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Tumor Necrosis Factor-alpha 저해제가 결핵 발생에 미치는 영향

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Effects of Tumor Necrosis Factor-alpha Inhibitors on the Incidence of Tuberculosis

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ABSTRACT

Objective: Tumor necrosis factor-alpha (TNF-alpha) inhibitors are used as a treatment in various immune-mediated inflammatory diseases (IMIDs). Tuberculosis (TB) risk is reported in several meta-analyses in patients treated with TNF-alpha inhibitors. The purpose of this study is to collect, review, and evaluate the TB risk in TNF-alpha inhibitors according to IMIDs indications and between soluble-receptor TNF-alpha inhibitor and monoclonal-antibody TNF-alpha inhibitors. **Methods:** A systematic literature search on systematic reviews and meta-analyses was performed in PubMed, MEDLINE, Cochrane library, and EMBASE. We identified meta-analyses that evaluated TB infection risk of TNF-alpha inhibitors in IMIDs patients. **Results:** Thirteen meta-analyses including 41 study results were included in this umbrella review. IMIDs patients treated with TNF-alpha inhibitors had an increased risk of TB than control group (placebo with or without standard therapy patients) (relative risk ratio (RR) 2.057, 95% confidence interval (CI) 1.697 to 2.495). Among them, RA patients with TNF-alpha inhibitors had a higher risk of TB than control group (RR 1.847, 95% CI 1.385 to 2.464), and non-RA patients with TNF-alpha inhibitors had an increased risk of TB (RR 2.236, 95% CI 1.284 to 3.894). In subgroup analysis on TB risk between soluble-receptor TNF-alpha inhibitor and monoclonal-antibody TNF-alpha inhibitors in RA patients, the analysis indicated that monoclonal-antibody TNF-alpha inhibitors had higher risk of TB than soluble-receptor TNF-alpha inhibitor (RR 2.880, 95% CI 1.730 to 4.792). **Conclusion:** This umbrella review confirms that the risk of TB is significantly increased in TNF-alpha inhibitor treated patients compared to control group.

KEY WORDS: Tumor necrosis factor-alpha inhibitor, tuberculosis, immune-mediated inflammatory disease, rheumatoid arthritis, umbrella review

Tumor necrosis factor-alpha (TNF-alpha) is a pleiotropic cytokine that has proinflammatory and immune-regulatory function.[1] TNF-alpha has been the therapeutic target in immune-mediated inflammatory diseases (IMIDs), such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD) -ulcerative colitis (UC) and Crohn's disease (CD), ankylosing spondylitis (AS), psoriasis (Ps), psoriatic arthritis (PsA), and spondyloarthritis (SpA).[1] Although the exact mechanism of action of IMIDs is unknown, as IMIDs are all inflammatory diseases, they share some common pathological pathways.[2] IMIDs commonly involve dysregulation of immune systems due to imbalance of inflammatory cytokines such as interleukin (IL)-12, IL-6, and TNF-alpha.[2,3] Among these cytokines, TNF-alpha has been recognized as a pivotal cytokine in the pathophysiology of IMIDs.[4]

Since FDA's first approval of TNF-alpha inhibitor, etanercept (ETA), to date, five TNF-alpha inhibitors have been approved for IMIDs: ETA, infliximab (IFX), adalimumab (ADA), golimumab (GOL), and certolizumab pegol (CZP).[1] TNF-alpha inhibitors have been used in Korea since 2001 to treat RA and

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their use in other IMIDs has increased. Along with the increased use of TNF-alpha inhibitors, there are also increased safety concerns related to TNF-alpha inhibitors. Because these agents inhibit TNF-alpha from promoting inflammation, these agents suppress immune system in patients which in result cause patients become more susceptible to infections.[5] Especially, tuberculosis (TB) infection risk associated with TNF-alpha inhibitors has been recognized in various studies including observational studies, administrative data studies, and meta-analyses.[6-22] Because TNF-alpha inhibitors play a major role in host defense mechanisms against *Mycobacterium tuberculosis*, reactivation of latent TB has become a major safety issue of these agents.[23]

Several systematic reviews and meta-analyses have already examined the risk of TB of TNF-alpha inhibitors. However, already existing systematic reviews and meta-analyses examined TB risk in single TNF-alpha inhibitor or in single IMID indication rather than overall IMIDs.[9-12,18-20] Also several existing meta-analyses evaluated an overall infection risk or adverse event risk in TNF-alpha inhibitors rather than TB infection risk in specific.[10-16] Thus in this umbrella review, we aimed to integrate the existing meta-analyses data, examine the consistency of inferences from meta-analyses, and identify TB risk in IMIDs patients, RA patients, and non-RA patients and compared risk between soluble-receptor TNF-alpha inhibitor (ETA) and monoclonal-antibody TNF-alpha inhibitors (ADA, IFX, CZP, and GOL).

METHODS

Eligible criteria

Systematic reviews and meta-analyses of randomized controlled trials and observational studies that compared TB risk among TNF-alpha inhibitors (ADA, IFX, ETA, CZP, GOL) treated patients to placebo with or without standard therapy patients were included in the inclusion criteria.

These criteria were considered:

- Population: IMID patients such as RA, IBD (CD, UC), Ps, SpA, PsA, and AS
- Interventions: TNF-alpha inhibitors (ADA, IFX, ETA, CZP, and GOL)
- Comparison: placebo with or without standard treatment
- Outcome: TB infection

Exclusion criteria were: duplicated studies, reviews lacking meta-analysis statistical results, studies not including TB infection risk results.

Literature search

We searched PubMed, OVID MEDLINE, Cochrane Database of Systematic Reviews, and EMBASE databases to August 2018 for systematic review and meta-analyses. Search terms used were (adalimumab or humira or trudexa or certolizumab or cimzia or etanercept or Enbrel or golimumab or simponi or infliximab or remicade or remsima or inflectra) AND (tuberculosis or mycobacterium tuberculosis or TB) AND (meta-analysis or systematic review). Two independent researchers (HJ Park and BY Choi) conducted literature search. A third researcher, M Sohn, arbitrated any disagreement that could not be resolved by consensus.

