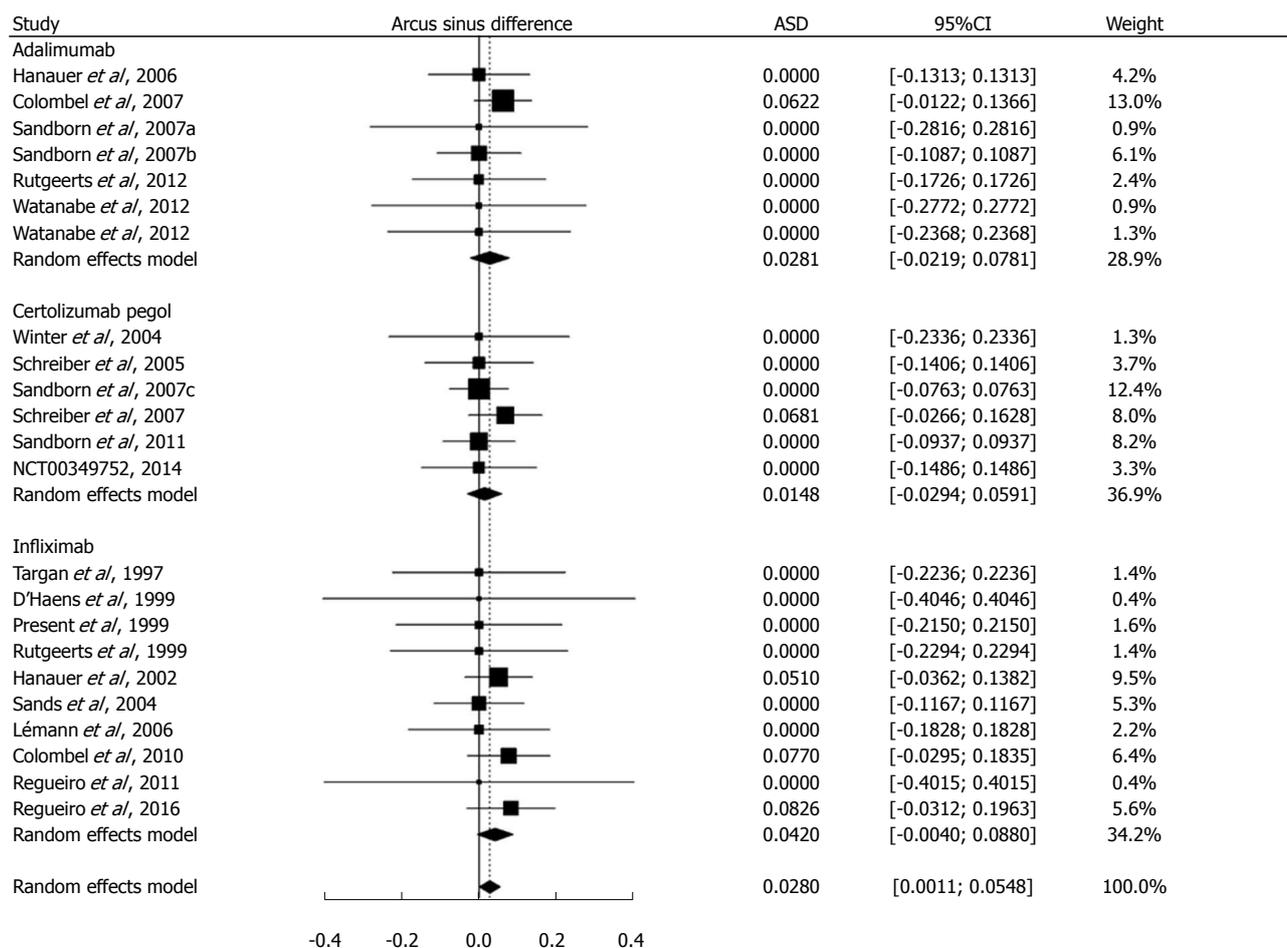
**Figure 1** Evidence collection and selection.

