Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis.

ABSTRACT

Introduction: Five anti-tumor necrosis factor (anti-TNF) agents have received regulatory approval for use in rheumatology: adalimumab, golimumab, infliximab, certolizumab, and etanercept. Apart from their well-documented therapeutic value, it is still uncertain to what extent they are associated with an increased risk of infectious adverse events.

Areas covered: We conducted a systematic review and meta-analysis of published randomized studies to determine the effect of anti-TNF drugs on the occurrence of infectious adverse events (serious infections; tuberculosis; opportunistic infections; any infection). We searched Medline, Embase, and the Cochrane Library up to May 2014 to identify eligible studies in adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis that evaluated anti-TNF drugs compared with placebo or no treatment.

Expert opinion: Our study encompassed data from 71 randomized controlled trials involving 22,760 participants (range of follow-up: 1 to 36 months) and seven open label extension studies with 2,236 participants (range of follow-up: 6 to 48 months). Quantitative synthesis of the available data found statistically significant increases in the occurrence of infections (20%), serious infections (40%), and tuberculosis (250%) associated with anti-TNF drug use, while the data for opportunistic infections were scarce. The quality of synthesized evidence was judged as moderate. Further evidence from registries and long-term epidemiological studies are needed to better define the relationship between anti-TNF agents and infection complications.

Keywords: ankylosing spondylitis; anti-TNF drugs; drug safety; infections; meta-analysis; opportunistic infections; psoriatic arthritis; rheumatoid arthritis; serious infections; systematic review; tuberculosis.

Article highlights:

- The association between anti-TNF drug use and infectious adverse events (AEs) is unclear.
- The authors conducted a systematic review and meta-analysis of published trials involving patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis to determine the effect of anti-TNF agents on the risk of infectious AEs (serious infections, tuberculosis, opportunistic infections, or any infection).
- 71 RCTs with 22,760 patients, and seven OLE studies with 2,236 patients, met eligibility criteria and reported the occurrence of infectious AEs.
- Synthesis of the evidence supports the hypothesis that the use of anti-TNF drugs significantly increases the risk of infectious AEs. The meta-analysis showed an increase in the occurrence of infections (20%), serious infections (40%), and tuberculosis (250%) associated with anti-TNF drug use, while the data for opportunistic infections were scarce.
- Given the increasing use of TNF inhibitors in adult patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, it is important to continue monitoring their safety profiles through complementary sources (e.g., registries, and long-term epidemiological studies).

1. Introduction

Five anti-tumor necrosis factor (anti-TNF) agents have received regulatory approval for clinical use in rheumatology: adalimumab, golimumab, infliximab, certolizumab, and etanercept. Adalimumab and golimumab are fully human monoclonal antibodies; infliximab is a chimeric monoclonal antibody with a murine variable region; certolizumab is a humanized Fab fragment conjugated to polyethylene glycol; and etanercept is a fusion protein of two TNFR2 receptor extracellular domains and the Fc fragment of human immunoglobulin 1 [1].

Apart from their well-documented therapeutic value for several diseases including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS), it is still uncertain to what extent therapy with anti-TNF drugs may be associated with an increased risk of infectious adverse events (AEs). Post-marketing surveillance and observational studies provided the first indication that TNF inhibitors might be associated with an increased risk of serious infections [2,3]. Subsequently, a systematic review and meta-analysis of randomized controlled trials (RCTs), published in 2006, identified a statistically significant rise in the risk of infectious AEs in RA patients treated with infliximab and adalimumab (the odds ratio [OR] for serious infections was 2.0, with 95% confidence interval [CI]: 1.3 to 3.1) [4]. However, observational studies have been inconsistent on this issue with reports of both increased risk [5-9] and of no increased risk [10-12].

Considering the conflicting results published in the literature, the high number of RCTs that have been performed since 2006, and the increasing use of TNF inhibitors as induction or maintenance treatment for adult patients with RA, PsA, or AS, we conducted a systematic review and meta-analysis of published trials to determine the occurrence of infectious AEs associated with use of anti-TNF agents.

2. Methods

2.1 Protocol and registration

Our study protocol [13] is registered on PROSPERO, the international prospective register of systematic reviews. The current systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement [14].

2.2 Data sources and search strategy

A comprehensive search of MEDLINE and EMBASE bibliographic databases was conducted through May 2014. The following search terms were used: *adalimumab, golimumab, infliximab, certolizumab pegol, etanercept, anti-tumo(u)r necrosis factor(s), tumo(u)r necrosis factor(s), tumo(u)r necrosis factor alpha antibody(ies), tumo(u)r necrosis factor antibody(ies), anti-TNF, TNF, biologic(al) agent(s),* or *biologic(s),* combined with *rheumatoid arthritis, psoriatic arthritis,* or *ankylosing spondylitis*. The search was limited to RCTs and humans. No language, date, or publication status restrictions were applied. We also searched the Cochrane Library for any RCT included in the Cochrane Central Register of Controlled Trials, and for any systematic review on the subject.

Results were exported and compiled into a common reference database using EndNote. References were then de-duplicated to derive a unique set of records. Two investigators independently examined the search results and screened the titles and abstracts to exclude clearly irrelevant reports. The full text of the selected articles was critically evaluated for eligibility, and their reference lists (and of relevant reviews and meta-analyses) were manually scanned to identify further eligible studies. Experts were consulted for additional evidence, but there was no search for unpublished studies or data.

2.3 Study selection and data extraction

We considered RCTs or open label extension (OLE) studies that evaluated an anti-TNF agent (adalimumab, certolizumab, etanercept, golimumab, or infliximab) as induction or maintenance therapy for adults with RA, PsA or AS, and reported the occurrence of infectious AEs. Eligible outcomes were:

any infection, serious infections (infections that require antimicrobial therapy and/or hospitalization), tuberculosis, or opportunistic infections. We included studies that evaluated an anti-TNF therapy compared with placebo or no treatment, or multi-interventional therapies where the effect of anti-TNF treatment could be separated out (i.e. add-on to conventional disease-modifying anti-rheumatic drugs). In case of multiple publications from the same study, we selected the most updated one and extracted the data for the maximum follow-up time. OLE studies were eligible if they represented an extension of previous RCTs, and reported infectious AEs according to the group to which the patients were originally randomized.

Data extraction was undertaken by independent reviewers. Any discrepancy was resolved by consensus, referring back to the original article. The following data were extracted from each study: first author's last name, journal and year of publication, trial's acronym, study design and duration, number of participants, disease studied (RA, PsA, or AS), patient characteristics (age, concomitant treatments, duration of disease), intervention parameters (drug, dose, administration), and numbers of participants with events (serious infection; tuberculosis; opportunistic infection; or any infection) reported for the intervention and control groups.

2.4 Assessment of risk of bias

We evaluated the risk of bias (RoB) in included studies using the Cochrane Collaboration's tool [15,16], which addresses the following domains: sequence generation; allocation concealment; blinding; incomplete outcome data; and other sources of bias, such as extreme baseline imbalances in prognostic variables, selective crossover bias (i.e. subsequent anti-TNF treatment in the control groups), etc. These items were considered for the RoB assessment and were classified as "adequate" (low RoB), "inadequate" (high RoB), or "unclear". We considered only the information that was available in the full-text publications. Studies with adequate procedures in all domains were considered to have a low RoB; ones with inadequate procedures in one or more domains were considered to have a high RoB; and those with unclear procedures in one or more domains were considered to have unclear RoB. Discrepancies among reviewers were discussed, and agreement was reached by consensus.

On the other hand, OLE studies have higher RoB than the original trials. The study populations are no

longer randomly allocated, they are not blinded, and usually represent only a proportion of the participants recruited in the original trial (e.g., those with an adequate drug response and tolerance during the original study period). Therefore, we decided a priori that the items related to sequence generation, allocation concealment, masking of participants, personnel and outcome assessors, and incomplete outcome data, should be rated as high RoB in the OLE study assessment.

2.5 Data synthesis and analysis

OR was the metric of choice in all comparisons. Study-level ORs and their 95% CIs were calculated by reconstructing contingency tables based on the number of participants randomly assigned and the number of participants with the events of interest (analysis by intention to treat). When no events occurred in one group of the trial, we used a continuity correction that was inversely proportional to the relative size of the opposite group. In particular, the continuity correction for the treatment group was 1/(R+1), where R is the ratio of control group to treatment group sizes. Similarly, the continuity correction for the control group was R/(R+1). This methodological approach outperforms the use of a constant continuity correction of 0.5 in a setting of sparse data and imbalanced study groups [17]. Trials reporting zero-event data for both study groups were excluded from the analysis.

We used two techniques to calculate the pooled effect estimates: the fixed-effects model (Mantel-Haenszel approach [18]) and the random-effects model (DerSimonian & Laird approach [19]). In the absence of heterogeneity, the fixed- and the random-effects model provide similar results. When heterogeneity is found, the random-effects model might be more prudent, though both techniques may be biased.

After the overall meta-analysis, we conducted subgroup analyses by the anti-TNF drug (adalimumab, golimumab, infliximab, certolizumab, or etanercept) to investigate potentially different effects on risk. To assess any association between dose of TNF inhibitors and risk of infectious AEs, we also conducted a sensitivity analysis using (from the multi-arm trials) only the data referring to the intervention arms exposed to the highest doses. When no events were reported, the highest dose arm was merged with the second, the third highest, etc., in order to produce a group with at least one event, and include the study in the particular analysis. Full data were used from the two-arm trials.

Finally, we performed meta-regression analyses to investigate the impact of certain trial characteristics on the effect estimates. We converted all ORs by logarithmic transformation to achieve more symmetrical distributions. The natural logarithm of the OR was the dependent variable, and (i) age of participants enrolled and (ii) duration of follow-up were entered as covariates. This analysis was an indirect way to deal with aspects such as the possibility of effect modification by age, and to examine for increasing or decreasing risks with increasing duration of drug use, a feature associated with causal relationships. We applied a weighted regression model, so that the more precise studies have more influence in the analysis.

Regarding the open-label extension studies, their usefulness for generating reliable and valid data has been repeatedly challenged in the literature [20,21]. To avoid any biased or spuriously precise results, we did not include OLEs in our primary meta-analyses but synthesized their data separately.

Selective outcome reporting or publication bias was assessed using the funnel plot, Begg's test [22], and Egger's test [23]. The between-study heterogeneity was evaluated using Cochran's Q test [24] with a 0.10 level of significance. We also calculated the I-squared statistic [25], which describes the percentage variation across studies that is due to heterogeneity rather than chance. Negative values of I-squared were put equal to zero, so that I-squared lies between 0% and 100%. An I-squared value less than 40% was considered as indicative of "not important heterogeneity" and a value over 75% as indicative of "considerable heterogeneity" [26].

The quality of the meta-analytic evidence for each of the outcomes was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation) [27].

For all statistical analyses, we used Stata 11 software (Stata Corp., College Station, Texas, USA), and the R software environment [28], version 3.1.1, and the "meta" package for R [29], version 3.8-0. All p-values are two-tailed. For all tests (except for heterogeneity), a p-value less than 0.05 was regarded as statistically significant.

2.6 Role of the funding source

This study was supported by an unrestricted grant from *Pfizer Italia*. The funding source had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data;

preparation, review, or approval of the manuscript; and decision to submit it for publication.

3. Results

3.1 Search results

A summary of the evidence search and selection process is shown in **Figure 1**, and in the **Appendix**. Seventy-one RCTs [30-100] met the eligibility criteria and reported the occurrence of infectious AEs (serious infection, tuberculosis, opportunistic infection, or any infection) during the study period; we were thus able to conduct a post hoc analysis of these trials, calculate ORs for the outcomes of interest according to the intention-to-treat principle, and incorporate them in the meta-analyses.

These 71 RCTs evaluated infliximab (n=16), adalimumab (n=22), golimumab (n=11), certolizumab pegol (n=7), or etanercept (n=15) as induction or maintenance treatments for adult patients with RA (n=46), PsA (n=9), or AS (n=16). A total of 22,760 individuals participated in these trials; 14,766 in treatment groups, and 7,994 in control groups.

Substantial imbalance was observed between the treatment and control group sizes within studies (median ratio, 2:1; maximum ratio, 7:1). The mean age of participants ranged from 30 to 62 years, and follow-up times from 1 to 36 months, between studies. A total experience of approximately 15,100 person-years was reached (8 months per patient, on average). The publication dates of these trials ranged from 1999 to 2014. A summary of the trials' characteristics is given in **Table 1**.

Though most of the OLE studies were excluded because they did not report infectious AEs per study arm, we identified seven eligible OLEs [42,56,101-105] involving 2,236 participants. Their follow-up times ranged from 6 to 48 months. The outcomes of interest were reported according to the group to which patients were originally randomized, so we could calculate ORs and synthesize the evidence.

3.2 Risk of bias in the studies included in meta-analysis

Random sequence generation: 11 of 71 RCTs (15.5%) reported adequate methods for sequence generation and were judged to be at low RoB. Information in 60 trials (84.5%) was insufficient to permit judgement (i.e. unclear RoB).

Allocation concealment: 33 of 71 RCTs (46.5%) reported adequate methods for allocation concealment (low RoB). In 38 trials (53.5%) information was insufficient (unclear RoB).

Blinding of participants and personnel: 20 of 71 RCTs (28.2%) were double-blind, three were not (4.2%), while for the other 48 trials (67.6%) information was insufficient.