Data extraction and Data analysis

Two independent researchers extracted relevant data from the selected meta-analyses. We extracted treatment indication, study

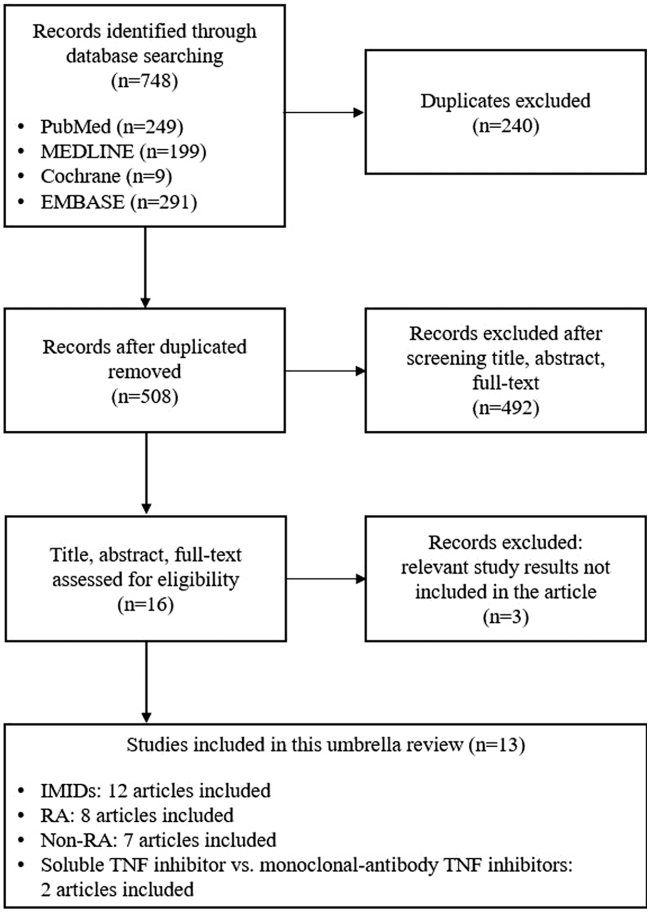


Fig. 1. Flow diagram of study selection. Abbreviation: IMIDs, immune-mediated inflammatory diseases; RA, rheumatoid arthritis; TNF, tumor necrosis factor

group and control group treatment, outcome (TB), number of studies, number of events, total number of participants in each group in the study, relative effect, confidence interval, and heterogeneity value for each meta-analysis. For studies reporting both random and fixed relative effects, we extracted the random effects value. Data extraction table was reproduced based on the guidance on conducting overviews of reviews.[24,25] Heterogeneity between studies was evaluated using I^2 statistics, which assess variability among studies. I^2 values from 0 to 40% might not be important; 30 to 60% may represent moderate heterogeneity; 50 to 90% may represent substantial heterogeneity; and 75 to 100% may represent considerable heterogeneity.[26]

From the extracted data for each meta-analysis, we calculated relative risk ratio (RR) from each relative effect value (odds ratio (OR) and incidence rate ratio (IRR)) using OR to RR and IRR to RR conversion equation.[27,28] We plotted pooled estimates from RR for the TB risk comparison. Comprehensive Meta-analysis software version 3 (Biostat, Englewood, NJ, USA) was used for analyses and plotting forest plot.

Table 1. Characteristics of meta-analyses included

Meta-analysis	Indication	Intervention group	Control group	No. of studies	Relative effect (95% CI)	I^2
RA						
Ai *et al.* 2015[9]	RA	TNF-alpha inhibitors (ADA, IFX, ETA, CZP, GOL)	placebo w/ or w/o MTX	4	IRR 4.03 (2.36-6.88)	45%
Cappogrosso *et al.* 2015[11]	RA	CZP 200 mg	placebo or the same DMARD medications allowed for the intervention group	12	RR 2.83 (0.50-16.01)	<40%
Cappogrosso *et al.* 2015[11]	RA	CZP 400 mg	placebo or the same DMARD medications allowed for the intervention group	N/A	RR 3.04 (0.37-25.22)	<40%
Ruiz *et al.* 2017[15]	RA	CZP overall	placebo w/ or w/o MTX	7	OR 1.91 (0.61-5.96)	0%
Ruiz *et al.* 2017[15]	RA	CZP 200 mg	placebo w/ or w/o MTX	6	OR 1.53 (0.40-5.77)	0%
Ruiz *et al.* 2017[15]	RA	CZP 400 mg	placebo w/ or w/o MTX	3	OR 3.52 (0.40-31.33)	0%
Singh *et al.* 2010[16]	RA	GOL 50 mg q4w	placebo w/ MTX	4	RR 3.04 (0.12-74.01)	NA
Singh *et al.* 2010[16]	RA	GOL 50 mg q4w, 50 mg q2w, 100 mg q4w, 100 mg q2w	placebo w/ MTX	4	RR 1.52 (0.06-37.08)	NA
Souto *et al.* 2014[17]	RA	TNF-alpha inhibitors (ADA, IFX, ETA, CZP, GOL)	placebo w/ or w/o MTX or other therapy	13	OR 1.87 (0.76-4.60)	0%
Wang *et al.* 2016[18]	RA	IFX	placebo w/ or w/o concomitant immuno-modulator therapy	7	OR 3.93 (0.91-16.91)	0%
Xie *et al.* 2013[19]	RA	IFX, ADA	placebo w/ MTX	7	OR 1.85 (0.62-5.52)	0%
Xie *et al.* 2013[19]	RA	IFX	placebo w/ MTX	4	OR 1.92 (0.50-7.47)	0%
Xie *et al.* 2013[19]	RA	ADA	placebo w/ MTX	3	OR 1.70 (0.26-10.87)	0%
Xie *et al.* 2013[19]	RA	IFX, ADA clinical or low dose ADA 40 mg qow, IFX 3 mg/kg q8w	placebo w/ MTX	6	OR 1.73 (0.52-5.76)	0%
Xie *et al.* 2013[19]	RA	IFX high dose 3 mg/kg q4w, 6 mg/kg q8w, 10 mg/kg q4w, q8w	placebo w/ MTX	3	OR 1.65 (0.28-9.56)	0%
Zhang *et al.* 2017[21]	RA	TNF-alpha inhibitors (ADA, IFX, ETA, CZP, GOL)	placebo w/ or w/o standard care or standard care treatment alone	17	OR 2.29 (1.09-4.78)	0%