infection incidence was 20 cases/100000 person-years as reported by Aberra *et al*<sup>[24]</sup>. If TNF $\alpha$  inhibitors had increased the TB infection risk by 5 times, there might have been about a 4% chance to observe 1 TB case in the anti-TNF $\alpha$  treatment arm. Meta-analysis provides excellent opportunities to pool multiple studies together to improve the estimation of the chance of observing a TB case. Discarding these double-zero studies (78% of the studies in our analysis) might decrease the value of meta-analysis.

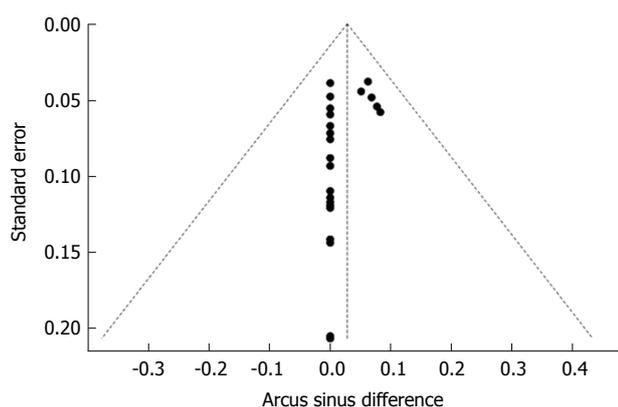
We regarded the risk difference calculated after arcsine transformation of incidence as the primary results. The ASD method does not call for any correction for zero counts. Additionally, the robustness of an ASD estimate is not contingent on the effect size and the treatment-to-control balance of sample size. These analytical features provided a distinct advantage over either the Yusuf-Peto method or the Mantel-Haenszel method. However, from a biological perspective, it is

possible that the TB infection risk from the use of TNF $\alpha$  inhibitors in patients with CD may be better described on a multiplicative scale (relative scale). Thus, a risk difference of 0.028 could be translated into increasing the risk of TB by a factor of 8, as the number needed to harm was calculated at 565 patients compared to the background number needed to harm of 5000 patients (Table 3). However, the 8 times increased risk of TB (based off ASD) only applies if the incidence of TB remains constant (20 cases/100000 person-years). We thus performed further analysis to better describe this multiplicative scale, for which we chose the Yusuf-Peto method because, as compared to the Mantel-Haenszel method, it can handle single-zero studies<sup>[61]</sup>. Unfortunately, the Yusuf-Peto method cannot handle double-zero studies.

We proposed an epidemiologically-based background correction (*i.e.*, EBC) to mathematically replace zeros. If metrics other than ASD (*e.g.*, odds ratio, hazard ratio or