Blinding of outcome assessment: In 26 of 71 RCTs (36.6%) the outcome assessment was blind, one was not blind (1.4%), while for the other 44 trials (62.0%) information was insufficient.

Incomplete outcome data: 49 of 71 RCTs (69.0%) were judged to be at high RoB. Fifteen trials (21.1%) were judged to be at low RoB, while for seven (9.9%) information was insufficient.

Other sources of bias: Nine studies (12.7%) suffered selective crossover across groups (high RoB).

Overall, the assessment indicated high RoB across 51 of the 71 included RCTs (71.8%) and unclear RoB for 19 RCTs (26.8%). Quality assessment items are presented in **Figure 2**. Regarding the OLE studies' assessment, all studies were rated as high RoB.

3.3 Results of meta-analyses

3.3.1 Serious infections

Fifty-eight RCTs [30-32,34-38,40-49,51-58,60-76,78,79,81,82,84-89,91,94,95,99,100] involving 20,796 adult patients with RA, PsA, or AS, evaluated anti-TNF drugs and reported the occurrence of serious infections (2.6% in treatment groups; and 2.0% in control groups). Exposure to anti-TNF agents was associated with increased risk of serious infectious AEs, under both a fixed-effects model (OR: 1.41, 95% CI: 1.16, 1.73) and a random-effects model (OR: 1.25, 95% CI: 1.01, 1.55) (**Table 2**). The ORs with their 95% CIs for the individual trials, and the pooled results are presented in a forest plot (**Figure 3**).

Cochran's Q test had a p-value of 0.78 and the corresponding I-squared statistic was 0%, both indicating very little variability between studies. In contrast, the p-values for the Begg's test (p=0.06) and the Egger's test (p=0.09) suggested a possible bias. Indeed, there was a funnel plot asymmetry, with the left corner of the pyramidal part of the funnel missing (**Figure 4A**). Small studies reporting relative risks lower than the unity are probably missing, and thus the estimated pooled OR for serious infections may have been overestimated.

The subgroup analysis investigating potentially different effects on risk by the anti-TNF drugs (adalimumab, golimumab, infliximab, certolizumab, or etanercept; **Figure 3**) was statistically significant under the fixed-effects model (p=0.05), while it was not under the random-effects model (p=0.14), suggesting that etanercept and golimumab might have a better safety profile for serious infections, with point effects estimates closer to 1.0 (**Figure 3**).

To assess any association between higher doses of TNF inhibitors and risk of serious infections, we conducted a sensitivity analysis. The results did not materially change (fixed-effects, OR: 1.46, 95% CI: 1.19, 1.79; random-effects, OR: 1.36, 95% CI: 1.09, 1.69) (**Table 2**).

Meta-regression analysis, using the age of participants and the duration of follow-up as covariates, did not reveal any significant association (univariate analysis: age, p=0.72; duration of follow-up, p=0.21; and in multivariate analysis: age, p=0.69; duration of follow-up, p=0.20).

The quantitative synthesis of six open-label extension phases of RCTs [42,56,101,103-105] did not provide any further evidence for the association between anti-TNF drugs and serious infections. The calculated summary effect estimate was not statistically significant assuming either a fixed-effects model (OR: 1.33, 95% CI: 0.77, 2.29) or a random-effects model (OR: 1.19, 95% CI: 0.68, 2.07). We found no evidence of selective outcome reporting or publication bias, or heterogeneity among the OLE studies (**Table 2**).

3.3.2 Tuberculosis

Nineteen RCTs [33,43,46,48,51,52,54,57,59,62,67,73,75,81,84,93,94,99,100] involving 8,320 adults with RA, PsA, or AS, evaluated anti-TNF drugs and reported the occurrence of tuberculosis; it was 0.6% in the treatment groups (5,339 patients; 32 events), while no event was reported in the control groups (2,981 patients). Thus, continuity corrections (inversely proportional to the relative size of the opposite arm) were used in the analysis. Exposure to anti-TNF agents was associated with a statistically significant 3-fold increase in the risk of tuberculosis (fixed-effects model, OR: 3.53, 95% CI: 1.58, 7.85; random-effects model, OR: 3.29, 95% CI: 1.48, 7.33) (**Table 2**). The ORs with their 95% CIs from the individual trials, and the pooled results, are presented in **Figure 5**. We found suggestive evidence of

selective outcome reporting or publication bias, but no heterogeneity among studies (**Table 2**).

The subgroup analysis by the type of anti-TNF drug (**Figure 5**) did not reveal any difference among the drug-specific effect estimates (tests for subgroup differences: fixed effects, p=0.98; random effects, p=0.99). However, the power of this analysis is typically low, and, therefore, we cannot exclude clinically important differences between anti-TNF drugs treatment and progression of tuberculosis.

In the sensitivity analysis conducted to assess any association between higher doses of TNF inhibitors and risk of tuberculosis, the results did not materially change (fixed-effects, OR: 3.32, 95% CI: 1.54, 7.15; random-effects, OR: 3.23, 95% CI: 1.50, 6.98) (**Table 2**).

Meta-regression analysis, using the age of participants and the duration of follow-up as covariates, did not reveal any association (univariate analysis: age, p=0.89; duration of follow-up, p=0.98; and in multivariate analysis: age, p=0.87; duration of follow-up, p=0.93).

3.3.3 Opportunistic infections

Only six RCTs [35,43,63,66,73,84] involving 3,886 adult patients reported the occurrence of opportunistic infections (0.3% in treatment groups; 0.3% in control groups). The association between anti-TNF drug use and the risk of opportunistic infections was neutral (fixed-effects, OR: 0.94, 95% CI: 0.33, 2.64; random-effects model, OR: 0.81, 95% CI: 0.23, 2.87). The ORs with their 95% CIs from the individual trials, and the pooled results, are presented in **Figure 6**. We found no evidence of heterogeneity among the studies, selective outcome reporting or publication bias (**Table 2**).

The subgroup analysis, investigating potentially different effects on risk between types of anti-TNF drugs, did not reveal any difference among the drug-specific effect estimates. However, the power of this analysis was considerably low. Moreover, the sensitivity analysis did not suggest association between higher doses of the anti-TNF drugs and the risk of developing opportunistic infections (**Table 2**).

3.3.4 Any infection

In this analysis, 37 trials [31,32,34-37,39,42-45,47,50-53,55-57,60,62,64,65,67-69,71,72,74,79,84,87,92,93,97-99] involving 12,796 adult patients with RA, PsA, or AS, were

incorporated. They examined anti-TNF agents and reported "the number of patients with at least one infection during the study" (frequency was 30.8% for the treatment groups, and 28.5% for control groups). Exposure to TNF inhibitors was associated with increased risk of any infectious AE (fixed-effects, OR: 1.20, 95% CI: 1.10, 1.30; random-effects, OR: 1.20, 95% CI: 1.06, 1.36) (**Table 2**). The ORs with their 95% CIs from the primary studies, and the pooled results, are shown in **Figure 7**.

The Cochran's Q test had a p-value lower than 0.01 and the corresponding I-squared was 46%, both indicating important heterogeneity between studies. In contrast, the funnel plot (**Figure 4B**), along with Begg's test (p=0.95) and Egger's test (p=0.75), showed no evidence of selective outcome reporting or publication bias.

The subgroup analysis by the type of anti-TNF drugs (**Figure 7**) did not reveal a significant difference among the drug-specific effect estimates (tests for subgroup differences: fixed effects, p=0.78; random effects, p=0.76).

The sensitivity analysis performed to assess any association between higher doses of TNF inhibitors and risk of any infection, confirmed the results reported above (fixed-effects, OR: 1.21, 95% CI: 1.11, 1.32; random-effects, OR: 1.22, 95% CI: 1.07, 1.39) (**Table 2**).

Importantly, in the meta-regression analysis, we obtained an estimate that was statistically significantly different from zero for the regression coefficient of the duration of follow-up (months) (coefficient=0.023; se=0.011; p=0.037; **Figure 8**). The between-trial heterogeneity was reduced by 17% when duration of follow-up was included as an explanatory variable in the model. The results did not substantially change when we included both the age of participants (p=0.88) and duration of follow-up (coefficient=0.023; se=0.011; p=0.039) in the model. This finding suggests that treatment with anti-TNF agents is associated with an increasing risk of infectious AEs, as duration of follow-up increases.

Synthesis of six OLE studies [42,56,101-104] with longer follow-up periods (range: 6 to 48 months) provided further evidence for the association between anti-TNF drug use and risk of any infectious AEs (fixed-effects, OR: 1.69, 95% CI: 1.31, 2.18; random-effects, OR: 1.56, 95% CI: 1.05, 2.33) (**Table 2**). We found no evidence of heterogeneity among the OLEs, selective outcome reporting, or publication bias (**Table 2**).

3.4 Quality of the evidence

In this meta-analysis, the quality of synthesized evidence is rated as "moderate" for the following reasons: (i) the evidence was derived from RCTs (randomized study design is considered the gold standard for assessing drugs); (ii) the meta-analytic effect estimates are precise (except for opportunistic infections); (iii) the results are consistent (heterogeneity was low or moderate across studies); and (iv) the vast majority of the RCTs included in our study are characterized by high or unclear RoB, as assessed with the Cochrane Collaboration's tool (a fact that downgrades the quality of evidence). A moderate quality of evidence means that we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

4. Conclusion

This systematic review encompassed data from 71 published RCTs involving 22,760 adult patients with rheumatologic disease (range of follow-up: 1 to 36 months), and from seven OLE studies with 2,236 patients (range of follow-up: 6 to 48 months). Quantitative synthesis of the available evidence supports the hypothesis that the use of anti-TNF drugs significantly affects the risk of infectious AEs. In particular, we found an increase in the occurrence of infections (20%), serious infections (40%), and tuberculosis (250%) associated with anti-TNF drug use, while the data for the opportunistic infections were scarce. Using the GRADE system [28], a summary of findings and strength of evidence is shown in **Table 3**.

Over the last years, use of anti-TNF drugs by rheumatologic patients has been constantly increasing, and evidence on their safety continues to be collected [106]. Given the uncertainty on the effect of these agents on the risk of infectious AEs, we undertook a systematic review and meta-analysis on the topic. Seventy-one RCTs with 22,760 adult patients met the eligibility criteria and reported the occurrence of infectious AEs, as a secondary (safety) endpoint. Study-level relative risk estimates were calculated, in accordance with the intention-to-treat principle, and were appropriately synthesized. Our results provide relevant evidence that the use of anti-TNF drugs significantly affects the risk of infectious AEs. Similar results were noted when we analyzed for higher drug doses or synthesized the seven eligible OLE studies. Thus, the findings of the present meta-analysis are in line with several observational studies reporting a significant rise in the risk of infectious AEs associated with anti-TNF drug use [5-9].

In 2006, Bongartz et al. published the first meta-analysis on this topic [4]. They identified a two-fold increase in the risk of serious infections associated with anti-TNF drugs (OR: 2.0, 95% CI: 1.3, 3.1), and an even higher increase when the analysis was restricted to high-dose groups vs. placebo (OR: 2.3, 95% CI: 1.5, 3.6). Since then, several meta-analyses have been published with conflicting results. Leombruno et al. [107] analyzed 18 RCTs involving over 8,800 RA patients treated over an average of 0.8 years. They did not identify an increased risk of serious infections (OR: 1.21, 95% CI: 0.89, 1.63). However, high-dose therapy was associated with a two-fold increase in the risk of serious infections. In 2010, Bernatsky et al. [108] published a meta-analysis of seven observational studies involving RA

patients. Anti-TNF therapy appeared to significantly increase the risk of serious infections (OR: 1.37, 95% CI: 1.18, 1.60). In 2011, Thompson et al. [109] conducted a meta-analysis of six RCTs and showed no increased risk of serious infection in patients with early RA receiving anti-TNF therapy (OR: 1.28, 95% CI: 0.82, 2.00). As compared to those studies, our meta-analysis uses a much broader evidence base, includes a large number of trials (n=71), and provides updated evidence that can be appropriately integrated into relevant clinical guidelines.

This study has some limitations. Firstly, our search was restricted to published studies and we did not search for unpublished/original data. Secondly, the trials included in our review are characterized by high or unclear RoB, as assessed with the Cochrane Collaboration's tool. This is of concern, because the quality of the meta-analysis depends on the quality of the primary studies; if they are biased, then the meta-analysis will be biased as well. However some studies were rated at low risk of bias, and the estimates from studies at low risk did not differ from studies at high risk of bias. This increases the overall confidence we have in the final estimates. Thirdly, because duration of follow-up was up to 36 months, risk estimates resulting from longer exposure to anti-TNF agents are not possible. Given the meta-regression finding that anti-TNF drug therapy is associated with higher risks of infectious AEs as duration of follow-up increases, evidence describing infection risk during longer durations of anti-TNF therapy is required. However, the present study also has merits. It was conducted using a rigorous and extensive bibliographic search that allowed the inclusion of all relevant published RCTs. Furthermore, the relatively precise meta-analytic effect estimates, the absence of significant between-study heterogeneity, and the stability of the results in the subgroup and sensitivity analyses, strengthen our confidence in the accuracy of our findings.

