The Risk of Adverse Effects of TNF-α Inhibitors in Patients With Rheumatoid Arthritis: A Network Meta-Analysis

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Objectives: To evaluate the safety of each anti-TNF therapy for patients with rheumatoid arthritis (RA) and then make the best choice in clinical practice.

Methods: We searched PUBMED, EMBASE, and the Cochrane Library. The deadline for retrieval is August 2021. The ORs, Confidence Intervals (CIs), and p values were calculated by STATA.16.0 software for assessment.

Result: 72 RCTs involving 28332 subjects were included. AEs were more common with adalimumab combined disease-modifying anti-rheumatic drugs (DMARDs) compared with placebo (OR = 1.60, 95% CI: 1.06, 2.42), DMARDs (1.28, 95% CI: 1.08, 1.52), etanercept combined DMARDs (1.32, 95% CI: 1.03, 1.67); certolizumab combined DMARDs compared with placebo (1.63, 95% CI: 1.07, 2.46), DMARDs (1.30, 95% CI: 1.10, 1.54), etanercept combined DMARDs (1.34, 95% CI: 1.05, 1.70). In SAEs, comparisons between treatments showed adalimumab (0.20, 95% CI: 0.07, 0.59), etanercept combined DMARDs (0.39, 95% CI: 0.15, 0.96), golimumab (0.19, 95% CI: 0.05, 0.77), infliximab (0.15, 95% CI: 0.03,0.71) decreased the risk of SAEs compared with golimumab combined DMARDs. In infections, comparisons between treatments showed adalimumab combined DMARDs (0.59, 95% CI: 0.37, 0.95), etanercept (0.49, 95% CI: 0.28, 0.88), etanercept combined DMARDs (0.56, 95% CI: 0.35, 0.91), golimumab combined DMARDs (0.51, 95% CI: 0.31, 0.83) decreased the risk of infections compared with infliximab combined DMARDs. No evidence indicated that the use of TNF-α inhibitors influenced the risk of serious infections, malignant tumors.

Conclusion: In conclusion, we regard etanercept monotherapy as the optimal choice for RA patients in clinical practice when the efficacy is similar. Conversely, certolizumab + DMARDs therapy is not recommended.

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Keywords: adverse effects, TNF-α inhibitors, rheumatoid arthritis, network meta-analysis, serious adverse events
INTRODUCTION

Rheumatoid arthritis (RA) is one of the most prevalent chronic inflammatory diseases, which can cause cartilage and bone damage as well as a disability that carries a substantial burden for both the individual and society (1). Currently, antitumors necrosis factor (anti-TNF) therapy has been established as an efficacious therapeutic strategy in RA (2). TNF-α is a pro-inflammatory cytokine known to have a key role in the pathogenesis of chronic immune-mediated diseases (3). Five TNF-α inhibitors have received regulatory approval for clinical use in rheumatology: adalimumab, golimumab, infliximab, certolizumab, and etanercept (4). They are commonly used in the treatment of rheumatoid arthritis.

Besides therapeutic effects, some studies reported that TNF-α inhibitors may also cause some adverse effects in patients with RA (5–8). Although there have been some pair-wise meta-analyses and network meta-analyses that evaluate the safety of different TNF-α inhibitors therapies for patients with RA. Nevertheless, most of the trials only focused on total AEs and SAEs or just one kind of detailed AEs, and some of the initial meta-analyses were contradicted by subsequent studies. For instance, Bongartz et al. reported that RA patients who were treated by anti-TNF therapies had an increased risk of serious infections and malignancies (9), while another trial evaluating malignancy risk in RA patients concluded that there was no significant evidence of an increased risk of malignancy using TNF-α inhibitors (10).

To evaluate the safety of TNF-α inhibitors in patients with RA, we choose six safety outcomes to systematically assess 10 anti-TNF therapies from 72 RCTs with a sample size of 28332 patients. Our network meta-analysis seeks to infer the risk of adverse effects of two therapies in patients with rheumatoid arthritis by direct and indirect comparisons. Simultaneously, it extracts and analyzes data from all randomized control trials (RCTs) to select the best therapy. The objective of the current study is to better characterize the safety of each anti-TNF therapy for patients with RA and then make the best choice in clinical practice.

METHOD

Study Selection
We searched PUBMED, EMBASE, and the Cochrane Library with the terms of drugs (adalimumab, certolizumab, etanercept, infliximab, and golimumab) and diseases (rheumatoid arthritis). After matching each “drug” and “disease”, restricting search results with the condition “randomized controlled trial”, we finally form the retrieval expressions that adapt to different databases. The deadline for retrieval is August 2021. Two investigators performed the literature screening according to the inclusion and exclusion criteria independently. The repeated studies were excluded firstly. Afterward, excluded unrelated studies by reading the titles and abstracts. The literature that met the inclusion and exclusion criteria was further screened by reading the full text. Disagreements were resolved by consensus Equations.