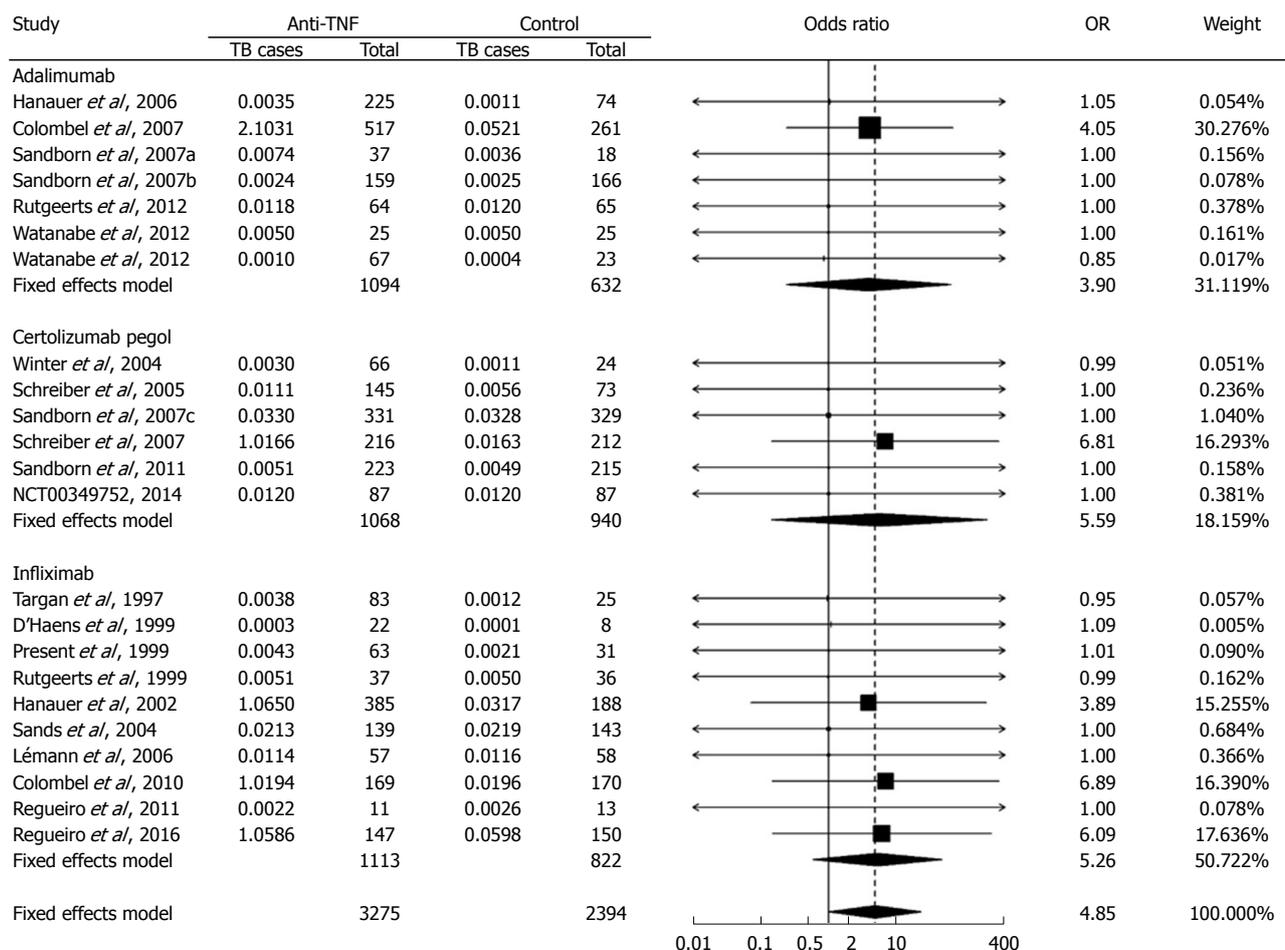
**Figure 2** Difference of the risk of *Mycobacterium tuberculosis* infection between patients with Crohn's disease treated with tumor necrosis factor-alpha inhibitors and those treated with placebo. Risk difference was calculated after arcsine transformation of *Mycobacterium tuberculosis* incidence (Arcus sinus difference, ASD) and indicated by the numbers on x-axis. Weight: the percentage contribution of an individual study to the overall estimation. The x-axis indicates the risk difference. The vertical dashed line indicates the overall point estimate. The solid horizontal lines show the confidence interval (CI). The size of the black box and diamond is proportional to the corresponding weight.



**Figure 3** Relationship between the estimated *Mycobacterium tuberculosis* infection risk difference and the corresponding standard error of the estimate. Risk difference was calculated after arcsine transformation of *Mycobacterium tuberculosis* incidence (Arcus sinus difference, ASD). The dashed vertical line indicates the overall arcsine difference found, and the diagonal lines indicate the expected 95% confidence intervals associated with the expected mean ASD for clinical trials with various numbers of study subjects.

rate ratio) have to be estimated and the risk of interest is so rare that even one occurrence is not expected, we recommend that EBC be used for continuity correction instead of adding 0.5 (or a similar number depending on the ratio of sample size between treatment and control groups) or statistical-model based estimates<sup>[62,63]</sup>. The latter approaches lack biological considerations, and in the case of adding a number around 0.5, artificially make a much larger background incidence than there actually is (it would have boosted the background incidence by ~60 times in this meta-analysis).