5. Expert opinion

The results of our meta-analyses raise concerns about the use of anti-TNF in patients with infectious diseases. Included trials carefully excluded patients with histories of infections such as latent tuberculosis. Even after careful selection of patients for inclusion, our meta-analysis provides definitive evidence that anti-TNF drugs can disturb physiological cytokine-mediated signaling. The tuberculosis meta-analysis is paradigmatic. All events were in the anti-TNF arms, while the control arms were

tuberculosis free. There are several prospective and retrospective studies exploring the association between anti-TNFs and tuberculosis [110-115]. The annual incidence rate varied depending on the country observed and the anti-TNF drug administered. Therefore, it is important to establish accurate latent tuberculosis infection screening strategy before commencing anti-TNF therapy in patients with immune-mediated inflammatory diseases [116]. The implementation of recommendations for latent tuberculosis infection screening and (prophylactic) treatment before initiation of anti-TNF therapy might reduce the infection incidence. Risk stratification scores associated with host demographic and clinical features, and previous or current non-biologic therapies are warranted to support the decision to start a treatment and the safest biologic choice [117]. For all anti-TNF drugs, the tuberculosis incidence rate was consistently higher than that in the general population, but infliximab and adalimumab were associated with the highest incidence rates when compared to etanercept [118]. Despite all anti-TNF neutralize TNF resulting in disruption of the granuloma that normally compartmentalizes *Mycobacterium tuberculosis*, etanercept might have a different impact on immunity that may allow the granuloma to reconstitute itself, thus preventing bacillary dissemination [119]. Our review did not identify substantial differences among the anti-TNFs drugs. However, the power of these subgroup analyses is typically limited: up to two cases of tuberculosis were included in trials exploring etanercept and golimumab, an inadequate number to demonstrate a definite association between the use of the drug and reactivation tuberculosis. Additionally concomitant corticosteroid and methotrexate therapies might be important confounding factors, hiding differences on drug inflammatory mechanisms and safety profile.

Given the increased risk of reoccurrence of infections, rheumatologists should further consider that the number of patients experiencing these adverse events is higher in studies other then RCTs such that the clinical consequences of the treatment might be more severe. There is not clear hypothesis for assuming that harms are different in directions or magnitude of effects across diseases, so we did not group studies by disease. We hypothesized that there were not strong differences in the case mix of patients across populations included in the RCTs, so harms, overall, should have been fairly consistent across studies. However there was some heterogeneity, so some differences between patient populations cannot be excluded.

In conclusion, synthesis of existing evidence from RCTs involving rheumatologic patients confirms that anti-TNF drug use significantly increases the risk of infectious AEs, especially the risk for serious infections and tuberculosis. Given the increasing use of anti-TNF agents in adult patients with RA, PsA, or AS, it is important to continue monitoring their safety profiles, through complementary sources of research data, such as registries and long-term epidemiological studies.

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Declaration of interest

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Legends for Figures

Figure 1. Summary of evidence search and selection (flow iagram).

Abbreviations. RCTs: randomized controlled trials; OLEs: open label extension studies; AEs: adverse events.

Figure 2. Risk-of-bias assessments for the randomized trials included in the meta-analysis.

Symbols. green (+): low risk of bias; yellow (?): unclear risk of bias; red (-): high risk of bias.

Figure 3. Forest plot for serious infections: results from individual studies and meta-analyses.

Abbreviations. OR: odds ratio; CI: confidence interval.

Figure 4A. Contour-enhanced funnel plot for serious infections.

Footnote. Ideally, the funnel plot should have a symmetrical shape with a wide base and a narrow peak. The figure indicates that smaller trials reporting odds ratios lower than the unity are probably missing, and thus the pooled effect estimate for serious infections may have been overestimated. Tests of publication bias: Begg's p=0.07; Egger's p=0.09.

Figure 4B. Contour-enhanced funnel plot for any infection.

Footnote. Tests of publication bias: Begg's p=0.95; Egger's p=0.75.

Figure 5. Forest plot for tuberculosis: results from individual studies and meta-analyses.

Abbreviations. OR: odds ratio; CI: confidence interval.

Figure 6. Forest plot for opportunistic infections: results from individual studies and meta-analyses.

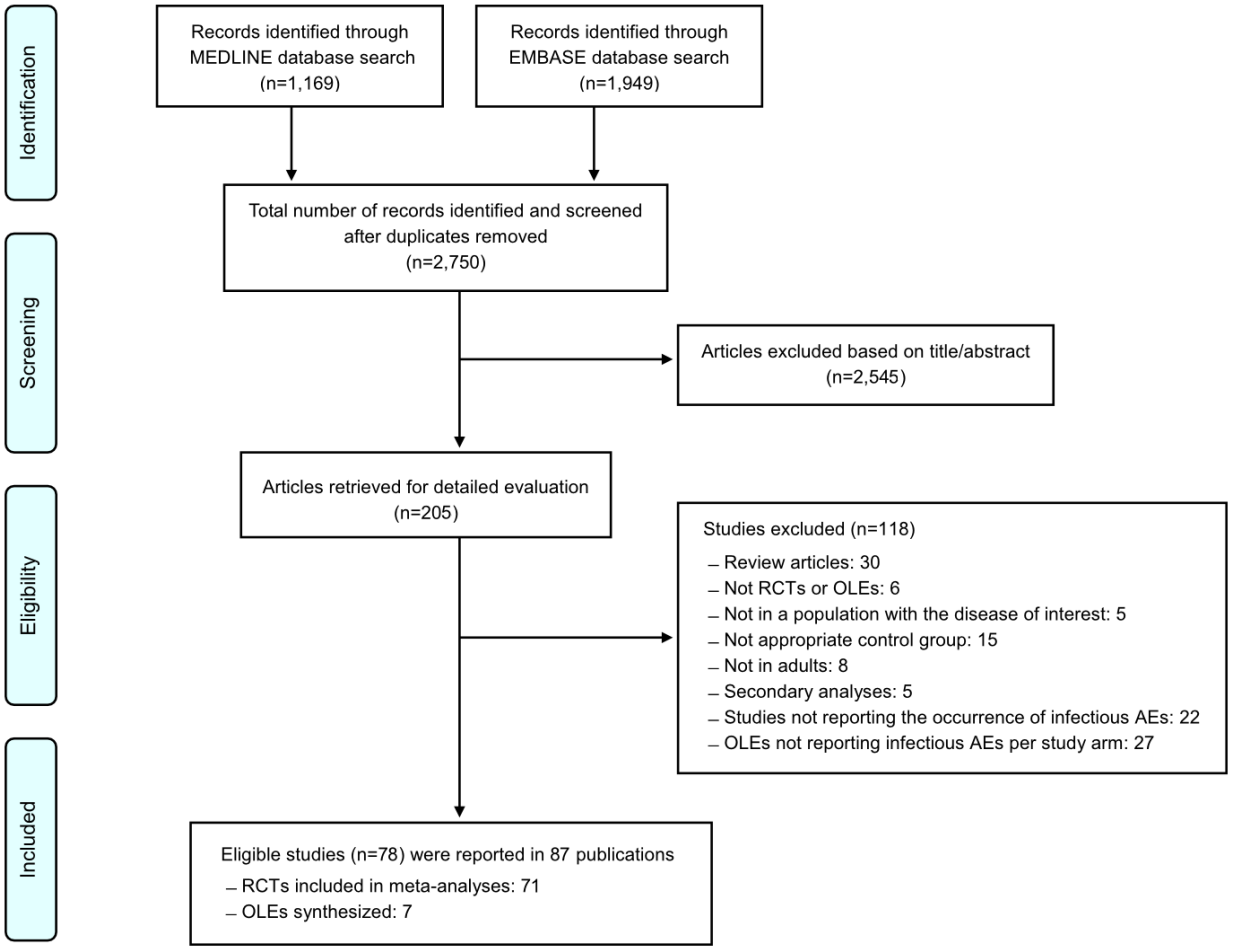
Abbreviations. OR: odds ratio; CI: confidence interval.

Figure 7. Forest plot for any infection: results from individual studies and meta-analyses.

Abbreviations. OR: odds ratio; CI: confidence interval.

Figure 8. Log odds ratios of any infection as a function of the duration of follow-up. The greater the variance of a study, the smaller the area of the circle and the less that observation contributes to the overall effect. The superimposed line is obtained by meta-regression analysis.

Figure 1


Identification
Screening
Eligibility
Included
Records identified through MEDLINE database search (n=1,169)
Records identified through EMBASE database search (n=1,949)
Total number of records identified and screened after duplicates removed (n=2,750)
Articles excluded based on title/abstract (n=2,545)
Articles retrieved for detailed evaluation (n=205)
Studies excluded (n=118)
– Review articles: 30
– Not RCTs or OLEs: 6
– Not in a population with the disease of interest: 5
– Not appropriate control group: 15
– Not in adults: 8
– Secondary analyses: 5
– Studies not reporting the occurrence of infectious AEs: 22
– OLEs not reporting infectious AEs per study arm: 27
Eligible studies (n=78) were reported in 87 publications
– RCTs included in meta-analyses: 71
– OLEs synthesized: 7

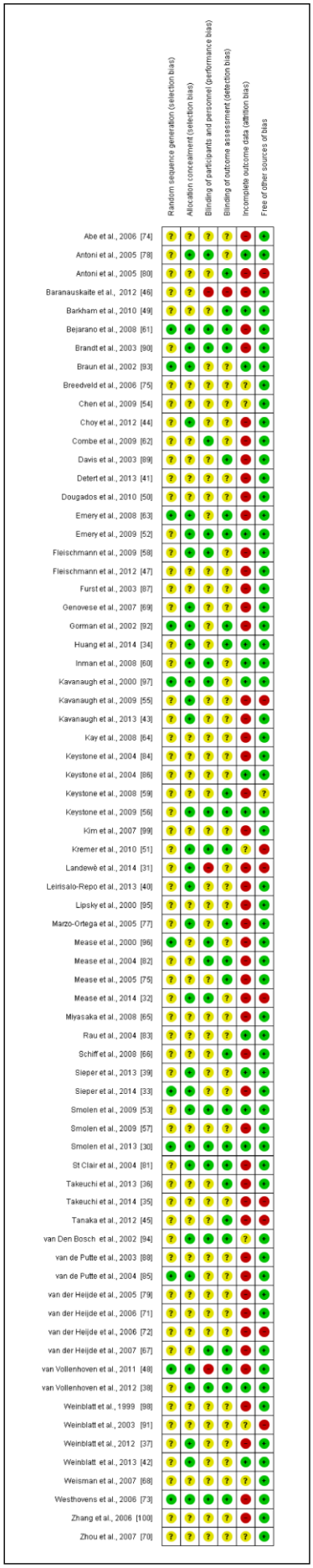

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Free of other sources of bias
Abe et al., 2006 [74]
Antoni et al., 2005 [78]
Antoni et al., 2005 [80]
Baranauskaite et al., 2012 [46]
Barkham et al., 2010 [49]
Bejarano et al., 2008 [61]
Brandt et al., 2003 [90]
Braun et al., 2002 [93]
Breedveld et al., 2006 [75]
Chen et al., 2009 [54]
Choy et al., 2012 [44]
Combe et al., 2009 [62]
Davis et al., 2003 [89]
Detert et al., 2013 [41]
Dougados et al., 2010 [50]
Emery et al., 2008 [63]
Emery et al., 2009 [52]
Fleischmann et al., 2009 [58]
Fleischmann et al., 2012 [47]
Furst et al., 2003 [87]
Genovese et al., 2007 [69]
Gorman et al., 2002 [92]
Huang et al., 2014 [34]
Inman et al., 2008 [60]
Kavanaugh et al., 2000 [97]
Kavanaugh et al., 2009 [55]
Kavanaugh et al., 2013 [43]
Kay et al., 2008 [64]
Keystone et al., 2004 [84]
Keystone et al., 2004 [86]
Keystone et al., 2008 [59]
Keystone et al., 2009 [56]
Kim et al., 2007 [99]
Kremer et al., 2010 [51]
Landewé et al., 2014 [31]
Leirisalo-Repo et al., 2013 [40]
Lipsky et al., 2000 [95]
Marzo-Ortega et al., 2005 [77]
Mease et al., 2000 [96]
Mease et al., 2004 [82]
Mease et al., 2005 [75]
Mease et al., 2014 [32]
Miyasaka et al., 2008 [65]
Rau et al., 2004 [83]
Schiff et al., 2008 [66]
Sieper et al., 2013 [39]
Sieper et al., 2014 [33]
Smolen et al., 2009 [53]
Smolen et al., 2009 [57]
Smolen et al., 2013 [30]
St Clair et al., 2004 [81]
Takeuchi et al., 2013 [36]
Takeuchi et al., 2014 [35]
Tanaka et al., 2012 [45]
van Den Bosch et al., 2002 [94]
van de Putte et al., 2003 [88]
van de Putte et al., 2004 [85]
van der Heijde et al., 2005 [79]
van der Heijde et al., 2006 [71]
van der Heijde et al., 2006 [72]
van der Heijde et al., 2007 [67]
van Vollenhoven et al., 2011 [48]
van Vollenhoven et al., 2012 [38]
Weinblatt et al., 1999 [98]
Weinblatt et al., 2003 [91]
Weinblatt et al., 2012 [37]
Weinblatt et al., 2013 [42]
Weisman et al., 2007 [68]
Westhovens et al., 2006 [73]
Zhang et al., 2006 [100]
Zhou et al., 2007 [70]