Table 1. Continued

Meta-analysis	Indication	Intervention group	Control group	No. of studies	Relative effect (95% CI)	I^2
Non-RA						
Bonovas *et al.* 2016[10]	IBD	ADA	Placebo	2	OR 3.22 (0.25-41.73)	NA
Bonovas *et al.* 2016[10]	IBD	CZP	Placebo	1	OR 3.00 (0.12-74.69)	NA
Bonovas *et al.* 2016[10]	IBD	GOL	Placebo	1	OR 0.25 (0.01-4.77)	NA
Bonovas *et al.* 2016[10]	IBD	IFX	Placebo	4	OR 2.80 (0.50-15.60)	NA
Cappogrosso *et al.* 2015[11]	CD	CZP 400 mg	placebo or the same DMARD medications allowed for the intervention group	NA	RR 2.94 (0.12-71.88)	<40%
Cappogrosso *et al.* 2015[11]	Ps	CZP 400 mg	placebo or the same DMARD medications allowed for the intervention group	NA	RR 3.05 (0.13-73.39)	<40%
Ford *et al.* 2013[12]	IBD	TNF-alpha inhibitors (ADA, IFX, ETA, CZP, GOL)	placebo	22	RR 2.52 (0.62-10.21)	0%
Souto *et al.* 2014[17]	AS, PsA, Ps, CD, UC	TNF-alpha inhibitors (ADA, IFX, ETA, CZP, GOL)	placebo w/ or w/o MTX or other therapy	6	OR 2.01 (0.54-7.50)	NA
Wang *et al.* 2016[18]	SpA	IFX	placebo w/ or w/o concomitant immuno-modulator therapy	8	OR 2.46 (0.38-15.92)	0%
Wang *et al.* 2016[18]	IBD	IFX	placebo w/ or w/o concomitant immuno-modulator therapy	9	OR 1.66 (0.26-10.57)	0%
Xu *et al.* 2017[20]	SpA	IFX	placebo (or other medications)	4	RR 2.52 (0.53-12.09)	0%
Zhang *et al.* 2017[21]	AS	TNF-alpha inhibitors (ADA, IFX, ETA, CZP, GOL)	Placebo w/ or w/o standard care or standard care treatment alone	3	OR 2.43 (0.38-15.77)	0%

RESULTS

Search results

We searched a total of 748 articles in PubMed, MEDLINE, Cochrane, and EMBASE. After duplication exclusion, we screened titles, abstracts, and full texts for study exclusion which was narrowed down to 16 meta-analyses articles which met the inclusion criteria for this umbrella review. Three articles from those 16 articles were excluded because relevant data was not reported. Finally, we identified a total of 13 meta-analyses for final data extraction and data analysis.[9-21] (Fig. 1). Table 1 listed the characteristics of 13 articles included in this study analyses (IMIDs 12 articles, RA 8 articles, non-RA 7 articles, and soluble-receptor vs monoclonal-antibody TNF-alpha inhibitors 2 articles). Most of the articles included in this umbrella review reported more than 1 RR result on TB infection risk.

TB risk associated with TNF-alpha inhibitors in IMID patients

We conducted meta-analysis on 38 study results from 12 articles on TB risk in TNF-alpha inhibitors treated IMIDs patients (Fig. 2A). Pooled analysis determined that treatment with TNF-alpha inhibitors in IMIDs patients was associated with an increased risk of TB compared to control group (RR 2.057, 95% CI 1.697 to 2.495) and this result was statistically significant.

TB risk associated with TNF-alpha inhibitors in RA patients

An analysis on 16 study results from 8 meta-analyses showed an increased incidence of TB in TNF-alpha inhibitor treated RA patients with a relative risk of 1.847 (RR 1.847, 95% CI 1.385 to 2.464) compared to control group. Fig. 2B shows the forest plot of the analysis performed on those 16 study results.

