Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials

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Published online: 08 Aug 2014.

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Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: a systematic review of randomized controlled trials

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Objective. **Treatment with tumour necrosis factor antagonists (anti-TNF) has been recognized as a risk factor for tuberculosis (TB) reactivation. Our aim was to evaluate risk of TB reactivation in rheumatologic and non-rheumatologic diseases treated with the same anti-TNF agents with and without concomitant therapies.**
Methods. **We searched for randomized controlled trials (RCTs) evaluating infliximab, adalimumab, and certolizumab in both rheumatologic and non-rheumatologic diseases until 2012. Results were calculated as pooled rates and/or pooled odd ratios (OR).**
Results. **Overall, 40 RCTs with a total of 14,683 patients (anti-TNF: 10,010; placebo: 4673) were included. TB reactivation was 0.26% (26/10,010) in the anti-TNF group and 0% (0/4673) in the control group, corresponding to an OR of 24.8 (95% CI 2.4–133). TB risk was higher when anti-TNF agents were combined with methotrexate or azathioprine as compared with either controls (24/4241 versus 0/4673; OR 54; 95% CI 5.3–88) or anti-TNF monotherapy (24/4241 versus 2/5769; OR 13.3; 95% CI 3.7–100). When anti-TNF was used as monotherapy, TB risk tended to be higher than placebo (2/5769 versus 0/4673; OR 4; 95% CI 0.2–15.7).**
Conclusions. **TB risk with anti-TNF agents appeared to be increased when these agents were used in combination with methotrexate or azathioprine as compared with monotherapy regimen. TB risk seemed to be higher than placebo, even when monotherapy is prescribed.**

Key words: Ankylosing spondylitis, anti-TNF, inflammatory bowel diseases, methotrexate, psoriasis, rheumatoid arthritis, tuberculosis

Key messages

- Treatment with tumour necrosis factor antagonists (anti-TNF) has been recognized as a risk factor for tuberculosis (TB) reactivation.
- We found that TB risk was higher when anti-TNF agents were combined with immunosuppressive therapy as compared with either controls (OR 54) or anti-TNF monotherapy (OR 13.3).

Introduction

Tumour necrosis factor (TNF) has been shown to play a critical role in the host response against tuberculosis (TB), including granuloma integrity and containment of disease (1–3). A key aspect of host defence against TB is represented by the antigen-specific adaptive T cell response that is impaired by anti-TNF therapy. Recently, it was hypothesized that the depletion of a granulysin-expressing subset of effector memory $CD8^+$ T cells ($CD8^+$ TEMRA cells) induced by infliximab (IFX) could result in suboptimal control of mycobacterial growth, leading to the potential spreading of TB infection (4). Antibodies against TNF are known to cause a reactivation of latent TB in animal models of the disease (5), and TB cases have been consistently reported in patients with rheumatoid arthritis (RA) and Crohn's disease (CD) (6), especially in populations at high prevalence of TB infection (7,8). When considering the increasing use of anti-TNF therapies in these diseases, the burden of TB reactivation may be clinically relevant. TB reactivation tends to occur early following initiation of the drug, with extra-pulmonary and disseminated manifestations occurring relatively more frequently than in immunocompetent patients (6). Consequently, TB screening prior to anti-TNF treatment is currently recommended (9–12).

Because of its low incidence, anti-TNF-related TB risk has been mainly estimated in large uncontrolled populations, such as long-term open-label extension trials, registries, and post-marketing surveillance databases (8,13–18). However, these estimates were likely inaccurate due to several biases from lack of adequate

control groups and clinical under-reporting. On the other hand, estimates from individual randomized controlled trials (RCTs) are more likely to be reliable, but are limited by small sample size and/or short study duration. To overcome these limitations, the anti-TNF-related risk of TB reactivation has been estimated in systematic reviews, where pooling data from individual RCTs substantially increases the confidence in the final estimate (19–21). Although this methodology has been mainly applied to assess the treatment-related TB risk in individual diseases (19–21), a recent meta-analysis estimated the adverse effects of different biologic drugs—including anti-TNF—in several diseases (i.e. all but HIV infection) (22). A 4.7-fold increase of TB reactivation risk during anti-TNF therapy as compared to placebo has been shown in an overall study population of 163 RCTs (5010 participants) and 46 extension studies (11,954 participants) (23).