Figure 2

Figure 3

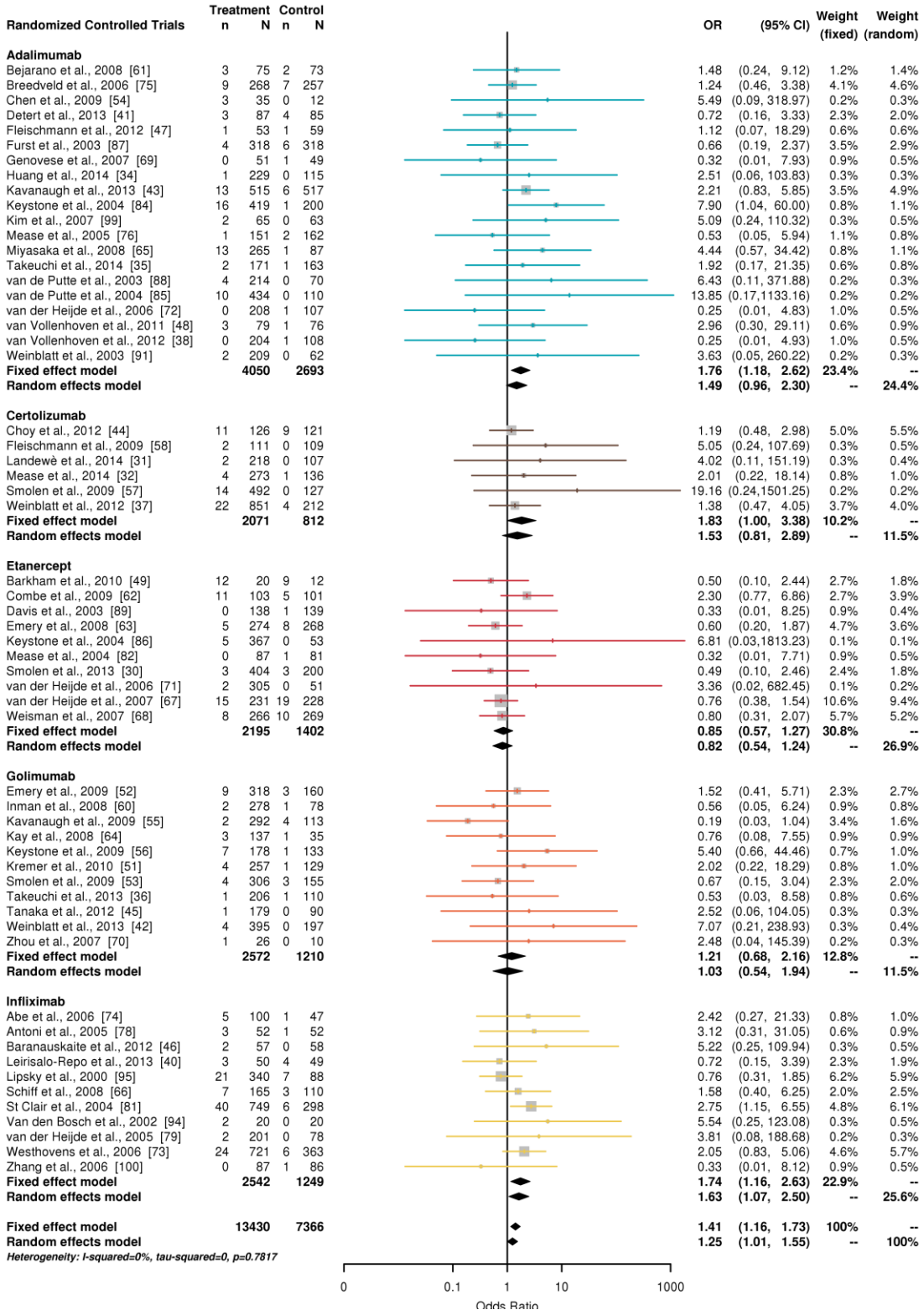

Randomized Controlled Trials
Treatment n N
Control n N
OR (95% CI)
Weight (fixed)
Weight (random)
Adalimumab
Bejarano et al., 2008 [61] 3 75 2 73 1.48 (0.24, 9.12) 1.2% 1.4%
Breedveld et al., 2006 [75] 9 268 7 257 1.24 (0.46, 3.38) 4.1% 4.6%
Chen et al., 2009 [54] 3 35 0 12 5.49 (0.09, 318.97) 0.2% 0.3%
Detert et al., 2013 [41] 3 87 4 85 0.72 (0.16, 3.33) 2.3% 2.0%
Fleischmann et al., 2012 [47] 1 53 1 59 1.12 (0.07, 18.29) 0.6% 0.6%
Furst et al., 2003 [87] 4 318 6 318 0.66 (0.19, 2.37) 3.5% 2.9%
Genovese et al., 2007 [69] 0 51 1 49 0.32 (0.01, 7.93) 0.9% 0.5%
Huang et al., 2014 [34] 1 229 0 115 2.51 (0.06, 103.83) 0.3% 0.3%
Kavanaugh et al., 2013 [43] 13 515 6 517 2.21 (0.83, 5.85) 3.5% 4.9%
Keystone et al., 2004 [84] 16 419 1 200 7.90 (1.04, 60.00) 0.8% 1.1%
Kim et al., 2007 [99] 2 65 0 63 5.09 (0.24, 110.32) 0.3% 0.5%
Mease et al., 2005 [76] 1 151 2 162 0.53 (0.05, 5.94) 1.1% 0.8%
Miyasaka et al., 2008 [65] 13 265 1 87 4.44 (0.57, 34.42) 0.8% 1.1%
Takeuchi et al., 2014 [35] 2 171 1 163 1.92 (0.17, 21.35) 0.6% 0.8%
van de Putte et al., 2003 [88] 4 214 0 70 6.43 (0.11, 371.88) 0.2% 0.3%
van de Putte et al., 2004 [85] 10 434 0 110 13.85 (0.17,1133.16) 0.2% 0.2%
van der Heijde et al., 2006 [72] 0 208 1 107 0.25 (0.01, 4.83) 1.0% 0.5%
van Vollenhoven et al., 2011 [48] 3 79 1 76 2.96 (0.30, 29.11) 0.6% 0.9%
van Vollenhoven et al., 2012 [38] 0 204 1 108 0.25 (0.01, 4.93) 1.0% 0.5%
Weinblatt et al., 2003 [91] 2 209 0 62 3.63 (0.05, 260.22) 0.2% 0.3%
Fixed effect model 4050 2693 1.76 (1.18, 2.62) 23.4% --
Random effects model 1.49 (0.96, 2.30) -- 24.4%
Certolizumab
Choy et al., 2012 [44] 11 126 9 121 1.19 (0.48, 2.98) 5.0% 5.5%
Fleischmann et al., 2009 [58] 2 111 0 109 5.05 (0.24, 107.69) 0.3% 0.5%
Landewè et al., 2014 [31] 2 218 0 107 4.02 (0.11, 151.19) 0.3% 0.4%
Mease et al., 2014 [32] 4 273 1 136 2.01 (0.22, 18.14) 0.8% 1.0%
Smolen et al., 2009 [57] 14 492 0 127 19.16 (0.24,1501.25) 0.2% 0.2%
Weinblatt et al., 2012 [37] 22 851 4 212 1.38 (0.47, 4.05) 3.7% 4.0%
Fixed effect model 2071 812 1.83 (1.00, 3.38) 10.2% --
Random effects model 1.53 (0.81, 2.89) -- 11.5%
Etanercept
Barkham et al., 2010 [49] 12 20 9 12 0.50 (0.10, 2.44) 2.7% 1.8%
Combe et al., 2009 [62] 11 103 5 101 2.30 (0.77, 6.86) 2.7% 3.9%
Davis et al., 2003 [89] 0 138 1 139 0.33 (0.01, 8.25) 0.9% 0.4%
Emery et al., 2008 [63] 5 274 8 268 0.60 (0.20, 1.87) 4.7% 3.6%
Keystone et al., 2004 [86] 5 367 0 53 6.81 (0.03,1813.23) 0.1% 0.1%
Mease et al., 2004 [82] 0 87 1 81 0.32 (0.01, 7.71) 0.9% 0.5%
Smolen et al., 2013 [30] 3 404 3 200 0.49 (0.10, 2.46) 2.4% 1.8%
van der Heijde et al., 2006 [71] 2 305 0 51 3.36 (0.02, 682.45) 0.1% 0.2%
van der Heijde et al., 2007 [67] 15 231 19 228 0.76 (0.38, 1.54) 10.6% 9.4%
Weisman et al., 2007 [68] 8 266 10 269 0.80 (0.31, 2.07) 5.7% 5.2%
Fixed effect model 2195 1402 0.85 (0.57, 1.27) 30.8% --
Random effects model 0.82 (0.54, 1.24) -- 26.9%
Golimumab
Emery et al., 2009 [52] 9 318 3 160 1.52 (0.41, 5.71) 2.3% 2.7%
Inman et al., 2008 [60] 2 278 1 78 0.56 (0.05, 6.24) 0.9% 0.8%
Kavanaugh et al., 2009 [55] 2 292 4 113 0.19 (0.03, 1.04) 3.4% 1.6%
Kay et al., 2008 [64] 3 137 1 35 0.76 (0.08, 7.55) 0.9% 0.9%
Keystone et al., 2009 [56] 7 178 1 133 5.40 (0.66, 44.46) 0.7% 1.0%
Kremer et al., 2010 [51] 4 257 1 129 2.02 (0.22, 18.29) 0.8% 1.0%
Smolen et al., 2009 [53] 4 306 3 155 0.67 (0.15, 3.04) 2.3% 2.0%
Takeuchi et al., 2013 [36] 1 206 1 110 0.53 (0.03, 8.58) 0.8% 0.6%
Tanaka et al., 2012 [45] 1 179 0 90 2.52 (0.06, 104.05) 0.3% 0.3%
Weinblatt et al., 2013 [42] 4 395 0 197 7.07 (0.21, 238.93) 0.3% 0.4%
Zhou et al., 2007 [70] 1 26 0 10 2.48 (0.04, 145.39) 0.2% 0.3%
Fixed effect model 2572 1210 1.21 (0.68, 2.16) 12.8% --
Random effects model 1.03 (0.54, 1.94) -- 11.5%
Infliximab
Abe et al., 2006 [74] 5 100 1 47 2.42 (0.27, 21.33) 0.8% 1.0%
Antoni et al., 2005 [78] 3 52 1 52 3.12 (0.31, 31.05) 0.6% 0.9%
Baranauskaite et al., 2012 [46] 2 57 0 58 5.22 (0.25, 109.94) 0.3% 0.5%
Leirisalo-Repo et al., 2013 [40] 3 50 4 49 0.72 (0.15, 3.39) 2.3% 1.9%
Lipsky et al., 2000 [95] 21 340 7 88 0.76 (0.31, 1.85) 6.2% 5.9%
Schiff et al., 2008 [66] 7 165 3 110 1.58 (0.40, 6.25) 2.0% 2.5%
St Clair et al., 2004 [81] 40 749 6 298 2.75 (1.15, 6.55) 4.8% 6.1%
Van den Bosch et al., 2002 [94] 2 20 0 20 5.54 (0.25, 123.08) 0.3% 0.5%
van der Heijde et al., 2005 [79] 2 201 0 78 3.81 (0.08, 188.68) 0.2% 0.3%
Westhovens et al., 2006 [73] 24 721 6 363 2.05 (0.83, 5.06) 4.6% 5.7%
Zhang et al., 2006 [100] 0 87 1 86 0.33 (0.01, 8.12) 0.9% 0.5%
Fixed effect model 2542 1249 1.74 (1.16, 2.63) 22.9% --
Random effects model 1.63 (1.07, 2.50) -- 25.6%
Fixed effect model 13430 7366 1.41 (1.16, 1.73) 100% --
Random effects model 1.25 (1.01, 1.55) -- 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.7817
0
0.1
1
10
1000
Odds Ratio