Table 1. Continued

Meta-analysis	Indication	Intervention group	Control group	No. of studies	Relative effect (95% CI)	I^2
RA + non-RA						
Cappogrosso *et al.* 2015[11]	RA, CD, SpA, PsA, Ps	CZP over all	placebo or the same DMARD medications allowed for the intervention group	18	RR 2.47 (0.64-9.56)	<40%
Cappogrosso *et al.* 2015[11]	RA, CD, SpA, PsA, Ps	CZP 200 mg	placebo or the same DMARD medications allowed for the intervention group	12	RR 2.83 (0.50-16.01)	<40%
Cappogrosso *et al.* 2015[11]	RA, CD, SpA, PsA, Ps	CZP 400 mg	placebo or the same DMARD medications allowed for the intervention group	14	RR 3.02 (0.65-14.12)	<40%
Minozzi *et al.* 2016[14]	RA, PsA, AS	TNF-alpha inhibitors (ADA, IFX, ETA, CZP, GOL)	placebo or no treatment	19	OR 3.29 (1.48-7.33)	0%
Souto *et al.* 2014[17]	RA, AS, PsA, Ps, UC, CD	TNF-alpha inhibitors (ADA, IFX, ETA, CZP, GOL)	placebo w/ or w/o MTX or other therapy	18	OR 1.92 (0.91-4.03)	0%
Wang *et al.* 2016[18]	RA, SpA, IBD	IFX	placebo w/ or w/o concomitant immuno-modulator therapy	24	OR 2.86 (1.09-7.52)	0%
Zhang *et al.* 2017[21]	IMIDs	TNF-alpha inhibitors (ADA, IFX, ETA, CZP, GOL)	Placebo w/ or w/o standard care or standard care treatment alone	29	OR 1.94 (1.10-3.44)	0%
Zhang *et al.* 2017[21]	IMIDs	IFX	Placebo w/ or w/o standard care or standard care treatment alone	14	OR 1.82 (0.82-4.06)	0%
Zhang *et al.* 2017[21]	IMIDs	ADA	Placebo w/ or w/o standard care or standard care treatment alone	9	OR 2.11 (0.73-6.12)	0%
Zhang *et al.* 2017[21]	IMIDs	CZP	Placebo w/ or w/o standard care or standard care treatment alone	3	OR 2.38 (0.42-13.42)	0%
Monoclonal-antibody vs. soluble-receptor TNF-alpha inhibitors						
Ai *et al.* 2015[9]	RA	IFX	ETA	10	IRR 2.78 (2.10-3.69)	46%
Ai *et al.* 2015[9]	RA	ADA	ETA	7	IRR 3.88 (2.31-6.53)	0%
Liao *et al.* 2017[13]	RA	IFX, ADA	ETA	6	RR 4.17 (1.52-11.11)	0%

Abbreviation: CI, confidence interval; RA, rheumatoid arthritis; TNF-alpha, tumor necrosis factor-alpha; ADA, adalimumab; IFX, infliximab; ETA, etanercept; CZP, certolizumab pegol; GOL, golimumab; MTX, methotrexate; IRR, incidence rate ratio; DMARD, disease-modifying antirheumatic drug; RR, relative risk; N/A, not available; w/, with; w/o, without; OR, odds ratio; q4w, every 4 weeks; q2w, every 2 weeks; qow, every other week; q8w, every 8 weeks; IBD, inflammatory bowel disease; CD, Crohn's disease; Ps, psoriasis; AS, ankylosing spondylitis; PsA, psoriatic arthritis; UC, ulcerative colitis; SpA, spondyloarthritis; IMID, immune-mediated inflammatory disease

TB risk associated with TNF-alpha inhibitors in non-RA patients

There was a total of 12 pooled estimates from 7 articles reported for TB risk in TNF-alpha inhibitor treated non-RA patients. TNF-alpha inhibitors in non-RA patients were consistently associated with a higher risk of TB infection compared to placebo (RR 2.236, 95% CI 1.284 to 3.894). Forest plot of this analysis is shown in Fig. 2C.

TB risk associated with monoclonal-antibody TNF-alpha inhibitors vs. soluble-receptor TNF-alpha inhibitor in RA patients

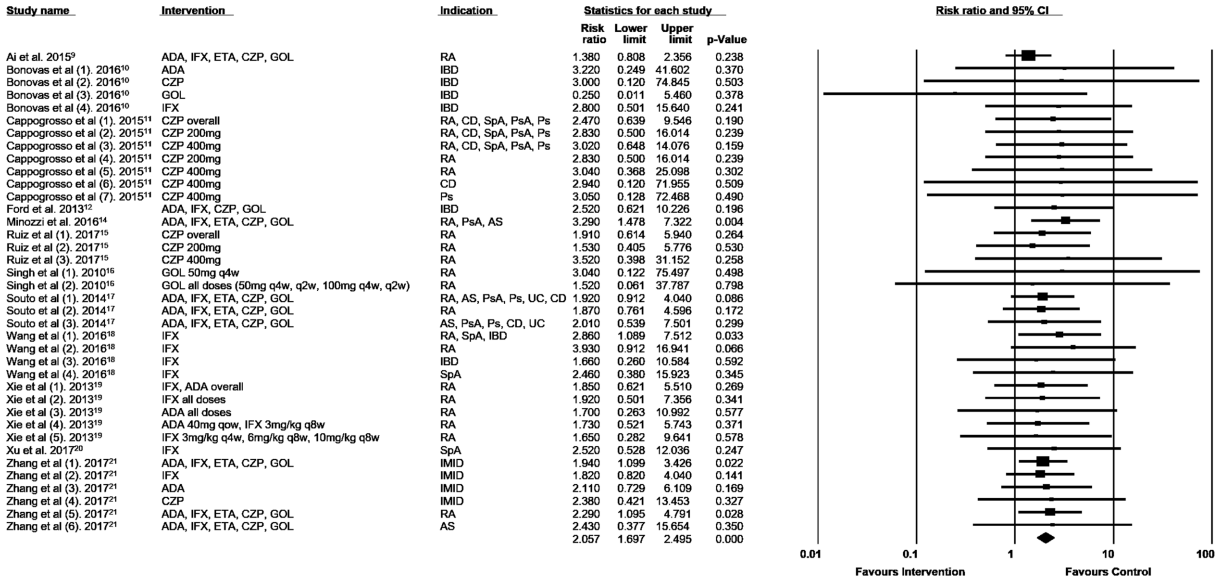
In addition to overall TNF-alpha inhibitor-induced TB risk, we performed a subgroup analysis of TB risk between monoclonal-antibody TNF-alpha inhibitors and soluble-receptor TNF-alpha inhibitor specifically in RA patients. A total of 3 study results from 2 studies were included in this subgroup

analysis. Compared to soluble-receptor TNF-alpha inhibitor, non-soluble monoclonal-antibody TNF-alpha inhibitors had increased TB risk with RR of 2.880 (RR 2.880, 95% CI 1.730 to 4.792). The results are shown in Fig. 3.