However, the role of other factors potentially associated with TB reactivation during anti-TNF therapy has not been fully ascertained. Therefore, we performed a systematic review of RCTs of only three anti-TNF agents used in both rheumatologic and non-rheumatologic diseases—IFX, adalimumab (ADA), and certolizumab pegol (CERT)—in order to compare the risk of TB between the treatment and placebo groups, and to identify potential predictive factors associated with TB reactivation such as the type of disease or the concomitant use of immunosuppressive drugs.

Methods

Methods of the analysis and inclusion criteria were based on PRISMA recommendations (24). The present review is a selective update of a previously published systematic review by Singh et al. which included articles published up to January 2010 (22).

Eligibility criteria

We considered all RCTs in which the selected anti-TNF agents were compared with at least one arm of placebo, and the risk of TB reactivation was assessed. For this analysis, we decided to limit the present review to RCTs including anti-TNF used in more than one disease, namely IFX, ADA, and CERT that are applied in RA, ankylosing spondylitis (AS), inflammatory bowel diseases (IBD), psoriasis, and psoriatic arthritis (PA). We decided to exclude the very few trials in which anti-TNF agents were sporadically used in other diseases, such as viral hepatitis, sarcoidosis, etc. We also excluded RCTs with < 30 patients or with a follow-up duration < 12 weeks. These criteria were applied both when extracting studies already included in the previous review (22), and when considering new studies from the literature search. If there was any suspicion of cohort overlap between studies, only the most recent study was considered for inclusion. RCTs with an open-label phase with anti-TNF before randomization were also excluded.

Information sources

A literature search was performed for the period January 2010 to March 2012. Relevant publications were identified by MEDLINE and Cochrane databases. We identified eligible studies with the MeSH terms *Tuberculosis*, *Rheumatic diseases*, *Inflammatory bowel diseases*, *Psoriasis*, *Infliximab*, *Adalimumab*, *Certolizumab pegol*, and *Randomized controlled trial*. Only RCTs published in English language were considered. We used bibliographies of all relevant studies identified to do a recursive search. When the selected randomized study provided insufficient information regarding the TB risk, authors were contacted.

Study selection

Titles and abstracts of papers were screened by four reviewers (R.L., A.Z., V.B., C.H.). Studies were independently evaluated for relevance by the reviewers (using the full text of the study). Any disagreements were resolved through discussion. Data were extracted from the included studies by one of the four reviewers and checked by a second reviewer, and the data were extracted into tables. Any disagreements were resolved through discussion with a third reviewer.

Data collection

From each paper, reviewers independently abstracted the following information: country of origin, type of disease, type and dose of anti-TNF, number of patients included in the RCT, study duration, concomitant therapies systematically included in the active arms or in the control arm according to study protocol, performance of TB screening prior to therapy, and number of TB cases in each arm. In addition, clinical information about TB cases was collected when available.

Risk of bias in individual studies

Information on the methodological quality of each study was recorded, and quality assessment was performed using the CONSORT checklist (24). However, since our study focused on a secondary end-point of these studies (i.e. TB reactivation), we simplified the interpretation of the quality of the primary end-point (i.e. therapeutic response). Thus, studies with random sequence generation, adequate concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, and adequate outcome were considered at low risk of bias. Regarding our study end-point (i.e. TB incidence), we evaluated whether a systematic reporting of adverse events was provided in each individual study.

Summary measures

The primary end-point of this systematic review was to address the risk of TB in the anti-TNF arms as compared with those allocated in the control group, and whether there was an association of such risk with other variables, such as the type of disease or concomitant medications.

Planned methods of analysis

For each of the two arms (anti-TNF and controls), we aggregated the absolute number of cases with TB. Comparison among groups was performed by chi-square test. Pooled estimates and 95% confidence intervals (CI) were calculated. The Number Cruncher Statistical System software (NCSS, Kaysville, UT, USA) was used for the computations. When considering the rare incidence of TB in any of the two arms, we preferred not to adopt a more complex meta-analytical approach, because of the well-known bias of this methodology with rare events (25).