Figure 4A

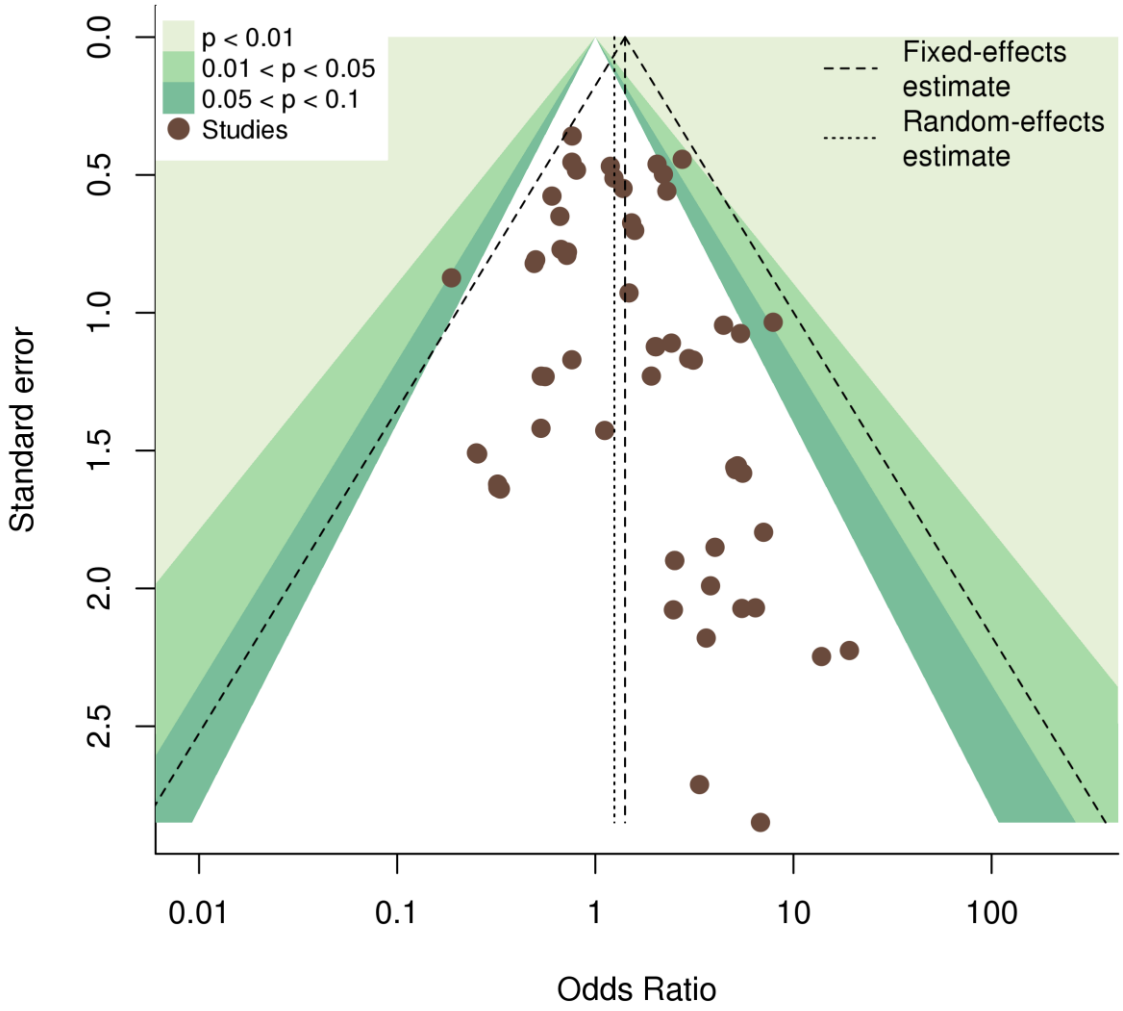

p < 0.01
0.01 < p < 0.05
0.05 < p < 0.1
Studies
Fixed-effects estimate
Random-effects estimate
Standard error
0.0
0.5
1.0
1.5
2.0
2.5
0.01
0.1
1
10
100
Odds Ratio

Figure 4B

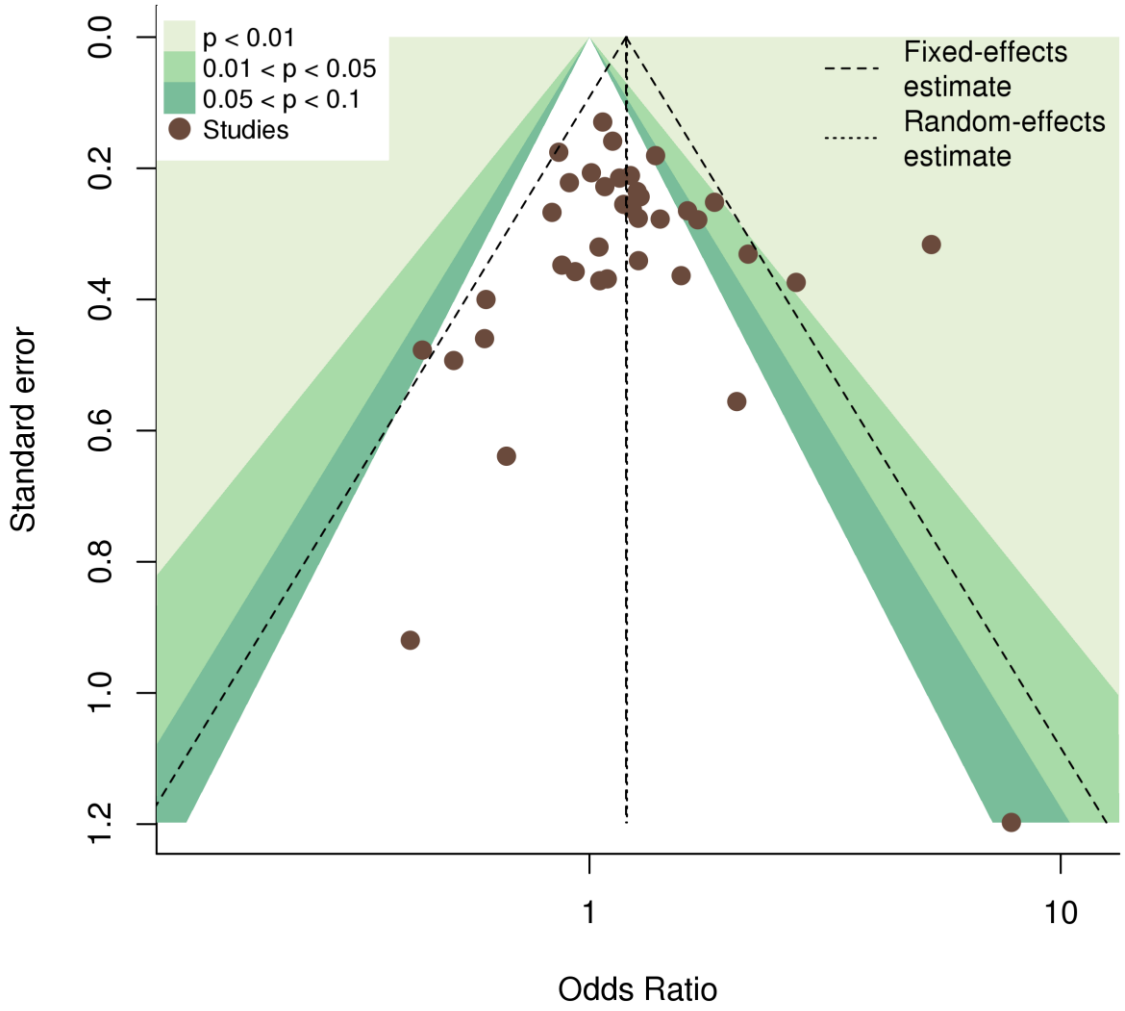

p < 0.01
0.01 < p < 0.05
0.05 < p < 0.1
Studies
Fixed-effects estimate
Random-effects estimate
Standard error
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1
10
Odds Ratio

Figure 5

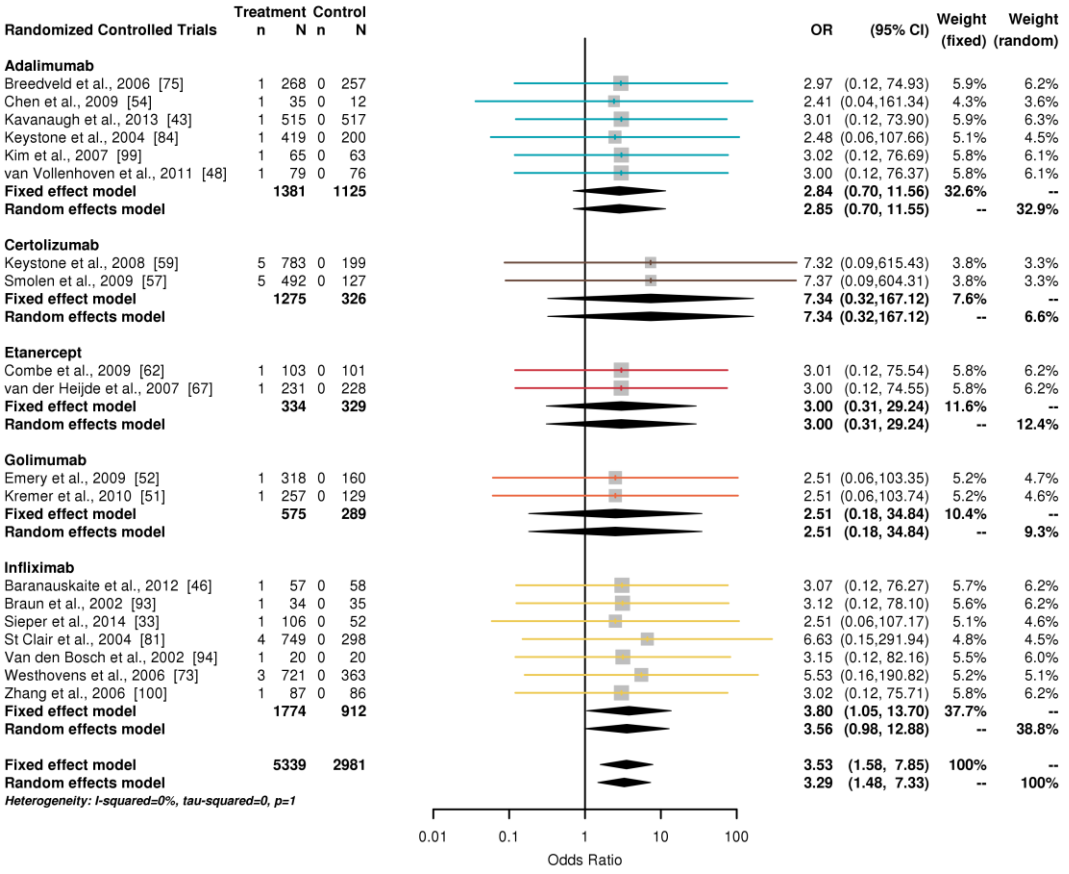

Randomized Controlled Trials
Treatment n N
Control n N
OR (95% CI)
Weight (fixed)
Weight (random)
Adalimumab
Breedveld et al., 2006 [75] 1 268 0 257 2.97 (0.12, 74.93) 5.9% 6.2%
Chen et al., 2009 [54] 1 35 0 12 2.41 (0.04,161.34) 4.3% 3.6%
Kavanaugh et al., 2013 [43] 1 515 0 517 3.01 (0.12, 73.90) 5.9% 6.3%
Keystone et al., 2004 [84] 1 419 0 200 2.48 (0.06,107.66) 5.1% 4.5%
Kim et al., 2007 [99] 1 65 0 63 3.02 (0.12, 76.69) 5.8% 6.1%
van Vollenhoven et al., 2011 [48] 1 79 0 76 3.00 (0.12, 76.37) 5.8% 6.1%
Fixed effect model 1381 1125 2.84 (0.70, 11.56) 32.6% --
Random effects model 2.85 (0.70, 11.55) -- 32.9%
Certolizumab
Keystone et al., 2008 [59] 5 783 0 199 7.32 (0.09,615.43) 3.8% 3.3%
Smolen et al., 2009 [57] 5 492 0 127 7.37 (0.09,604.31) 3.8% 3.3%
Fixed effect model 1275 326 7.34 (0.32,167.12) 7.6% --
Random effects model 7.34 (0.32,167.12) -- 6.6%
Etanercept
Combe et al., 2009 [62] 1 103 0 101 3.01 (0.12, 75.54) 5.8% 6.2%
van der Heijde et al., 2007 [67] 1 231 0 228 3.00 (0.12, 74.55) 5.8% 6.2%
Fixed effect model 334 329 3.00 (0.31, 29.24) 11.6% --
Random effects model 3.00 (0.31, 29.24) -- 12.4%
Golimumab
Emery et al., 2009 [52] 1 318 0 160 2.51 (0.06,103.35) 5.2% 4.7%
Kremer et al., 2010 [51] 1 257 0 129 2.51 (0.06,103.74) 5.2% 4.6%
Fixed effect model 575 289 2.51 (0.18, 34.84) 10.4% --
Random effects model 2.51 (0.18, 34.84) -- 9.3%
Infliximab
Baranauskaite et al., 2012 [46] 1 57 0 58 3.07 (0.12, 76.27) 5.7% 6.2%
Braun et al., 2002 [93] 1 34 0 35 3.12 (0.12, 78.10) 5.6% 6.2%
Sieper et al., 2014 [33] 1 106 0 52 2.51 (0.06,107.17) 5.1% 4.6%
St Clair et al., 2004 [81] 4 749 0 298 6.63 (0.15,291.94) 4.8% 4.5%
Van den Bosch et al., 2002 [94] 1 20 0 20 3.15 (0.12, 82.16) 5.5% 6.0%
Westhovens et al., 2006 [73] 3 721 0 363 5.53 (0.16,190.82) 5.2% 5.1%
Zhang et al., 2006 [100] 1 87 0 86 3.02 (0.12, 75.71) 5.8% 6.2%
Fixed effect model 1774 912 3.80 (1.05, 13.70) 37.7% --
Random effects model 3.56 (0.98, 12.88) -- 38.8%
Fixed effect model 5339 2981 3.53 (1.58, 7.85) 100% --
Random effects model 3.29 (1.48, 7.33) -- 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=1
0.01
0.1
1
10
100
Odds Ratio