DISCUSSION & CONCLUSION

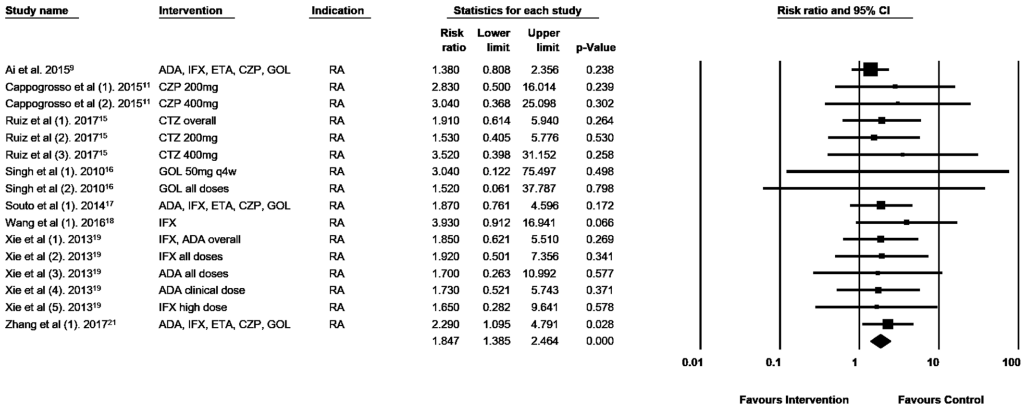
To our knowledge, this study is the first umbrella review conducted in evaluating risk of TB in TNF-alpha inhibitors treated patients. With increasing number of systematic reviews and meta-analyses on tuberculosis risk associated with TNF-alpha inhibitor treatment, this study conducted a methodology, umbrella review, to integrate, manage, and provide a comprehensive evidence on this safety issue.[25,29)]

Most meta-analyses included in this umbrella review demonstrated statistically insignificant TB risk associated with TNF-alpha inhibitors.[9-21)] In addition to statistically insignificant results, previous meta-analyses examined TB risk in single IMID indication in TNF-alpha inhibitor patients[9,10,12,15,16,19,20)] or analyzed overall infection risk or overall safety profile of TNF-alpha inhibitors[10-16,19,20)] rather than TB risk in specific. Also, among those meta-analyses, there were several studies



Study name	Intervention	Indication	Statistics for each study			
			Risk ratio	Lower limit	Upper limit	p-Value
Ai et al. 2015[9]	ADA, IFX, ETA, CZP, GOL	RA	1.380	0.808	2.356	0.238
Bonovas et al (1). 2016[10]	ADA	IBD	3.220	0.249	41.602	0.370
Bonovas et al (2). 2016[10]	CZP	IBD	3.000	0.120	74.845	0.503
Bonovas et al (3). 2016[10]	GOL	IBD	0.250	0.011	5.460	0.378
Bonovas et al (4). 2016[10]	IFX	IBD	2.800	0.501	15.640	0.241
Cappogrosso et al (1). 2015[11]	CZP overall	RA, CD, SpA, PsA, Ps	2.470	0.639	9.546	0.190
Cappogrosso et al (2). 2015[11]	CZP 200mg	RA, CD, SpA, PsA, Ps	2.830	0.500	16.014	0.239
Cappogrosso et al (3). 2015[11]	CZP 400mg	RA, CD, SpA, PsA, Ps	3.020	0.648	14.076	0.159
Cappogrosso et al (4). 2015[11]	CZP 200mg	RA	2.830	0.500	16.014	0.239
Cappogrosso et al (5). 2015[11]	CZP 400mg	RA	3.040	0.368	25.098	0.302
Cappogrosso et al (6). 2015[11]	CZP 400mg	CD	2.940	0.120	71.955	0.509
Cappogrosso et al (7). 2015[11]	CZP 400mg	Ps	3.050	0.128	72.468	0.490
Ford et al. 2013[12]	ADA, IFX, CZP, GOL	IBD	2.520	0.621	10.226	0.196
Minozzi et al. 2016[14]	ADA, IFX, ETA, CZP, GOL	RA, PsA, AS	3.290	1.478	7.322	0.004
Ruiz et al (1). 2017[15]	CZP overall	RA	1.910	0.614	5.940	0.264
Ruiz et al (2). 2017[15]	CZP 200mg	RA	1.530	0.405	5.776	0.530
Ruiz et al (3). 2017[15]	CZP 400mg	RA	3.520	0.398	31.152	0.258
Singh et al (1). 2010[16]	GOL 50mg q4w	RA	3.040	0.122	75.497	0.498
Singh et al (2). 2010[16]	GOL all doses (50mg q4w, q2w, 100mg q4w, q2w)	RA	1.520	0.061	37.787	0.798
Souto et al (1). 2014[17]	ADA, IFX, ETA, CZP, GOL	RA, AS, PsA, Ps, UC, CD	1.920	0.912	4.040	0.086
Souto et al (2). 2014[17]	ADA, IFX, ETA, CZP, GOL	RA	1.870	0.761	4.596	0.172
Souto et al (3). 2014[17]	ADA, IFX, ETA, CZP, GOL	AS, PsA, Ps, CD, UC	2.010	0.539	7.501	0.299
Wang et al (1). 2016[18]	IFX	RA, SpA, IBD	2.860	1.089	7.512	0.033
Wang et al (2). 2016[18]	IFX	RA	3.930	0.912	16.941	0.066
Wang et al (3). 2016[18]	IFX	IBD	1.660	0.260	10.584	0.592
Wang et al (4). 2016[18]	IFX	SpA	2.460	0.380	15.923	0.345
Xie et al (1). 2013[19]	IFX, ADA overall	RA	1.850	0.621	5.510	0.269
Xie et al (2). 2013[19]	IFX all doses	RA	1.920	0.501	7.356	0.341
Xie et al (3). 2013[19]	ADA all doses	RA	1.700	0.263	10.992	0.577
Xie et al (4). 2013[19]	ADA 40mg qow, IFX 3mg/kg q8w	RA	1.730	0.521	5.743	0.371
Xie et al (5). 2013[19]	IFX 3mg/kg q4w, 6mg/kg q8w, 10mg/kg q8w	RA	1.650	0.282	9.641	0.578
Xu et al. 2017[20]	IFX	SpA	2.520	0.528	12.036	0.247
Zhang et al (1). 2017[21]	ADA, IFX, ETA, CZP, GOL	IMID	1.940	1.099	3.426	0.022
Zhang et al (2). 2017[21]	IFX	IMID	1.820	0.820	4.040	0.141
Zhang et al (3). 2017[21]	ADA	IMID	2.110	0.729	6.109	0.169
Zhang et al (4). 2017[21]	CZP	IMID	2.380	0.421	13.453	0.327
Zhang et al (5). 2017[21]	ADA, IFX, ETA, CZP, GOL	RA	2.290	1.095	4.791	0.028
Zhang et al (6). 2017[21]	ADA, IFX, ETA, CZP, GOL	AS	2.430	0.377	15.654	0.350
			2.057	1.697	2.495	0.000