Results

Study selection

A flow diagram of this systematic review, with the number of papers retrieved, included, and excluded, as well as the reasons for exclusion, is shown in Figure 1. In summary, 259 studies were identified by the included databases for the selected period, including 59 extracted from the previous meta-analysis (22). After removing non-pertinent papers, 109 were regarded as relevant. Out of these, 69 were excluded for the reasons
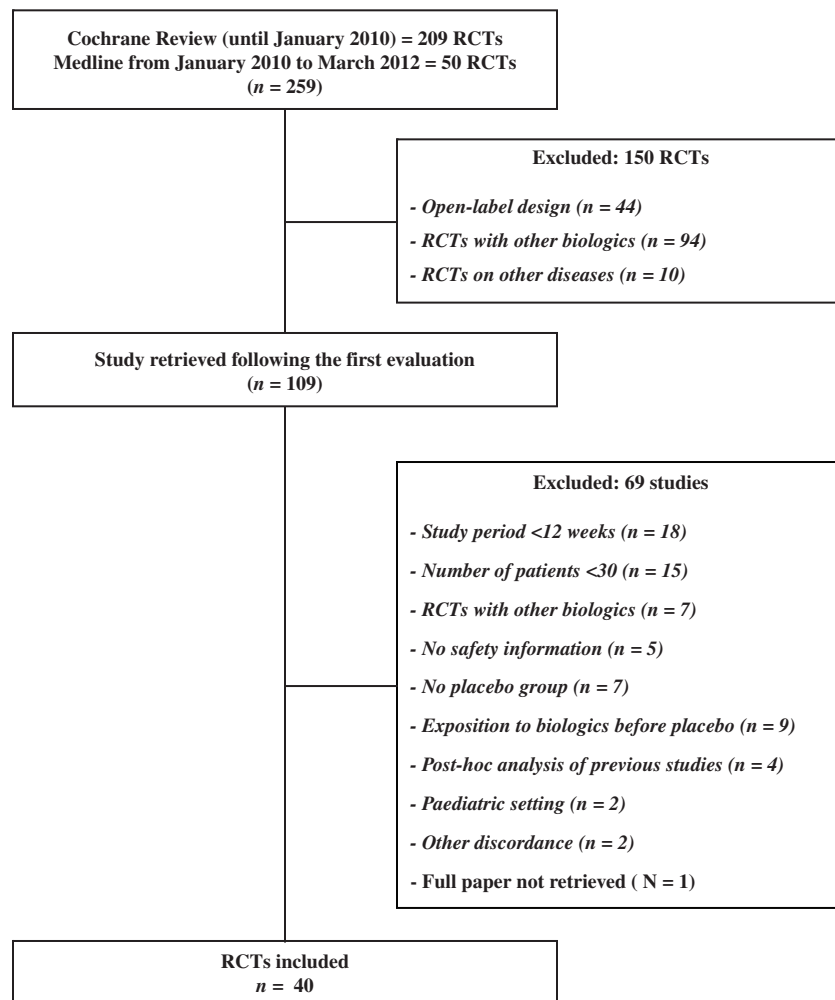
Figure 1. Flow chart of the systematic review.

reported in Figure 1, while 40 trials were selected for inclusion in the systematic review (26–65).

Characteristics of the included studies

Main characteristics of the included studies are provided in Table I. The studies were performed in either USA and Europe ($n = 18$), only USA ($n = 11$), only Europe ($n = 6$), or non-USA/European countries ($n = 5$). RA was the underlying disease in 14 studies, AS in 5, psoriasis in 9, PA in 4, and IBD in 8 cases (7 Crohn's disease; 1 ulcerative colitis). The anti-TNF agent used was IFX in 20 studies, ADA in 14, and CERT in 6. In 13 studies, the anti-TNF agent was used with a concomitant immunosuppressive agent according to the study protocol (11 studies with methotrexate and 2 with azathioprine), and in 28 studies anti-TNF agent was used as monotherapy (in one study the active group was divided in IFX as monotherapy and IFX + AZA) (32).