There are major limitations with the use of EBC. The EBC was based off TB incidence rate in the UK IBD populations. Although the RCTs in this study were largely conducted in Western countries, the TB incidence of Crohn's patients in the UK may not represent the TB incidence of the countries in which the clinical trials were conducted, let alone the patients who participated in the clinical trial. Furthermore, the TB incidence rate was found in populations with IBD, which may not be



**Figure 4** Odds of patients developing active *Mycobacterium tuberculosis* when treated with tumor necrosis factor-alpha inhibitors for Crohn's disease relative to those treated with placebo. Odds ratio (OR) was calculated using the Yusuf-Peto method and indicated by the numbers on the x-axis. Number of *Mycobacterium tuberculosis* cases was modified using the background *Mycobacterium tuberculosis* incidence, *i.e.*, adding to the reported number of *Mycobacterium tuberculosis* cases with a number (less than 1) that might be expected from a given number of patients (listed under "Total"). Weight: the percentage contribution of an individual study to the pooled estimate. The vertical dashed line indicates the pooled odds ratio. The solid horizontal lines show the confidence interval (CI). The size of the black box and diamond is proportional to the corresponding weight. *Mycobacterium tuberculosis* here denotes tuberculosis.

representative of TB incidence in the population with CD.

Aside from the analytical approach to avoid Simpson's paradox, the validity to pool results from individual studies in this meta-analysis largely resides in the fact that each study had a placebo-treatment arm. The impact from the difference of study populations was therefore minimized, as the end point (risk difference or odds ratio) mainly reflected the effect of TNF $\alpha$  inhibitors [the effect of confounders was either subtracted out (for ASD) or normalized (for ORs)]. Thus, common factors restricting the use of meta-analysis, such as geographic location, population characteristics, exposure, maintenance vs induction trials, status (*e.g.*, phase 3 vs phase 4) of the clinical trials, secular trend, and TB screening methods could be assumed to be not of major concern.

Perhaps the fact that only studies in English were included in the analysis may limit the generalizability of the results, considering that the demographics and trends of CD and TB infection differ among different

regions or different populations<sup>[64]</sup>. The included studies were mainly EMA- and FDA-regulated clinical trials conducted in western countries. In fact, only one study that contained strictly Asian populations was included in this meta-analysis<sup>[28]</sup>. EBC may also be compromised, as the prevalence and incidence of TB infection was higher in Asian countries<sup>[65]</sup>. Thus, caution should be taken when extrapolating the results from this analysis to predict TB infection risk of TNF $\alpha$  inhibitors treating CD in non-western countries.

Additional attention should be paid to TB screening. Patients could have had either latent TB infection that was reactivated or acquired TB infection through exposure. The screening methods of trials varied and often went unreported. Furthermore, screening out patients based on a positive tuberculin skin test may have different impacts on the TB infection occurrence due to the different practices of Bacillus Calmette-Guérin vaccinations<sup>[66]</sup>. Lastly, two studies did not report screening methods<sup>[39,45]</sup>. Close examination of the additional details of TB screening may provide further

insight on the nature of TB infection - whether it was acquired or reactivated.