Figure 6

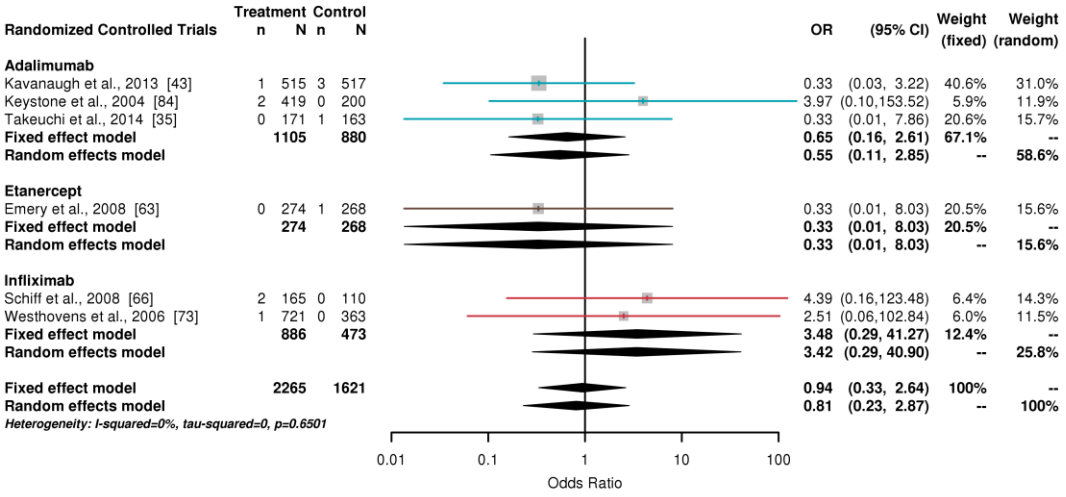

Randomized Controlled Trials
Treatment n N
Control n N
OR (95% CI)
Weight (fixed)
Weight (random)
Adalimumab
Kavanaugh et al., 2013 [43] 1 515 3 517 0.33 (0.03, 3.22) 40.6% 31.0%
Keystone et al., 2004 [84] 2 419 0 200 3.97 (0.10,153.52) 5.9% 11.9%
Takeuchi et al., 2014 [35] 0 171 1 163 0.33 (0.01, 7.86) 20.6% 15.7%
Fixed effect model 1105 880 0.65 (0.16, 2.61) 67.1% --
Random effects model 0.55 (0.11, 2.85) -- 58.6%
Etanercept
Emery et al., 2008 [63] 0 274 1 268 0.33 (0.01, 8.03) 20.5% 15.6%
Fixed effect model 274 268 0.33 (0.01, 8.03) 20.5% --
Random effects model 0.33 (0.01, 8.03) -- 15.6%
Infliximab
Schiff et al., 2008 [66] 2 165 0 110 4.39 (0.16,123.48) 6.4% 14.3%
Westhovens et al., 2006 [73] 1 721 0 363 2.51 (0.06,102.84) 6.0% 11.5%
Fixed effect model 886 473 3.48 (0.29, 41.27) 12.4% --
Random effects model 3.42 (0.29, 40.90) -- 25.8%
Fixed effect model 2265 1621 0.94 (0.33, 2.64) 100% --
Random effects model 0.81 (0.23, 2.87) -- 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.6501
0.01
0.1
1
10
100
Odds Ratio

Figure 7

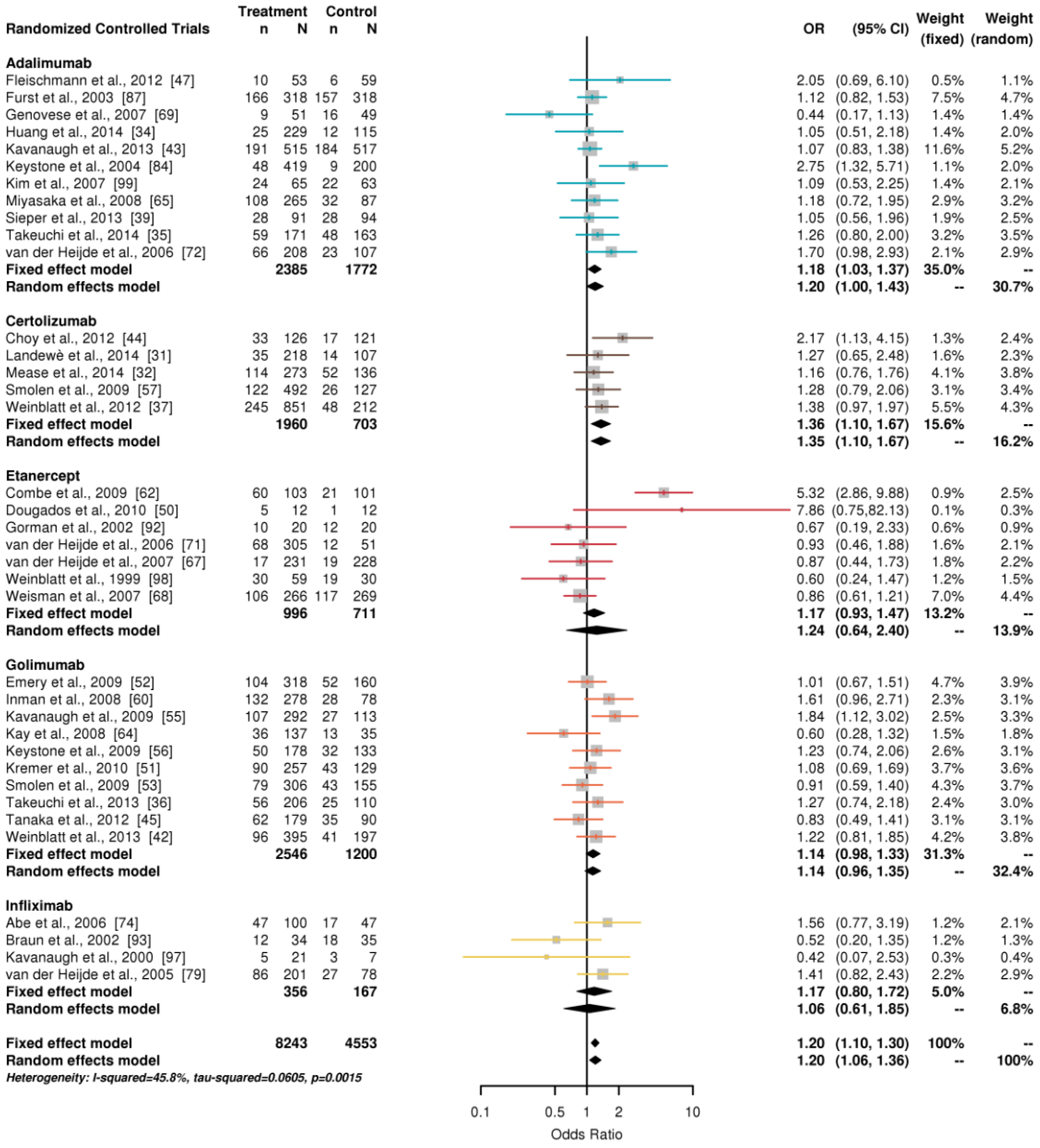

Randomized Controlled Trials
Treatment n N
Control n N
OR (95% CI)
Weight (fixed)
Weight (random)
Adalimumab
Fleischmann et al., 2012 [47] 10 53 6 59 2.05 (0.69, 6.10) 0.5% 1.1%
Furst et al., 2003 [87] 166 318 157 318 1.12 (0.82, 1.53) 7.5% 4.7%
Genovese et al., 2007 [69] 9 51 16 49 0.44 (0.17, 1.13) 1.4% 1.4%
Huang et al., 2014 [34] 25 229 12 115 1.05 (0.51, 2.18) 1.4% 2.0%
Kavanaugh et al., 2013 [43] 191 515 184 517 1.07 (0.83, 1.38) 11.6% 5.2%
Keystone et al., 2004 [84] 48 419 9 200 2.75 (1.32, 5.71) 1.1% 2.0%
Kim et al., 2007 [99] 24 65 22 63 1.09 (0.53, 2.25) 1.4% 2.1%
Miyasaka et al., 2008 [65] 108 265 32 87 1.18 (0.72, 1.95) 2.9% 3.2%
Sieper et al., 2013 [39] 28 91 28 94 1.05 (0.56, 1.96) 1.9% 2.5%
Takeuchi et al., 2014 [35] 59 171 48 163 1.26 (0.80, 2.00) 3.2% 3.5%
van der Heijde et al., 2006 [72] 66 208 23 107 1.70 (0.98, 2.93) 2.1% 2.9%
Fixed effect model 2385 1772 1.18 (1.03, 1.37) 35.0% --
Random effects model 1.20 (1.00, 1.43) -- 30.7%
Certolizumab
Choy et al., 2012 [44] 33 126 17 121 2.17 (1.13, 4.15) 1.3% 2.4%
Landewè et al., 2014 [31] 35 218 14 107 1.27 (0.65, 2.48) 1.6% 2.3%
Mease et al., 2014 [32] 114 273 52 136 1.16 (0.76, 1.76) 4.1% 3.8%
Smolen et al., 2009 [57] 122 492 26 127 1.28 (0.79, 2.06) 3.1% 3.4%
Weinblatt et al., 2012 [37] 245 851 48 212 1.38 (0.97, 1.97) 5.5% 4.3%
Fixed effect model 1960 703 1.36 (1.10, 1.67) 15.6% --
Random effects model 1.35 (1.10, 1.67) -- 16.2%
Etanercept
Combe et al., 2009 [62] 60 103 21 101 5.32 (2.86, 9.88) 0.9% 2.5%
Dougados et al., 2010 [50] 5 12 1 12 7.86 (0.75,82.13) 0.1% 0.3%
Gorman et al., 2002 [92] 10 20 12 20 0.67 (0.19, 2.33) 0.6% 0.9%
van der Heijde et al., 2006 [71] 68 305 12 51 0.93 (0.46, 1.88) 1.6% 2.1%
van der Heijde et al., 2007 [67] 17 231 19 228 0.87 (0.44, 1.73) 1.8% 2.2%
Weinblatt et al., 1999 [98] 30 59 19 30 0.60 (0.24, 1.47) 1.2% 1.5%
Weisman et al., 2007 [68] 106 266 117 269 0.86 (0.61, 1.21) 7.0% 4.4%
Fixed effect model 996 711 1.17 (0.93, 1.47) 13.2% --
Random effects model 1.24 (0.64, 2.40) -- 13.9%
Golimumab
Emery et al., 2009 [52] 104 318 52 160 1.01 (0.67, 1.51) 4.7% 3.9%
Inman et al., 2008 [60] 132 278 28 78 1.61 (0.96, 2.71) 2.3% 3.1%
Kavanaugh et al., 2009 [55] 107 292 27 113 1.84 (1.12, 3.02) 2.5% 3.3%
Kay et al., 2008 [64] 36 137 13 35 0.60 (0.28, 1.32) 1.5% 1.8%
Keystone et al., 2009 [56] 50 178 32 133 1.23 (0.74, 2.06) 2.6% 3.1%
Kremer et al., 2010 [51] 90 257 43 129 1.08 (0.69, 1.69) 3.7% 3.6%
Smolen et al., 2009 [53] 79 306 43 155 0.91 (0.59, 1.40) 4.3% 3.7%
Takeuchi et al., 2013 [36] 56 206 25 110 1.27 (0.74, 2.18) 2.4% 3.0%
Tanaka et al., 2012 [45] 62 179 35 90 0.83 (0.49, 1.41) 3.1% 3.1%
Weinblatt et al., 2013 [42] 96 395 41 197 1.22 (0.81, 1.85) 4.2% 3.8%
Fixed effect model 2546 1200 1.14 (0.98, 1.33) 31.3% --
Random effects model 1.14 (0.96, 1.35) -- 32.4%
Infliximab
Abe et al., 2006 [74] 47 100 17 47 1.56 (0.77, 3.19) 1.2% 2.1%
Braun et al., 2002 [93] 12 34 18 35 0.52 (0.20, 1.35) 1.2% 1.3%
Kavanaugh et al., 2000 [97] 5 21 3 7 0.42 (0.07, 2.53) 0.3% 0.4%
van der Heijde et al., 2005 [79] 86 201 27 78 1.41 (0.82, 2.43) 2.2% 2.9%
Fixed effect model 356 167 1.17 (0.80, 1.72) 5.0% --
Random effects model 1.06 (0.61, 1.85) -- 6.8%
Fixed effect model 8243 4553 1.20 (1.10, 1.30) 100% --
Random effects model 1.20 (1.06, 1.36) -- 100%
Heterogeneity: I-squared=45.8%, tau-squared=0.0605, p=0.0015
0.1
0.5
1
2
10
Odds Ratio