Participants

A total of 14,683 subjects were randomized in the selected studies (Table I). Of these, 10,010 were allocated in the active arm, and the remaining 4673 in the control arm. In detail, 2941 controls received only placebo, while the remaining 1732 were allocated to placebo plus methotrexate (MTX) or azathioprine (AZA). The number of patients enrolled for study ranged from 47 to 1212, with a median of 275. The median duration of follow-up was 24 weeks, ranging from 12 to 54 weeks. The doses ranged from

5 to 20 mg/kg for IFX, from 100 to 400 mg for CERT, from 20 to 80 mg for ADA, from 2 to 2.5 mg/kg for AZA, and from 12.5 to 25 mg for MTX. TB screening was clearly stated to be performed in 27 RCTs, no screening was carried out in 3 series, while this information was unavailable in other 10 trials (Table II). In detail, TB screening was performed with only chest X-ray in 5 studies, only purified protein derivative (PPD) test in 2, and with PPD plus chest X-ray in the remaining 20 series. Only a few studies provided information on how TB screening-positive cases were evaluated. As shown in Table II, positive cases were excluded from the RCT in 18 studies, while preventive TB therapy was administered in 8 studies. Finally, 4 studies excluded those with a clinical history of TB.

Quality of the studies

All the included trials appeared to be at low risk of bias when evaluated by criteria defining the quality of the primary end-point. All of the included studies systematically reported adverse events.

TB risk

Overall, 26 (0.26%) out of 10,010 patients developed TB in the active treatment group, corresponding to an incidence rate of 481 cases per 100,000 patient-years. No cases of TB were observed in the 4673 patients receiving placebo or placebo plus immuno-suppressive therapy (Table III). This difference was statistically

Table I. Characteristics of included trials.

Reference	Country	Patients	Disease	Drug	Control	FU
Targan et al. (26)	USA, Europe	108	CD	IFX	Placebo	12
Present et al. (27)	USA, Europe	94	CD	IFX	Placebo	18
Winter et al. (28)	USA, Europe, South Africa	92	CD	CERT	Placebo	12
Schreiber et al. (29)	USA, Canada, Europe	292	CD	CERT	Placebo	12
Lemann et al. (30)	France	113	CD	IFX+ AZA	Placebo+ AZA	52
Sandborn et al. (31)	USA, Canada, Europe, South Africa	660	CD	CERT	Placebo	26
Colombel et al. (32)	Europe, USA, Israel	508	CD	IFX+ AZA/IFX[a]	Placebo+ AZA	26
Sandborn et al. (33)	USA, Canada, Europe,	728	UC	IFX	Placebo	54
Maini et al. (34)	USA, Europe	428	RA	IFX+ MTX	Placebo+ MTX	30
Weinblatt et al. (35)	USA	271	RA	ADA+ MTX	Placebo+ MTX	24
Furst et al. (36)	USA, Europe	636	RA	ADA	Placebo	24
van de Putte et al. (37)	The Netherlands	544	RA	ADA	Placebo	26
Keystone et al. (38)	USA, Canada	619	RA	ADA+ MTX	Placebo+ MTX	52
St Clair et al. (39)	USA, Canada, Europe	1049	RA	IFX+ MTX	Placebo+ MTX	46
Abe et al. (40)	Japan	147	RA	IFX+ MTX	Placebo+ MTX	14
Westhovens et al. (41)	USA, Europe, Argentina	1084	RA	IFX+ MTX	Placebo+ MTX	22
Schiff et al. (42)	USA, South America	275	RA	IFX+ MTX	Placebo+ MTX	52
Miyasaka (43)	Japan	352	RA	IFX+ MTX	Placebo	24
Keystone et al. (44)	USA, Canada, Europe	982	RA	CERT+ MTX	Placebo+ MTX	52
Fleischmann et al. (45)	USA, Europe	220	RA	CERT	Placebo	24
Smolen et al. (46)	USA, Europe	619	RA	CERT+ MTX	Placebo+ MTX	24
Chen et al. (47)	Taiwan	47	RA	ADA+ MTX	Placebo+ MTX	12
Braun et al. (48)	Germany	69	AS	IFX	Placebo	12
van der Heijde et al. (49)	USA, Europe	279	AS	IFX	Placebo	24
van der Heijde et al. (50)	USA, Europe	315	AS	ADA	Placebo	24
Lambert et al. (51)	USA, Canada	82	AS	ADA	Placebo	24
Inman et al. (52)	Canada	76	AS	IFX	Placebo	12
Gottlieb et al. (53)	USA	249	P	IFX	Placebo	30
Reich et al. (54)	Europe, Canada	378	P	IFX	Placebo	24
Gordon et al. (55)	USA	147	P	ADA	Placebo	12
Menter et al. (56)	USA, Canada	835	P	IFX	Placebo	14
Saurat et al. (57)	Switzerland	161	P	ADA	Placebo	16
Menter et al. (58)	USA	1212	P	ADA	Placebo	16
Asahina et al. (59)	Japan	169	P	ADA	Placebo	24
Torii et al. (60)	USA, Canada	54	P	IFX	Placebo	16
Leonardi et al. (61)	USA, Canada, Europe	72	P	ADA	Placebo	16
Antoni et al. (62)	USA, Canada, Europe	104	PA	IFX	Placebo	16
Antoni et al. (63)	USA, Canada, Europe	200	PA	IFX	Placebo	24
Mease et al. (64)	USA	313	PA	ADA	Placebo	24
Genovese et al. (65)	USA, Canada	100	PA	ADA	Placebo	12