Fig. 2A. Tuberculosis risk associated with TNF-alpha inhibitors in immune-mediated inflammatory diseases patients. Abbreviations: CI, confidence interval; ADA, adalimumab; IFX, infliximab; ETA, etanercept; CZP, certolizumab pegol; GOL, golimumab; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; CD, Crohn's disease; SpA, spondyloarthritis; PsA, psoriatic arthritis; Ps, psoriasis; AS, ankylosing spondylitis; UC, ulcerative colitis; q4w, every 4 weeks; q2w, every 2 weeks; qow, every other week; q8w, every 8 weeks; IMID, immune-mediated inflammatory disease



Study name	Intervention	Indication	Statistics for each study			
			Risk ratio	Lower limit	Upper limit	p-Value
Ai et al. 2015[9]	ADA, IFX, ETA, CZP, GOL	RA	1.380	0.808	2.356	0.238
Cappogrosso et al (1). 2015[11]	CZP 200mg	RA	2.830	0.500	16.014	0.239
Cappogrosso et al (2). 2015[11]	CZP 400mg	RA	3.040	0.368	25.098	0.302
Ruiz et al (1). 2017[15]	CTZ overall	RA	1.910	0.614	5.940	0.264
Ruiz et al (2). 2017[15]	CTZ 200mg	RA	1.530	0.405	5.776	0.530
Ruiz et al (3). 2017[15]	CTZ 400mg	RA	3.520	0.398	31.152	0.258
Singh et al (1). 2010[16]	GOL 50mg q4w	RA	3.040	0.122	75.497	0.498
Singh et al (2). 2010[16]	GOL all doses	RA	1.520	0.061	37.787	0.798
Souto et al (1). 2014[17]	ADA, IFX, ETA, CZP, GOL	RA	1.870	0.761	4.596	0.172
Wang et al (1). 2016[18]	IFX	RA	3.930	0.912	16.941	0.066
Xie et al (1). 2013[19]	IFX, ADA overall	RA	1.850	0.621	5.510	0.269
Xie et al (2). 2013[19]	IFX all doses	RA	1.920	0.501	7.356	0.341
Xie et al (3). 2013[19]	ADA all doses	RA	1.700	0.263	10.992	0.577
Xie et al (4). 2013[19]	ADA clinical dose	RA	1.730	0.521	5.743	0.371
Xie et al (5). 2013[19]	IFX high dose	RA	1.650	0.282	9.641	0.578
Zhang et al (1). 2017[21]	ADA, IFX, ETA, CZP, GOL	RA	2.290	1.095	4.791	0.028
			1.847	1.385	2.464	0.000

Fig. 2B. Tuberculosis risk associated with TNF-alpha inhibitors in rheumatoid arthritis patients. Abbreviations: CI, confidence interval; ADA, adalimumab; IFX, infliximab; ETA, etanercept; CZP, certolizumab pegol; GOL, golimumab; q4w, every 4 weeks

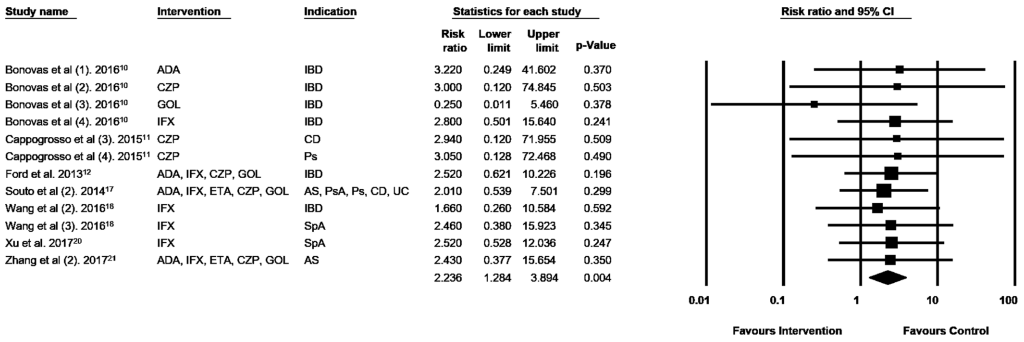


Fig. 2C. Tuberculosis risk associated with TNF-alpha inhibitors in non-rheumatoid arthritis patients. Abbreviations: CI, confidence interval; ADA, adalimumab; IBD, inflammatory bowel disease; CZP, certolizumab pegol; GOL, golimumab; IFX, infliximab; CD, Crohn's disease; Ps, psoriasis; ETA, etanercept; AS, ankylosing spondylitis; PsA, psoriatic arthritis; UC, ulcerative colitis; SpA, spondyloarthritis