Figure 8

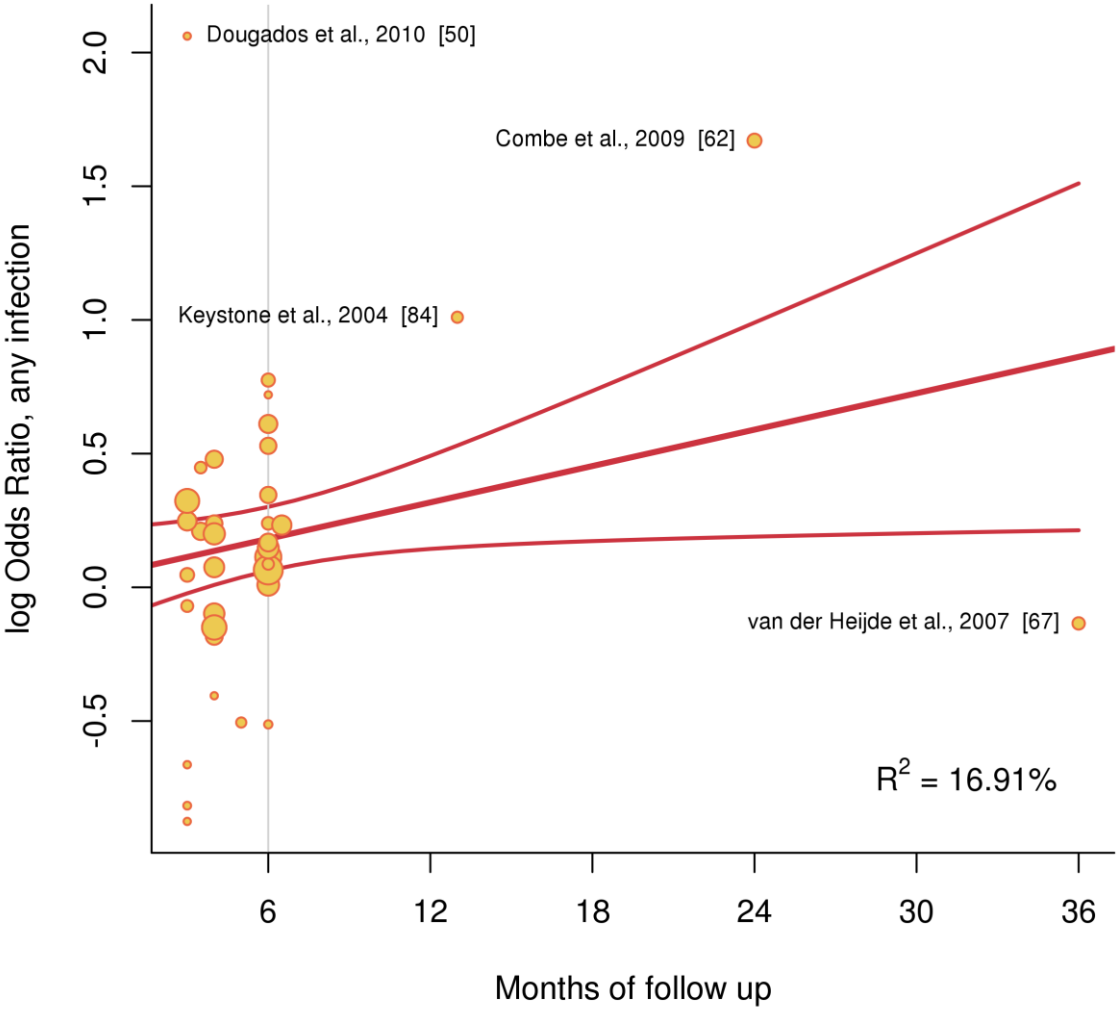

Dougados et al., 2010 [50]
Combe et al., 2009 [62]
Keystone et al., 2004 [84]
van der Heijde et al., 2007 [67]
R^2 = 16.91%
log Odds Ratio, any infection
-0.5
0.0
0.5
1.0
1.5
2.0
6
12
18
24
30
36
Months of follow up

Table 1. Characteristics of the RCTs included in the meta-analysis (n=71).

Study	Acronym	Disease	Study arms	Intervention parameters	Patients randomized	Follow-up duration (months)	Age of patients (years)	Disease duration (months)
Abe *et al.,* 2006 [74]		RA	IFX+MTX	3 mg/kg, wk: 0,2,6	(n=49)	3.5	55.2	9.1
			IFX+MTX	10 mg/kg wk: 0,2,6	(n=51)	3.5	56.8	7.1
			PBO+MTX		(n=47)	3.5	55.1	7.5
Antoni *et al.,* 2005 [80]	IMPACT 2	PsA	IFX+MTX	5 mg/kg, wk: 0,2,6,14	(n=100)	6	47.1	100.8
			PBO+MTX		(n=100)	6	46.5	90.0
Antoni *et al.,* 2005 [78]	IMPACT 1	PsA	IFX+MTX	5 mg/kg, wk: 0,2,6,14	(n=52)	4	45.7	140.4
			PBO+MTX		(n=52)	4	45.2	132.0
Baranauskaite *et al.,* 2012 [46]	RESPOND	PsA	IFX+MTX	5 mg/kg, wk: 0,2,6,14	(n=57)	4	40.1	33.6
			MTX		(n=58)	4	42.3	44.4
Barkham *et al.,* 2010 [49]		AS	ETA+MTX	25 mg	(n=20)	3	40.8	132.0*
			PBO+MTX		(n=12)	3	39.4	240.0*
Bejarano *et al*., 2008 [61]		RA	ADA+MTX	NR	(n=75)	56	47.0	9.5
			PBO+MTX		(n=73)	56	47.0	7.9
Brandt *et al.,* 2003 [90]		AS	ETA	25 mg/2wk	(n=16)	7.5	39.8	14.9
			PBO		(n=17)	7.5	32.0	11.4
Braun *et al.*, 2002 [93]		AS	IFX	5 mg/kg, wk: 0,2,6	(n=34)	3	40.6	16.4
			PBO		(n=35)	3	39.0	14.9
Breedveld *et al*., 2006 [75]	PREMIER	RA	ADA+MTX	40 mg/2 wks	(n=268)	24	51.9	8.4
			PBO+MTX		(n=257)	24	52.0	9.6
Chen *et al*., 2009 [54]		RA	ADA+MTX	40 mg/2 wks	(n=35)	3	53.0*	74.4*
			PBO+MTX		(n=12)	3	53.0*	99.6*
Choy *et al*., 2012 [44]		RA	CTP+MTX	400 mg/4 wks	(n=126)	6	53.0	9.4
			PBO+MTX		(n=121)	6	55.6	9.9
Combe *et al*., 2009 [62]		RA	ETA	25 mg/twice per wk	(n=103)	24	50.6	78.0
			PBO		(n=101)	24	53.3	67.2
Davis *et al.,* 2003 [89]		AS	ETA+DMARDs	25 mg/2 wks	(n=138)	6	42.1*	10.1*

			PBO+DMARDs		(n=139)	6	41.9*	10.5*
Detert *et al.,* 2013 [41]		RA	ADA+MTX	40 mg eow	(n=87)	6	47.2	1.8
			PBO+MTX		(n=85)	6	52.5	1.6
Dougados *et al.,* 2011 [50]	SPINE	AS	ETA+DMARDs	50 mg/wk	(n=39)	3	46.0	228.0
			PBO+DMARDs		(n=43)	3	48.0	276.0
Emery *et al.,* 2009 [52]	GO BEFORE	RA	GLM+MTX	100 mg/4 wks	(n=159)	6	50.2	43.2
			GLM+MTX	50 mg/4 wks	(n=159)	6	50.9	42.0
			PBO+MTX		(n=160)	6	48.6	34.8
Emery *et al.,* 2008 [63]	COMET	RA	ETA+MTX	50 mg/wk	(n=274)	24	50.5	8.8
			PBO+MTX		(n=268)	24	52.3	9.3
Fleischmann *et al.,* 2012 [47]		RA	ADA	40 mg eow	(n=53)	6	54.0	7.7*
			PBO		(n=59)	6	53.0	10.8*
Fleischmann *et al.,* 2009 [58]	FAST4WARD	RA	CTP	400 mg/4 wks	(n=111)	6	52.7	104.4
			PBO		(n=109)	6	54.9	124.8
Furst *et al.,* 2003 [87]	STAR	RA	ADA+DMARDs	40 mg eow	(n=318)	6	55.0	9.3
			PBO+DMARDs		(n=318)	6	55.8	11.5
Genovese *et al.,* 2007 [69]		PsA	ADA+DMARDs	40 mg/2 wks	(n=51)	3	50.4	90.0
			PBO+DMARDs		(n=49)	3	47.7	86.4
Gorman *et al.,* 2002 [92]		AS	ETA+DMARDs	25 mg/2 wks	(n=20)	4	38.0	180.0
			PBO+DMARDs		(n=20)	4	39.0	144.0
Huang *et al.,* 2014 [34]		AS	ADA+DMARDs	40 mg	(n=229)	3	30.1	36.0
			PBO+DMARDs		(n=115)	3	29.6	36.0
Inman *et al.,* 2008 [60]	GO RAISE	AS	GLM+DMARDs	50 mg	(n=138)	4	38.0*	61.8*
			GLM+DMARDs	100 mg	(n=140)	4	38.0*	62.4*
			PBO+DMARDs		(n=78)	4	41.0*	87.0*
Kavanaugh *et al.,* 2013 [43]	OPTIMA	RA	ADA+MTX	40 mg	(n=515)	6	50.7	4.0
			PBO+MTX		(n=517)	6	50.4	4.5
Kavanaugh *et al.,* 2009 [55]	GO REVEAL	PsA	GLM	50 mg/4 wks	(n=146)	6	45.7	86.4
			GLM	100 mg/4 wks	(n=146)	6	48.2	92.4
			PBO		(n=113)	6	47.0	91.2
Kavanaugh *et al.,* 2000 [97]		RA	IFX+MTX	5 mg/kg single injection	(n=7)	3	47.0	88.8
			IFX+MTX	10 mg/kg single injection	(n=7)	3	53.0	90.0
			IFX+MTX	20 mg/kg single injection	(n=7)	3	37.4	58.8
			PBO+MTX		(n=7)	3	44.6	58.8
Kay *et al.,* 2008 [64]		RA	GLM+MTX	50 mg/4 wks	(n=35)	5	57.0*	98.4*

			GLM+MTX	50 mg/2 wks	(n=34)	5	48.0*	98.4*
			GLM+MTX	100 mg/4 wks	(n=34)	5	57.5*	75.6*
			GLM+MTX	100 mg/2 wks	(n=34)	5	53.5*	108.0*
			PBO+MTX		(n=35)	5	52.0*	67.2*
Keystone *et al.,* 2009 [56]	GO FORWARD	RA	GLM+MTX	100 mg/4 wks	(n=89)	3.5	50.0*	80.4*
			GLM+MTX	50 mg/4 wks	(n=89)	3.5	52.0*	54.0*
			PBO+MTX		(n=133)	3.5	52.0*	78.0*
Keystone *et al.,* 2008 [59]	RAPID 1	RA	CTP+MTX	200 mg/2 wks	(n=393)	13	51.4	73.2
			CTP+MTX	400 mg/2 wks	(n=390)	13	52.4	74.4
			PBO+MTX		(n=199)	13	52.2	74.4
Keystone *et al.,* 2004 [84]		RA	ADA+MTX	40 mg eow	(n=419)	4.3	56.1	11.0
			PBO+MTX		(n=200)	4.3	56.1	10.9
Keystone *et al.,* 2004 [86]		RA	ETA+MTX	50 mg/wk	(n=214)	2	53.0*	9.0*
			ETA+MTX	25 mg/2 wks	(n=153)	2	52.0*	8.2*
			PBO+MTX		(n=53)	2	54.0*	10.8*
Kim *et al.,* 2007 [99]		RA	ADA+MTX	40 mg	(n=65)	6	48.5	6.8
			PBO+MTX		(n=63)	6	49.8	6.9
Kremer *et al.,* 2010 [51]		RA	GLM+MTX	2 mg/kg, wk: 0,12,24,36,48	(n=129)	12	49.7	97.2
			GLM+MTX	4 mg/kg, wk: 0,12,24,36,48	(n=128)	12	49.6	112.8
			PBO+MTX		(n=129)	12	50.2	88.8
Landewè *et al.,* 2014 [31]	RAPID	AS	CTP+MTX	200 mg/wk: 0,2,4	(n=111)	6	39.1	NR
			CTP+MTX	400 mg/wk: 0,2,4	(n=107)	6	39.8	NR
			PBO+MTX		(n=107)	6	39.9	NR
Leirisalo-Repo *et al*., 2013 [40]	NEO RACO	RA	IFX	3 mg/kg/wk: 4,6,10,18,26	(n=50)	24	47.0	4.0
			PBO		(n=49)	24	46.0	4.0
Lipsky *et al.,* 2000 [95]	ATTRACT	RA	IFX+MTX	3 mg/kg/4 wks	(n=86)	13.5	52.0	9.0
			IFX+MTX	10 mg/kg/8 wks	(n=87)	13.5	54.0	11.0
			IFX+MTX	10 mg/kg/4 wks	(n=81)	13.5	52.0	12.0
			IFX+MTX	3 mg/kg/8 wks	(n=86)	13.5	54.0	10.0
			PBO+MTX		(n=88)	13.5	51.0	11.0
Marzo-Ortega *et al.,* 2005 [77]		AS	IFX+MTX	5 mg/kg/wk: 0,2,6,14,22	(n=28)	7.5	41*	8*
			PBO+MTX		(n=14)	7.5	39*	10*
Mease *et al.,* 2014 [32]	RAPID PsA	PsA	CTP+MTX	200 mg/2 wks	(n=138)	6	48.2	115.2
			CTP+MTX	400 mg/4 wks	(n=135)	6	47.1	97.2
			PBO+MTX		(n=136)	6	47.3	94.8