ADA = adalimumab; AS = ankylosing spondylitis; AZA = azathioprine; CD = Crohn's disease; CERT = certolizumab pegol; FU = follow-up (weeks); IFX = infliximab; MTX = methotrexate; P = psoriasis; PA = psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis.
[a]Active group was divided between IFX and IFX+ AZA.

significant (OR 24.8; 95% CI 2.4–133; $P < 0.01$). When stratifying for concomitant therapy, patients treated with anti-TNF in monotherapy (2/5769 versus 0/4673; OR 4; 95% CI 0.2–15.7; $P = 0.5$), as well as those treated with anti-TNF agents combined with MTX or AZA (24/4241 versus 0/4673; OR 54; 95% CI 5.3–288; $P < 0.001$), appeared to be at higher TB risk, although a statistically significant difference was showed only in the latter group. When differentiating between the two types of controls, TB risk with combination therapy was significantly higher than both placebo alone (24/4241 versus 0/2941; OR 34; 95% CI 3.3–181; $P < 0.001$) and placebo plus immunosuppressive agents (24/4241 versus 0/1732; OR 20; 95% CI 2–107; $P < 0.001$). TB risk was also significantly higher when comparing combined therapy with monotherapy (24/4241 versus 2/5769; OR 13.3; 95% CI 3.7–100; $P < 0.001$), observing in the former group an incidence rate of 832 cases per 100,000 patient-years and of 91 in latter group. When stratifying for disease, patients treated with anti-TNF agents for rheumatologic diseases were not at higher TB risk as compared with non-rheumatologic diseases (24/8367 versus 2/1643; OR 1.9; 95% CI 0.5–14; $P = 0.29$).

TB cases

Data on TB cases are provided in Table IV. There were 9 pulmonary localizations, 9 extra-pulmonary infections (including

2 disseminated), and information about site of infection was missing for the remaining 7 patients. Overall, 10 (40%) TB cases were observed in Russia, Estonia, Ukraine, and Bulgaria, whilst only 1 case occurred in USA. Screening for TB at entry was performed in 21 (84%) of these patients, being negative and positive in 11 and 6 cases, respectively (in 4 cases not reported). Of note, TB infection occurred in 2 patients who had positive screening despite the fact that a preventive anti-TB therapy was performed. Nineteen patients recovered with anti-TB therapy, and 1 died; outcome information was missing for the remaining 5.