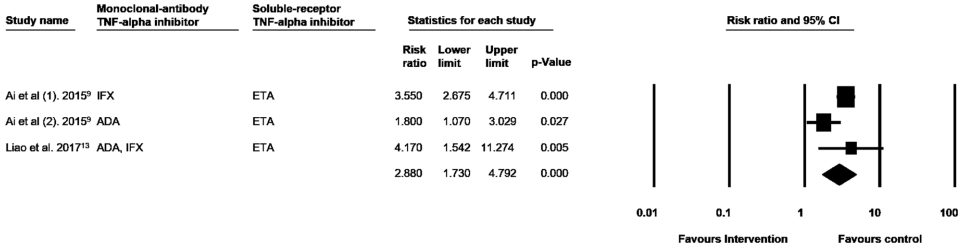


Fig. 3. Tuberculosis risk associated with monoclonal-antibody vs. soluble-receptor TNF-alpha inhibitors in rheumatoid arthritis patients. Abbreviations: TNF-alpha, tumor necrosis factor-alpha; CI, confidence interval; IFX, infliximab; ETA, etanercept; ADA, adalimumab

that included single TNF-alpha inhibitor[15,16,18], without integrating risk in TNF-alpha inhibitors in general. Thus, we aimed to synthesize and analyze those results to examine the trend and consistency compared to the existing studies on TB risk in TNF-alpha inhibitors treated IMIDs, RA, and non-RA patients, and between monoclonal-antibody TNF-alpha inhibitors and soluble-receptor TNF inhibitor as a subgroup analysis.

We identified 12 meta-analyses with 38 study results that examined the risk of TB in TNF-alpha inhibitors in IMIDs patients-including RA and non-RA IMID patients. Our study confirms the current knowledge on TB risk related to TNF-alpha inhibitors.[30] Compared to control group treatment, TNF-alpha inhibitors were consistently associated with increased risk of TB across all therapeutic indications including IMIDs, RA, and non-RA patients.

Moreover, consistent with the known association, non-soluble monoclonal-antibody TNF-alpha inhibitors were more associated with the risk of TB than soluble-receptor TNF-alpha inhibitor. This significantly higher TB risk for monoclonal-antibody TNF-alpha inhibitors than soluble-receptor TNF-alpha inhibitor might be explained by the different structures and mechanisms of action in TNF-alpha inhibitors.[13,31] Monoclonal-antibody TNF-alpha inhibitors bind to membrane-bound TNF as well as both active and inactive soluble TNF, which then form fixed complexes, lyse the TNF-expressed cells, and reduce host immune response. Different from monoclonal-antibody TNF-alpha inhibitors, soluble-receptor TNF-alpha inhibitor binds to active soluble TNF and forms relatively unstable complexes allowing easier dissociation of TNF.[32,33,34] This different mechanism of action between the two types of TNF-alpha inhibitors may explain the different TB risk between the two TNF-alpha inhibitor types.

Even though it is not on the exact same research question, Bonovas *et al*.[35] conducted an umbrella review on the safety issue of biological therapies in patients with ulcerative colitis and evaluated TB risk results as one of the safety measurements in the study. However, this study examined overall safety issues in biological agents including ADA, GOL, IFX, along with vedolizumab which is not a TNF-alpha inhibitor and reported insignificant results for TB risk in biologics group. Also, Bonovas *et al*.[35] performed a descriptive review of meta-analyses and did not perform a statistical analysis. Compared to Bonovas *et al*.[35], our umbrella review has focused specifically on TB infection risk associated with TNF-alpha inhibitors extended from this Bonovas et al.[35] study.

There are some limitations in this study that should be

addressed. Since meta-analyses included in this umbrella review varied in their treatment follow up period, our study analysis was performed on varying study follow up period. In addition, because we did not directly analyze the raw data for each included study, we could not directly compare TB infection risk between TNF-alpha inhibitors treated RA patients and non-RA patients. Since RA patients tend to use marginally higher induction dose of TNF-alpha inhibitors for treatment than non-RA patients[36-40], further research is needed to compare the TB risk between RA patients and non-RA patients.

In summary, this umbrella review provides an evidence-based synthesis of meta-analyses on TB risk in TNF-alpha inhibitors. This umbrella review could be an informative review which provides integrated results of the existing meta-analysis. Our results confirm that the risk of TB increases in TNF-alpha inhibitors treated IMIDs patients – including RA patients and non-RA patients. Therefore, in clinical settings, TNF-alpha inhibitors treated IMIDs patients should be carefully monitored of TB infection risk.