We conclude that there is sufficient evidence to assert that using TNF $\alpha$  inhibitors increases the risk of developing TB infection in patients with CD. Twenty-three studies were analyzed, and multiple statistical methods repeatedly gave significant risk. To our knowledge, these 23 studies represented all appropriate literature available for the topic at hand, with an extensive and careful review conducted. No studies were excluded, provided that they used a placebo control and were randomized and masked. The randomization minimized potential confounding such as age, duration of IBD, and disease activity. These results challenge findings of previous studies, which reported no significantly increased risk of TB infection when TNF $\alpha$  inhibitors were used to manage patients with CD<sup>[10,14]</sup>. Based on the risk difference found in this study, on average 565 patients treated with TNF $\alpha$  inhibitors may result in 1 patient getting infected with TB, vs 5000 patients not treated with TNF $\alpha$  inhibitors producing 1 case of TB, if the background incidence of TB infection in moderately severe CD is similar to the rates found in the UK IBD population.

The etiology of CD remains uncertain. Evidence suggests that CD may be caused by an immune response to commensal enteric bacteria<sup>[67]</sup>. Recent research also suggests that CD is intimately linked to MAP, which is a TB-like bacterium<sup>[11,55,57]</sup>. The use of TNF $\alpha$  inhibitors in these patients could favor MAP infection and worsen the patient condition. It is currently difficult to come to conclusions considering that the RCTs did not test for MAP infection - much less reported it. Further research could be done on looking at patient outcomes and determining which patients had MAP infection and what their susceptibility to infection was.

## ARTICLE HIGHLIGHTS

### Research background

Recent literature has identified many adverse effects from the use of tumor necrosis factor alpha (TNF $\alpha$ ) inhibitors. Among these are an increased risk of opportunistic infections and serious adverse events. However, previous meta-analyses have not identified a significantly increased risk of tuberculosis (TB) infection, which is especially pertinent considering that *Mycobacterium avium* subspecies *paratuberculosis* (MAP) is suspected to have an intimate role in the etiology of Crohn's disease (CD).

### Research motivation

Due to the suspected role of MAP in the etiology of CD and previous literature on the topic, TNF $\alpha$  inhibitors likely increase the risk of TB infection, which would guide future clinical decisions. However, such an association has not been adequately quantified. Additionally, current statistical models commonly used in meta-analyses fail to adequately analyze data where events are rare (defined as less than 1 case per 1000 person-years). Our research would not only bring additional considerations when making clinical decisions about anti-TNF $\alpha$  therapy but also introduce existing statistical models and novel corrections that can help deal with rare events.

### Research objectives

In this study, we seek to advance the awareness of and quantify the association

between TNF $\alpha$  inhibitors and TB in CD patients. We seek to include all qualified studies - including studies with zero events in the treatment and control groups - without using corrections, which previous meta-analyses have failed to do. Finally, we seek to introduce a novel, epidemiologically-based background correction (EBC) that can adjust for zero counts.

### Research methods

The Preferred Reporting Items for the Systematic reviews and Meta-Analyses (PRISMA) protocol was followed. Only randomized, placebo-controlled trials (RCTs) were considered. Arcsine differences were used to calculate risk differences in a non-biased way. Odds ratios were calculated using the Yusuf-Peto method both with and without corrections (EBC).

### Research results

Twenty-three RCTs were analyzed, and all the statistical methods repeatedly provided significantly increased risk of TB infection. A risk difference (RD) of 0.028 (95%CI: 0.0011-0.055) was calculated. The odds ratio (OR) was 4.85 (95%CI: 1.02-22.99) when all studies were included using EBCs and 5.85 (95%CI: 1.13-30.38) when studies reporting zero tuberculosis cases were excluded.

### Research conclusions

There is an increased risk of TB infection in patients with Crohn's disease who use TNF $\alpha$  inhibitors. This risk could range from 5 times (OR) to as high as 8 times (RD). Alternative therapy such as using more antibiotics and less immunosuppressive agents may be evaluated.

### Research perspectives

This study provided us with additional approaches that can be considered when conducting future meta-analyses. ASD is a particularly useful method that can contribute to future meta-analyses. The relationship between MAP and TB is still unclear. Further research on the validity of the EBC should be pursued.

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