Discussion

According to our systematic review, the combination therapy of anti-TNF agents with MTX or AZA results in a 13-fold increase in the risk of TB reactivation, as compared with anti-TNF agents used in monotherapy. Combination therapy is usually performed in rheumatic diseases and, more recently, also in IBD patients (30,32,66). Our findings are relevant for several reasons. First, our estimates are based on pooling of 40 RCTs with an overall population of over 14,683 patients. The high quality of the underlying studies is likely to exclude allocation bias between active and placebo arms, as well as an under-reporting of

Table II. Screening for tuberculosis (TB) infection and incidence of TB in the included studies.

Reference	Screening for TB	Measure adopted when positive	TB cases in Therapy (*n*)	TB cases in Control (*n*)
Targan et al. (26)	No	–	0/83	0/25
Present et al. (27)	No	–	0/63	0/31
Winter et al. (28)	No	–	0/68	0/24
Schreiber et al. (29)	Chest radiograph	Excluded	0/219	0/73
Lemann et al. (30)	PPD test	Excluded	0/57	0/56
Sandborn et al. (31)	PPD test plus chest radiograph	Excluded	0/331	0/329
Colombel et al. (32)	PPD test plus chest radiograph	Excluded	1/338[a]	0/170
Sandborn et al. (33)	PPD test plus chest radiograph	Excluded	1/484	0/244
Maini et al. (34)	NA	–	1/340	0/88
Weinblatt et al. (35)	PPD test	Therapy	0/209	0/62
Furst et al. (36)	PPD test plus chest radiograph	Therapy in some	0/318	0/318
van de Putte et al. (37)	Chest radiograph	Excluded	0/434	0/110
Keystone et al. (38)	PPD test plus chest radiograph	Therapy in some	1/419	0/200
St Clair et al. (39)	PPD test plus chest radiograph	NA	4/751	0/298
Abe et al. (40)	NA	–	0/100	0/47
Westhovens et al. (41)	PPD test plus chest radiograph	Excluded	4/721	0/363
Schiff et al. (42)	PPD test plus chest radiograph		2/165	0/110
Miyasaka (43)	PPD test plus chest radiograph		0/265	0/87
Keystone et al. (44)	PPD test plus chest radiograph	Therapy	5/783	0/199
Fleischmann et al. (45)	PPD test plus chest radiograph		0/111	0/109
Smolen et al. (46)	PPD test plus chest radiograph		5/492	0/127
Chen et al. (47)	NA	–	1/35	0/12
Braun et al. (48)	Chest radiograph	Excluded	1/34	0/35
van der Heijde et al. (49)	PPD test plus chest radiograph	Therapy	0/201	0/78
van der Heijde et al. (50)	PPD test plus chest radiograph	Excluded	0/208	0/107
Lambert et al. (51)	NA	–	0/38	0/44
Inman et al. (52)	NA	Excluded if history	0/39	0/37
Gottlieb et al. (53)	NA	Excluded if history	0/198	0/51
Reich et al. (54)	NA	Excluded if history	0/301	0/77
Gordon et al. (55)	PPD test plus chest radiograph	Excluded	0/95	0/52
Menter et al. (56)	NA	–	0/627	0/208
Saurat et al. (57)	PPD test plus chest radiograph	Excluded	0/108	0/53
Menter et al. (58)	PPD test plus chest radiograph	Therapy	0/814	0/398
Asahina et al. (59)	PPD test plus chest radiograph	Therapy	0/123	0/46
Torii et al. (60)	NA	Excluded if history	0/35	0/19
Leonardi et al. (61)	NA	–	0/49	0/23
Antoni et al. (62)	PPD test plus chest radiograph	Excluded	0/52	0/52
Antoni et al. (63)	PPD test plus chest radiograph	Excluded	0/100	0/100
Mease et al. (64)	Chest radiograph	Excluded	0/151	0/162
Genovese et al. (65)	Chest radiograph	Excluded	0/51	0/49

NA = not available; PPD = purified protein derivative.
[a]This case occurred in the IFX+ AZA arm.