Inclusive Criteria
RCTs associated with adalimumab, certolizumab, etanercept, infliximab, and golimumab in the treatment of rheumatic diseases are included. Subjects should be greater than or equal to 18 years old and should be diagnosed with rheumatoid arthritis according to American College of Rheumatology criteria or other authoritative criteria. Disease progression, race, nationality, and complications are not limited. For the types of interventions, the experimental groups use TNF-α inhibitors, with or without disease-modifying antirheumatic drugs (DMARDs). The control groups use placebo (with or without DMARDS) or DMARDs alone.

Exclusive Criteria
RCTs that accord with any of the following criteria will be excluded: (1) studies with no accessible records of AE, SAE, malignant tumors, infections, severe infections, or malignant tumors (requiring intravenous antibiotic treatment or hospitalization or threatening patient's life); (2) repetitive studies with shorter follow-up time; (3) studies with improper control (other therapy in experimental group or control group); (4) studies with Jadad score lower than or equal to 3 points; (5) studies with full texts not available.

Data Extraction
Data extraction was performed independently by He Bei and Li Yun, and the EndNote software was used to filter duplications and irrelevant literature by reading titles and abstracts. The remaining articles were then browsed in full text to determine whether they met the inclusion criteria. After removing ineligible publications, the two reviewers independently extracted data from each study, and disagreements were resolved by reaching a consensus. From each eligible study, we extracted and summarized the following details: the first author, year of publication, country, the total number of participants, type of TNF-α inhibitors, age range, follow-up time, duration of trials.

Assessment of Risk of Bias
Two investigators independently assessed each study’s risk of bias as low, unclear, and high. Disagreements were resolved by consensus. The items included: Random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; other bias.

Quality Assessment
Two reviewers independently used the modified Jadad scale to assess the quality of RCTs (randomized control trials). NOS includes three aspects (selection, comparability, and exposure for case-control studies or outcomes for cohort studies), as well as scores of 4, 2, and 3, respectively. The modified Jadad scale comprises four parts: generation of the allocation sequence, concealment of allocation, blinding, and incomplete outcome data, and scores of 2, 2, 2, and 1 for four parts, respectively. Studies with scores of 1-3 were considered to be of low quality; 4-7 high quality.
Data Synthesis and Analysis
Network meta-analysis was performed to compare each of the 10 anti-TNF therapies. Based on the multivariate framework, the network meta-analysis was conducted using frequency theory, and two program packages, network, and mvmeta, developed by STATA 16 software based on multiple regression theory, were used for statistical analysis. Firstly, an evidence network diagram was drawn to show the comparison between interventions, and the consistency test was conducted according to the existence of closed rings. Second, for counting data, OR was used for calculation, the network meta of adverse drug reactions was analyzed, 95% confidence interval was used for all effect sizes, and 95%CI of OR did not cross effect line 1, indicating that P<0.05 was statistically significant. SUCRA analysis was used to seek therapies that had the highest probability of adverse events, with the higher the SUCRA value, the higher the risk. Stata 16.0 draws a comparative-correction funnel plot to determine whether there is a small sample effect in the analysis and recognition network, to evaluate the publication bias of the final screening. All tests were two-sided with a significance level of 0.05.

RESULT
By searching databases, we retrieved 3200 original records. After excluding duplicates and irrelevant articles, 211 full-text articles were assessed for eligibility. By reading full-text, 72 articles met the inclusive criteria and exclusive criteria (11–82). The following diagram of the study selection process for this meta-analysis is shown in Figure 1. The 72 articles included 28332 patients, followed up for about 16-104 weeks. 72 articles involved RCT experiments, including 21 adalimumab trials, 13 certolizumab trials, 21 etanercept trials, 9 golimumab
trials, and 8 infliximab trials. Table 1 summarizes the relevant characteristics.