Mease *et al.,* 2005 [75]		PsA	ADA+MTX	40 mg/2 wk	(n=151)	6	48.6	117.6
			PBO+MTX		(n=162)	6	49.2	110.4
Mease *et al.,* 2004 [82]		PsA	ETA+MTX	25 mg/twice wk	(n=87)	6	47.6	108.0
			PBO+MTX		(n=81)	6	47.3	110.4
Mease *et al.,* 2000 [96]		PsA	ETA+MTX	25 mg/twice wk	(n=30)	3	46.0*	108*
			PBO+MTX		(n=30)	3	43.5*	114*
Miyasaka *et al.,* 2008 [65]	CHANGE	RA	ADA	80 mg/2 wks	(n=87)	6	54.3	114.0
			ADA	40 mg/2 wks	(n=91)	6	56.9	118.8
			ADA	20 mg/2 wks	(n=87)	6	54.8	120.0
			PBO		(n=87)	6	53.4	100.8
Rau *et al.,* 2004 [83]		RA	ADA+MTX	1 mg/Kg (iv) 0, 29 week	(n=18)	1.5	52.3	133.2
			ADA+MTX	1 mg/Kg (sc) 0, 29 week	(n=18)	1.5	53.3	127.2
			PBO+MTX		(n=18)	1.5	54.1	138.0
Schiff *et al.,* 2008 [66]	ATTEST	RA	IFX+MTX	0-3 mg/kg/8 wks	(n=165)	6	49.1	87.6
			PBO+MTX		(n=110)	6	49.4	100.8
Sieper *et al.,* 2014 [33]	INFAST	AS	IFX	5 mg/kg, wk: 0,2,6,12,18,24	(n=106)	7	31.7	10.1
			PBO		(n=52)	7	30.7	8.3
Sieper *et al.,* 2013 [39]	ABILITY 1	AS	ADA+DMARDs	40 mg/1wk	(n=91)	3	37.6	36.0
			PBO+DMARDs		(n=94)	3	38.4	32.4
Smolen *et al.,* 2009 [57]	RAPID 2	RA	CTP+MTX	400 mg/2 wks	(n=246)	3	51.9	78.0
			CTP+MTX	200 mg/2 wks	(n=246)	3	52.2	73.2
			PBO+MTX		(n=127)	3	51.5	67.2
Smolen *et al.,* 2009 [53]	GO AFTER	RA	GLM+DMARDs	50 mg/4 wks	(n=153)	4	55.0*	115.2*
			GLM+DMARDs	100 mg/4 wks	(n=153)	4	55.0*	104.4*
			PBO+DMARDs		(n=155)	4	54.0*	117.6*
Smolen *et al.,* 2013 [30]	PRESERVE	RA	ETA+MTX	50 mg	(n=202)	12	48.1	81.6
			ETA+MTX	25 mg	(n=202)	12	46.4	76.8
			PBO+MTX		(n=200)	12	48.3	87.6
St Clair *et al.,* 2004 [81]		RA	IFX+MTX	3 mg/kg/4 wks	(n=373)	13.5	51.0	10
			IFX+MTX	6 mg/kg/4 wks	(n=376)	13.5	50.0	11
			PBO+MTX		(n=298)	13.5	50.0	11
Takeuchi *et al.,* 2014 [35]	HOPEFUL 1	RA	ADA+MTX	40 mg eow	(n=171)	6.5	54.0	3.6
			PBO+MTX		(n=163)	6.5	54.0	3.6
Takeuchi *et al.,* 2013 [36]	GO-MONO	RA	GLM	50 mg every 4 w	(n=102)	4	52.9	97.2
			GLM	100 mg every 4 w	(n=104)	4	51.6	112.8

			PBO		(n=110)	4	52.4	110.4
Tanaka *et al.,* 2012 [45]	GO-FORTH	RA	GLM+MTX	50 mg, wk: 0, 4, 8, 12, 16, 20, 24	(n=89)	6	50.4	105.6
			GLM+MTX	100 mg, wk: 0, 4, 8, 12, 16, 20, 24	(n=90)	6	50.0	97.2
			PBO+MTX		(n=90)	6	51.1	104.4
Van de Putte *et al.,* 2004 [85]		RA	ADA	20 mg eow	(n=106)	6.5	53.1	111.6
			ADA	20 mg weekly	(n=112)	6.5	54.4	135.6
			ADA	40 mg eow	(n=113)	6.5	52.7	127.2
			ADA	40 mg weekly	(n=103)	6.5	51.8	142.8
			PBO		(n=110)	6.5	53.5	139.2
Van de Putte *et al.,* 2003 [88]		RA	ADA	20 mg weekly	(n=72)	3	53.7	10.4
			ADA	40 mg weekly	(n=70)	3	52.6	10.0
			ADA	80 mg weekly	(n=72)	3	53.2	10.1
			PBO		(n=70)	3	50.2	9.4
Van den Bosch *et al.,* 2002 [94]		AS	IFX	5 mg/kg, wk: 0,2,6	(n=20)	3	46.0*	78.0*
			PBO		(n=20)	3	47.5*	96.0*
Van der Heijde *et al.,* 2007 [67]	TEMPO	RA	ETA+MTX	25 mg/2w	(n=231)	36	52.5	6.8
			MTX		(n=228)	36	53.0	6.8
Van der Heijde *et al.,* 2006 [71]		AS	ETA+DMARDs	50 mg/once weekly	(n=155)	3	41.5	108.0
			ETA+DMARDs	25 mg/twice weekly	(n=150)	3	39.8	120.0
			PBO+DMARDs		(n=51)	3	40.1	102.0
Van der Heijde *et al.,* 2006 [72]	ATLAS	AS	ADA+DMARDs	40 mg/2wk	(n=208)	6	41.7	11.3
			PBO+DMARDs		(n=107)	6	43.4	10.0
Van der Heijde *et al.,* 2005 [79]	ASSERT	AS	IFX	5 mg/kg, wk: 0,2,6,12,18	(n=201)	6	40.0*	92.4*
			PBO		(n=78)	6	41.0*	158.4*
Van Vollenhoven *et al.,* 2012 [38]	ORAL standard	RA	ADA+MTX	40 mg/2wk	(n=204)	3	52.5	97.2
			PBO+MTX		(n=108)	3	53.7	79.5
Van Vollenhoven *et al.,* 2011 [48]	AUGUST II	RA	ADA+MTX	40 mg/2wk	(n=79)	9.5	53.0	105.6
			PBO+MTX		(n=76)	9.5	54.0	100.8
Weinblatt *et al.,* 2013 [42]	GO-FURTHER	RA	GLM+MTX	2 mg/kg, wk: 0,4 and every 8 wk	(n=395)	4	51.9	82.8
			PBO+MTX		(n=197)	4	51.4	84.0
Weinblatt *et al.,* 2012 [37]	REALISTIC	RA	CTP	400 mg/wk: 0,2,4 then 200 mg/2wk	(n=851)	3	55.4	103.2
			PBO		(n=212)	3	53.9	106.8
Weinblatt *et al.,* 2003 [91]	ARMADA	RA	ADA+MTX	20 mg/2wk	(n=69)	6	53.5	157.2
			ADA+MTX	40 mg/2wk	(n=67)	6	57.2	146.4
			ADA+MTX	80 mg/2wk	(n=73)	6	55.5	153.6

		PBO+MTX		(n=62)	6	56.0	133.2
Weinblatt *et al.,* 1999 [98]	RA	ETA+MTX	25 mg/twice wk	(n=59)	6	48	156
		PBO+MTX		(n=30)	6	53	156
Weisman *et al.,* 2007 [68]	RA	ETA+DMARDs	25 mg/twice wk	(n=266)	4	60.6*	121.2*
		PBO+DMARDs		(n=269)	4	59.3*	112.8*
Westhovens *et al.,* 2006 [73]	RA	IFX+MTX	3 mg/kg, wk: 0, 2, 6, 14	(n=360)	5.5	53.0*	93.6*
		IFX+MTX	10 mg/kg, wk: 0, 2, 6, 14	(n=361)	5.5	52.0*	75.6*
		PBO+MTX		(n=363)	5.5	52.0*	100.8*
Zhang *et al.,* 2006 [100]	RA	IFX+MTX	3 mg/kg, wk: 0, 2, 6, 14	(n=87)	4.5	47.9	85.6
		PBO+MTX		(n=86)	4.5	48.9	96.0
Zhou *et al.,* 2007 [70]	RA	GLM+DMARDs	0.1 mg/kg	(n=3)	4	48.0	NR
		GLM+DMARDs	0.3 mg/kg	(n=3)	4	44.0	NR
		GLM+DMARDs	1 mg/kg	(n=5)	4	43.0	NR
		GLM+DMARDs	3 mg/kg	(n=5)	4	67.0	NR
		GLM+DMARDs	6 mg/kg	(n=5)	4	50.0	NR
		GLM+DMARDs	10 mg/kg	(n=5)	4	46.0	NR
		PBO+DMARDs		(n=10)	4	60.0	NR

Abbreviations. ADA: adalimubab; AS: ankylosing spondylitis; CTP: certolizumab pegol; DMARDs: disease-modifying anti-rheumatic drugs; eow: every other week; ETA: etanercept; GLM: golimubab; IFX: infliximab; MTX: methotrexate; NR: not reported; PsA: psoriatic arthritis; PBO: placebo; RA: rheumatoid arthritis; wk: week.

Footnote. Mean values are given for *"age of patients"* and *"disease duration",* or median values when indicated with an asterisk.

Table 2. Meta-analysis results.

		Fixed-effects model		Random-effects model		Tests of homogeneity			Tests of publication bias	
	No. of studies	OR	(95% CI)	OR	(95% CI)	Q value (d.f.)	P-value	I^2	Begg's p-value	Egger's p-value
Serious Infections										
– All RCTs	58	1.41	(1.16, 1.73)	1.25	(1.01, 1.55)	48.48 (57)	0.78	0%	0.06	0.09
– RCT high-dose arms*	58	1.46	(1.19, 1.79)	1.36	(1.09, 1.69)	45.68 (57)	0.86	0%	0.25	0.16
– OLE studies	6	1.33	(0.77, 2.29)	1.19	(0.68, 2.07)	4.39 (5)	0.49	0%	0.45	0.22
Tuberculosis										
– All RCTs	19	3.53	(1.58, 7.85)	3.29	(1.48, 7.33)	0.62 (18)	0.99	0%	0.94	0.05
– RCT high-dose arms*	19	3.32	(1.54, 7.15)	3.23	(1.50, 6.98)	0.48 (18)	0.99	0%	0.03	0.07
Opportunistic Infections										
– All RCTs	6	0.94	(0.33, 2.64)	0.81	(0.23, 2.87)	3.32 (5)	0.65	0%	0.13	0.12
– RCT high-dose arms*	6	0.98	(0.35, 2.73)	0.87	(0.25, 3.00)	3.59 (5)	0.61	0%	0.02	0.16
Any Infection										
– All RCTs	37	1.20	(1.10, 1.30)	1.20	(1.06, 1.36)	66.45 (36)	<0.01	46%	0.95	0.75
– RCT high-dose arms*	37	1.21	(1.11, 1.32)	1.22	(1.07, 1.39)	67.44 (36)	<0.01	47%	0.80	0.74
– OLE studies	6	1.69	(1.31, 2.18)	1.56	(1.05, 2.33)	9.11 (5)	0.10	45%	0.26	0.61

RCTs: randomized controlled trials; OLE: open label extension; OR: odds ratio; CI: confidence interval; d.f.: degrees of freedom.

*analysis using (from the multi-arm trials) only the data referring to the intervention arm exposed to the highest dose.

Table 3. Summary of findings.

Population: Adult patients with rheumatologic disease (rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis)
Intervention: Anti-TNF drugs (adalimumab, certolizumab, etanercept, golimumab, or infliximab)
Comparison: Placebo or no treatment
Follow-up: 1–36 months (8 months per patient, on average)

	Illustrative comparative risks (95% CI)		
	Assumed risk	Corresponding risk	
	PBO or no treatment	Anti-TNF drugs	
Serious Infections	20 per 1000	28 per 1000 (23 to 34)	*Relative effect (95% CI):* OR, 1.41 (1.16, 1.73) *No. of participants:* 20,796 *No. of RCTs:* 58 *Quality of the evidence (GRADE):* ⊕⊕⊕⊖ (Moderate)
Opportunistic Infections	3 per 1000	3 per 1000 (1 to 8)	*Relative effect (95% CI):* OR, 0.94 (0.33, 2.64) *No. of participants:* 3,886 *No. of RCTs:* 6 *Quality of the evidence (GRADE):* ⊕⊕⊖⊖ (Low)
Any Infection	285 per 1000	324 per 1000 (305 to 341)	*Relative effect (95% CI):* OR, 1.20 (1.10, 1.30) *No. of participants:* 12,796 *No. of RCTs:* 37 *Quality of the evidence (GRADE):* ⊕⊕⊕⊖ (Moderate)

Footnotes:
(i) the basis for the assumed risk is the overall event occurrence across RCT control groups,
(ii) the corresponding risk is based on the assumed risk in the comparison group and the relative effect of the intervention,
(iii) the relative effect and its 95% CI come from a fixed-effects meta-analytic model,
(iv) a corresponding risk could not be estimated for Tuberculosis, because no event was reported in the control groups,
(v) the overall quality of the synthesized evidence is "moderate" for the following reasons: Data was derived from RCTs (randomized study design is considered the gold standard for assessing drugs); the meta-analytic effect estimates are precise (except for opportunistic infections); the results are consistent (heterogeneity was low or moderate across studies); and all the RCTs included in meta-analysis are characterized by high or unclear RoB in several important quality domains, such as allocation concealment and incomplete outcome data (a fact that downgrades the quality of evidence). A moderate quality of evidence means that *"we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different"*.
(vi) explanations for *Summary of findings Tables* can be found at: www.thecochranelibrary.com/view/0/SummaryFindings.html

Abbreviations. CI: confidence interval; OR: odds ratio; PBO: placebo; RoB: risk of bias.