TB cases between combined and monotherapy. Due to the large number of patients pooled, it is unlikely that new individual RCTs will affect the main result of our analysis. Second, we showed for the first time that TB risk is affected by concomitant medications. This is in agreement with the results of a recent meta-analysis of RCTs of ADA and IFX—where > 70% of patients were treated with a combination therapy—that showed a 2-fold increased risk of serious infections compared with placebo (19). Thus, a more intensive screening and surveillance approach seems to be advisable when combined therapy is used. Of note, our results are also in agreement with a recent analysis from the FDA adverse event-reporting system (67), showing a 4-fold increased risk of mycobacterial infections in those with combined therapy versus monotherapy. Third, we confirmed a higher risk of TB reactivation also in patients with anti-TNF monotherapy. The fact that the difference as compared with placebo did not reach statistical significance in our analysis may be simply referred to the small number of events, since only two

Table III. TB risk according to different treatments.

Comparison	TB yes/no	TB yes/no	*P* value	OR	95% CI
Any active therapy versus controls	26/10,010	0/4,673	< 0.001	2.4	2.5–133
Anti-TNFα+ MTX/AZA versus controls	24/4,241	0/4,673	< 0.001	54	5.3–288
Anti-TNFα+ MTX/AZA versus placebo+ MTX/AZA	24/4,241	0/1,732	< 0.001	20	2–107
Anti-TNFα+ MTX/AZA versus placebo	24/4,241	0/2,941	< 0.001	34	3.3–181
Anti-TNFα alone (monotherapy) versus controls	2/5,769	0/4,673	0.5	4	0.2–15.7
Anti-TNFα alone (monotherapy) versus placebo+ MTX/AZA	2/5,769	0/1,732	0.9	1.5	0.07–5.9
Anti-TNFα alone (monotherapy) versus placebo	2/5,769	0/2,941	0.55	2.5	0.1–9.9
Anti-TNFα+ MTX/AZA versus anti-TNFα alone (monotherapy)	24/4,241	2/5,769	< 0.001	13.3	3.7–100
Rheumatologic diseases[a] versus non-rheumatologic diseases[a]	24/8,367	2/1,643	0.29	1.9	0.5–14

Anti-TNFα = tumour necrosis factor-α antagonists; AZA = azathioprine; CI = confidence interval; MTX = methotrexate; OR = odds ratio.
[a]Only active treatment arms.

Table IV. Data of patients who developed tuberculosis (TB) in different trials.

Ref.	Disease	Therapy	Screening (result)	Site of TB	Timing (weeks)	Country	Outcome
(33)	UC	IFX	yes (neg)	lung	NA	NA	recovered
(34)	RA	IFX + MTX	no	disseminated	30–54	NA	dead
(38)	RA	ADA + MTX	yes (neg)	lymph nodes	NA	NA	recovered
(39)	RA	IFX + MTX	1 yes (neg)	1 lung	6	1 Europe	recovered
			1 yes (neg)	1 lung	6	1 Europe	recovered
			1 no	1 lung	14	1 Europe	recovered
			1 no	1 lung	46	1 USA	recovered
(41)	RA	IFX + MTX	1 yes (NA)	1 lung	28	1 Europe	recovered
			1 yes (NA)	1 extra-lung	23	1 Europe	recovered
			1 yes (NA)	1 extra-lung	12	1 Europe	recovered
			1 yes (NA)	1 extra-lung	26	1 Europe	recovered
(42)	RA	IFX + MTX	1 yes (neg)	1 lung	26–52	1 NA	recovered
			1 yes (neg)	1 peritoneum	26–52	1 NA	recovered
(44)	RA	CERT + MTX	1 yes (neg)	NA	6–36	1 Russia	NA
			1 yes (neg)	NA	6–36	1 Russia	NA
			1 yes (pos)[a]	NA	6–36	1 Estonia	NA
			1 yes (pos)[a]	NA	6–36	1 Ukraine	NA
			1 yes (pos)[a]	NA	6–36	1 Bulgaria	NA
(46)	RA	CERT + MTX	1 yes (pos)[b]	1 disseminated	7–24	1 Russia	recovered
			1 yes (pos)[b]	1 lung	7–24	1 Russia	recovered
			1 yes (pos)[a]	1 peritoneum	7–24	1 Russia	recovered
			1 yes (neg)	1 NA	7–24	1 Poland	recovered
			1 yes (neg)	1 NA	7–24	1 Latvia	recovered
(47)	RA	ADA + MTX	yes (neg)	lung	6	Taiwan	recovered
(48)	AS	IFX	no	lymph nodes/spleen	6	NA	recovered