**Adverse Events**

58 articles (12, 15, 16, 19, 21–26, 28–38, 40–42, 44–47, 49–56, 58–69, 71–75, 77, 79–82) reported the occurrence of AEs and 23778 RA patients was included. The network of eligible comparisons is shown in Figure 2. Network meta-analysis showed that adalimumab combined DMARDs compared with placebo therapy statistically significantly increased the risk of AEs by 60% (1.60, 95% CI: 1.06, 2.42); compared with DMARDs, the risk of AEs increased by 28% (1.28, 95% CI: 1.08, 1.52) (Table 2 and Figure 3). Certolizumab also found that compared with placebo therapy, the risk of AE increased by 127% (2.27, 95% CI: 1.22, 4.24). In addition, certolizumab combined DMARDs compared with placebo therapy statistically significantly increased the risk of AEs by 63% (1.63, 95% CI: 1.07, 2.46); compared with DMARDs, the risk of AEs increased by 30% (1.30, 95% CI: 1.10, 1.54). Comparisons between treatments showed certolizumab combined DMARDs increased the risk of AEs compared with etanercept combined DMARDs (1.34, 95% CI: 1.05, 1.70); adalimumab combined DMARDs increased the risk of AEs compared with etanercept combined DMARDs (1.32, 95% CI: 1.03, 1.67) (Table 2). There was no statistically significant difference between other comparisons.

We have made global consistency. The test result p-value was 0.9095, so the consistency model could be used. We also established local consistency and the p-value of the test result exceeded 0.05, which was considered local. We analyzed SUCRA to research the probability of adverse events for each therapy. The results indicated that certolizumab had the highest probability to cause AEs (SUCRA = 0.906), while PBO had the lowest probability to cause AEs (SUCRA = 0.066) compared with the other therapies (Figure 3). There was a funnel plot with no obvious asymmetry, indicating no publication bias (Figure 4).

**Serious Adverse Events**

58 articles (12, 13, 15, 17–19, 22, 24–27, 29–32, 34–36, 38, 40–52, 54, 56–60, 62–70, 72–82) reported the occurrence of SAEs and 23805 RA patients was included. The network of eligible comparisons was shown in Figure 5. Network meta-analysis showed that golimumab combined DMARDs compared with placebo therapy statistically significantly increased the risk of SAEs by 227% (3.27, 95% CI: 1.08, 9.92); Compared with DMARDs, the risk of SAEs increased by 170% (2.70, 95% CI: 1.15, 6.32). Comparisons between treatments showed adalimumab (0.20, 95% CI: 0.07, 0.59), etanercept (0.35, 95% CI: 0.12, 1.00), etanercept combined DMARDs (0.39, 95% CI: 0.15, 0.96), golimumab (0.19, 95% CI: 0.05, 0.77) decreased the risk of SAEs compared with golimumab combined DMARDs; adalimumab (0.39, 95% CI: 0.18, 0.84) decreased the risk of SAEs compared with certolizumab combined DMARDs; golimumab combined DMARDs increased the risk of SAEs compared with infliximab (6.50, 95% CI: 1.41, 29.90) (Table 3). There was no statistically significant difference between other comparisons.

We did the global consistency test. The test result p-value was 0.8840. We also made local consistency and the test result p-value was greater than 0.05, which was considered to be locally consistent. According to the SUCRA analysis, golimumab combined DMARDs had the highest risk to cause SAEs (SUCRA = 0.940), while adalimumab had the lowest risk to cause SAEs (SUCRA = 0.0130) compared with the other 11 therapies (Figure 6). There was a funnel plot asymmetry, with the right corner of the pyramidal part of the funnel missing, which suggested a possible bias (Figure 7).

**Infections**

40 articles (12, 15, 17, 22, 25–28, 30, 31, 33, 34, 36, 38, 40–42, 45, 49, 54–56, 58–60, 62–66, 72–77, 79–82) reported the occurrence of AEs and 15285 RA patients was included. The network of eligible comparisons was shown in the Supplementary Figure 1. Network meta-analysis showed that golimumab combined DMARDs compared with DMARDs increased the risk of infections by 35% (1.35, 95% CI: 1.10, 1.66); infliximab combined DMARDs compared with DMARDs increased the risk of infections by 102% (2.02, 95% CI: 1.31, 3.11). Comparisons between treatments showed adalimumab combined DMARDs (0.59, 95% CI: 0.37, 0.95), etanercept (0.49, 95% CI: 0.28, 0.88), etanercept combined DMARDs (0.56, 95% CI: 0.35, 0.91), golimumab combined DMARDs (0.51, 95% CI: 0.31, 0.83) decreased the risk of infections compared with infliximab combined DMARDs (supplementary Table 1). There was no statistically significant difference between other comparisons.

We did the global consistency test. The test result p-value was 0.6713. We also established local consistency and the p-value of the test result exceeded 0.05, which was considered local. According to the SUCRA analysis, infliximab combined DMARDs had the highest risk to cause infections (SUCRA = 0.910), while DMARDs had the lowest risk to cause infections SUCRA = 0.210) compared with the other 11 therapies (Supplementary Figure 2). There was a funnel plot (Supplementary Figure 3) with no obvious asymmetry, indicating no publication bias.