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REFERENCES

1. Bradley JR. TNF-mediated inflammatory disease. J Pathol 2008;214:149-60.
2. Firestein GS, Corr M. Common mechanisms in immune-mediated inflammatory disease. J Rheumatol Suppl 2005;73:8-13.
3. Kuek A, Hazleman BL, Ostor AJ. Immunemediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J 2007;83:251-60.
4. Blandizzi C, Gionchetti P, Armuzzi A, *et al*. The role of tumour necrosis factor in the pathogenesis of immune-mediated diseases. Int J Immunopathol Pharmacol 2014;27(Suppl):1-10.
5. Burmester GR, Mariette X, Montecucco C, *et al*. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the research in active rheumatoid arthritis (ReAct) trial. Ann Rheum Dis 2007;66:732-9.
6. Sampaio-Barros PD, van der Horst-Bruinsma IE. Adverse effects of TNF inhibitors in SpA: are they different from RA? Best Pract Res Clin Rheumatol 2014;28:747-63.
7. Askling J, Fored CM, Brandt L, *et al*. Risk and case characteristics of tuberculosis in rheumatoidarthritis associated with tumor necrosis factor antagonists inSweden. Arthritis Rheum 2005;52:1986–92.
8. Dixon WG, Watson K, Lunt M, *et al*. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti–tumor necrosis factor therapy: results from the British society for rheumatology biologics register. Arthritis Rheum 2006;54:2368–76.
9. Ai JW, Zhang S, Ruan QL, *et al*. The risk of tuberculosis in patients with rheumatoid arthritis treated with tumor necrosis factor-a antagonist: a metaanalysis of both randomized controlled trials and registry/cohort studies. J Rheumatol 2015;42(12):2229-37.
10. Bonovas S, Fiorino G, Allocca M, *et al*. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. Clin Gastroenterol Hepatol 2016;14(10):1385-97.e10.
11. Capogrosso Sansone A, Mantarro S, Tuccori M, *et al*. Safety profile of certolizumab pegol in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis. Drug Saf 2015;38(10):869-88.
12. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor- α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. Am J Gastroenterol 2013;108(8):1268-76.
13. Liao H, Zhong Z, Liu Z, *et al*. Comparison of the risk of infections in different anti-TNF agents: a meta-analysis. Int J Rheum Dis 2017;20(2):161-8.
14. Minozzi S, Bonovas S, Lytras T, *et al*. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf 2016;15(suppl):11-34.
15. Ruiz Garcia V, Burls A, Cabello JB, *et al*. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. Cochrane Database Syst Rev 2017;9:CD007649. DOI: 10.1002/14651858.CD007649.pub4.
16. Singh JA, Nooribaloochi S, Singh G. Golimumab for theumatoid arthritis (Review). Cochrane Database Syst Rev 2010;1: CD008341. DOI: 10.1002/14651858.CD008341.
17. Souto A, Maneiro JR, Salgado E, *et al*. Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies. Rheumatology 2014;53:1872-85.
18. Wang Q, Wen Z, Cao Q. Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy: a meta-analysis. Exp Ther Med 2016;12(3):1693-704.
19. Xie X, Chen J, Peng Y, *et al*. Meta analysis of infection risks of anti-TNF-α treatment in rheumatoid arthritis. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2013;38(7):722-36.
20. Xu Z, Xu P, Fan W, *et al*. Risk of infection in patients with spondyloarthritis and ankylosing spondylitis receiving antitumor necrosis factor therapy: a meta-analysis of randomized controlled trials. Exp Ther Med 2017;14(4):3491-500.
21. Zhang Z, Fan W, Yang G, *et al*. Risk of tuberculosis in patients treated with TNF-α antagonists: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2017;7:e012567. DOI: 10.1136/bmjopen-2016-012567.
22. Ke WM, Chen LS, Parng IM, *et al*. Risk of tuberculosis in rheumatoid arthritis patients on tumour necrosis factor-alpha inhibitor treatment in Taiwan. Int J Tuberc Lung Dis 2017;17(12):1590–95.
23. Wallis RS. Reactivation of latent tuberculosis by TNF blockade: the role of interferon gamma. J Investig Dermatol Symp Proc

2007;12(1):16-21.
24. Green S, Higgins JPT, Alderson P, *et al*. Chapter 1: introduction. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. Available from http://www.handbook.cochrane.org. Accessed Oct 30, 2018.
25. Pollock M, Fernandes RM, Becker LA, *et al*. What guidance is available for researchers conducting overviews of reviews of healthcare interventions? A scoping review and qualitative metasummary. Syst Rev 2016;5(1):190. DOI: 10.1186/s13643-016-0367-5.
26. Deeks J, Higgins J, Altman D. Chapter 9: Analysing data and undertaking meta-analyses, Cochrane handbook for systematic reviews of interventions version 5.0.0 (updated February 2008). The Cochrane Collaboration. Available from http://www.cochrane-handbook.org. Accessed Oct 30, 2018.
27. Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. Evid Based Ment Health 2018;21(3):95-100.
28. Wang Z. Converting odds ratio to relative risk in cohort studies with partial data information. J Stat Soft 2013;55(5)1-11.
29. Becker LA, Oxman AD. Chapter 22: overviews of reviews. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0). The Cochrane Collaboration; 2011. Available from http://www.handbook.cochrane.org. Accessed Oct 30, 2018.
30. Solovic I, Sester M, Gomez-Reino JJ, *et al*. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. Eur Respir J 2010;36:1185-206.
31. Wallis RS. Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. Lancet Infect Dis 2008; 8(10):601-11.
32. Scallon B, Cai A, Solowski N, *et al*. Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther 2002;301(2):418-26.
33. Scallon BJ, Moore MA, Trinh H, *et al*. Chimeric anti-TNF-alpha monoclonal antibody cA2 binds recombinant transmembrane TNF-alpha and activates immune effector functions. Cytokine 1995; 7(3):251-9.
34. Banner DW, D'Arcy A, Janes W, *et al*. Crystal structure of the soluble human 55 kd TNF receptor-human TNF beta complex: implications for TNF receptor activation. Cell 1993;73(3):431-45.
35. Bonovas S, Pantavou K, Evripidou D, *et al*. Safety of biological therapies in ulcerative colitis: an umbrella review of meta-analyses. Best Pract Res Clin Gastroenterol 2018;32-33:43-7.
36. Adalimumab. Micromedex Solutions. Truven Health Analytics, Inc. Greenwood Village, CO. Available from http://www.micromedexsolutions.com. Accessed Oct 30, 2018.
37. Infliximab. Micromedex Solutions. Truven Health Analytics, Inc. Greenwood Village, CO. Available from http://www.micromedexsolutions.com. Accessed Oct 30, 2018.
38. Certolizumab pegol. Micromedex Solutions. Truven Health Analytics, Inc. Greenwood Village, CO. Available from http://www.micromedexsolutions.com. Accessed Oct 30, 2018.
39. Golimumab. Micromedex Solutions. Truven Health Analytics, Inc. Greenwood Village, CO. Available from http://www.micromedexsolutions.com. Accessed Oct 30, 2018.
40. Etanercept. Micromedex Solutions. Truven Health Analytics, Inc. Greenwood Village, CO. Available from http://www.micromedexsolutions.com. Accessed Oct 30, 2018.