ADA = adalimumab; AS = ankylosing spondylitis; CERT = certolizumab pegol; IFX = infliximab; MTX = methotrexate; NA = not available; RA = rheumatoid arthritis; UC = ulcerative colitis.
[a]No preventive therapy for TB.
[b]Preventive TB therapy performed.

TB cases occurred in the monotherapy arm. Of note, in previous systematic reviews (19–22), TB cases were not separated between monotherapy and combined therapy, so that it was more likely to reach the statistically significant difference. Thus, we confirm the importance of TB screening even in patients with anti-TNF monotherapy. Our data would indicate that the additional TB risk is related with a synergistic effect between anti-TNF agents and MTX or AZA rather than to an intrinsic risk of each immunosuppressive drug. Indeed, the simple addition of MTX or AZA to placebo did not increase the risk of TB as compared with placebo alone. This finding seems to be in contrast with the results of the CORRONA registry in which the combination therapy with MTX and TNF antagonists was not associated with a synergistic risk of overall and opportunistic infections compared with either agents prescribed alone (68). However, this result could be explained by the unexpectedly increased risk of opportunistic infections, including TB, found in the cohort of patients treated with MTX alone. Such a finding is not supported by the majority of previous studies which failed to show any increase of infection risk with MTX (69,70), so that no screening for TB is actually recommended in patients treated with MTX as well as AZA (71). Fourth, although TB development tended to be higher in patients with rheumatological diseases as compared to those with IBD or psoriasis (0.29% versus 0.12%), the difference was not statistically significant. Indeed, there is no plausible explanation in the pathogenesis and/or natural history of rheumatologic and non-rheumatologic diseases to support an intrinsic role of the underlying disease in affecting the TB risk. Indeed, although it has been reported that RA patients are at 2-fold increased risk of developing infections when compared with the general population (72), no increased TB risk was demonstrated.

There are limitations in the present analysis. Our results are not immediately generalizable to anti-TNF agents, such as etanercept, that are mainly used in rheumatologic conditions. Secondly, we did not use a formal meta-analytic approach for the well-known limitations when dealing with rare events (25). However, the very low frequency of TB events in any study marginalizes the relevance of inter-study heterogeneity. Third, there was some heterogeneity in the TB screening and intervention in positive cases among studies. However, the sensitivity analysis minimized the role of such heterogeneity. Fourth, the median duration of the studies included in our systematic review was only 24 weeks (range 12–54). However, we feel this interval to be adequate in order to assess TB risk, since > 70% of anti-TNF-related TB cases have been shown to occur within 90 days from the beginning of anti-TNF therapy (6). Of note, the absolute estimate of TB risk—ranging between 91 and 832 cases per 100,000 patient-years—is in agreement with previous incidence rates reported in the literature (8,13). Moreover, the overall risk of infections seems to be no longer increased after the first year of follow-up (73). Fifth, glucocorticoid use has been associated with an almost 8-fold increased risk of TB reactivation, especially in those receiving high doses (≥ 15 mg of prednisone) for prolonged periods (≥ 1 month), as well as with a 2–3-fold increase in the risk of hospitalized infections (74,75). Therefore, since the 'on demand' use of glucocorticoids was allowed in the RCTs analysed in our systematic review, this could have influenced the TB risk. However, glucocorticoid use appeared to be similar between active treatment and control arms, minimizing the chances of a selection bias.

In conclusion, our systematic review showed a 13-fold increase risk of TB reactivation when using anti-TNF therapy in combination with MTX or AZA as compared with monotherapy. This warrants the adoption of more intensive screening strategies for these patients. This should not obviously reduce the awareness of TB risk in patients with anti-TNF monotherapy, as already supported by the international guidelines.

Declaration of interest: The authors declare no conflicts of interest.

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