**Serious Infections**

55 articles (11–20, 22, 23, 26–38, 40, 42, 45, 47–49, 51, 52, 54, 56–60, 62–66, 68, 69, 72–77, 80–82) reported the occurrence of serious infections, involving a total of 24740 RA patients. The network of eligible comparisons was shown in the Supplementary Figure 4. Network meta-analysis showed that there was no statistically significant difference between 12 therapies (Supplementary Table 2).

We did the global consistency test. The resulting p-value was 0.4900. We also made local consistency and the test result p-value was greater than 0.05, which was considered to be locally consistent. According to the SUCRA analysis, certolizumab had the highest risk to cause serious infections (SUCRA = 0.817), while etanercept combined DMARDs had the lowest risk to cause serious infections (SUCRA = 0.285) compared with the other therapies (Supplementary Figure 5). There was a funnel plot asymmetry, with the right corner of the pyramidal part of the funnel missing, which suggested a possible bias (Supplementary Figure 6).
| Author, Year | Duration of trials (years) | Quality score | Follow-up time (Week) | Average age (years old) | Duration of rheumatoid arthritis (years) | Number of women (n) | Number of patients (n) | Total number of cases (n) | Intervention measures |
|--------------|---------------------------|---------------|-----------------------|-------------------------|-----------------------------------------|---------------------|------------------------|------------------------|---------------------|
| Den et al. (11) | NA | 4 | 4 | 55 | 11.9 | 22 | 31 | 120 | Placebo  
adalimumab 0.5mg/Kg  
adalimumab 1mg/Kg  
adalimumab 3mg/Kg  
adalimumab 5mg/Kg  
adalimumab 10mg/Kg  
adalimumab 40mg eow+DMARD  
adalimumab 20mg qw  
adalimumab 40mg qw  
adalimumab 80mg qw  
placebo  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo+MTX  |
| Frust et al. (15) | NA | 4 | 24 | 55.8 | 11.5 | 252 | 318 | 636 | Placebo  
adalimumab 40mg eow+DMARD  
adalimumab 20mg qw  
adalimumab 40mg qw  
adalimumab 80mg qw  
placebo  
adalimumab 20mg eow+MTX  |
| Van der Putte et al. (13) | NA | 4 | 12 | 53.7 | 10.4 | 61 | 72 | 284 | Placebo  
adalimumab 20mg eow+DMARD  
adalimumab 40mg eow+DMARD  
adalimumab 80mg eow+DMARD  
adalimumab 10mg/Kg  
adalimumab 10mg/Kg  |
| Weinblatt et al. (14) | NA | 5 | 24 | 53.5 | 13.1 | 52 | 69 | 271 | Placebo  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo+MTX  |
| Keystone et al. (16) | NA | 5 | 52 | 56.1 | 11 | 158 | 207 | 619 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo+MTX  |
| van der Putte et al. (19) | 2000.1-2001.6 | 7 | 26 | 53.1 | 9.3 | 84 | 106 | 544 | Placebo  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Kim et al. (25) | NA | 5 | 18 | 48.5 | 6.8 | 62 | 65 | 128 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Miyasaka et al. (31) | CHANGE | 2004.2-2005.6 | 5 | 24 | 54.8 | 9.3 | 84 | 106 | 544 | Placebo  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Bejarano et al. (28) | 2003.3.5-2004.12.2 | 7 | 56 | 47 | 9.5 | 44 | 75 | 148 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Chen et al. (33) | NA | 5 | 12 | 53 | 6.2 | 26 | 35 | 47 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| van Volkenhoven et al. (46) | PREMIER (NCT00195663) | 6 | 104 | 51.9 | 0.7 | 193 | 268 | 799 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Detert et al. (48) | HIT HARD | 2007.6-2010.9 | 5 | 24 | 47.2 | 0.15 | 61 | 87 | 172 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Kavanaugh et al. (49) | OPTIMA (NCT00420927) | 2006.12-2010.7 | 5 | 26 | 50.7 | 0.33 | 380 | 515 | 1032 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Horslev-Petersen et al. (57) | OPERA | 2007.8-2009.12 | 5 | 104 | 56.2 | 0.24 | 56 | 89 | 180 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Kennedy et al. (58) | ALTARA | 2010.11-2012.7 | 5 | 12 | 50.2 | 0.15 | 61 | 87 | 172 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Takeuchi et al. (62) | HOPEFUL 1 | 2009.3-2010.11 | 5 | 26 | 54 | 0.3 | 144 | 171 | 334 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Taylor et al. (74) | RA-BEAM | 2012.11-2015.9 | 5 | 24 | 53 | 0.3 | 144 | 171 | 334 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Fleischmann et al. (77) | SELECT - COMPARE (NCT01895764) | 2013.3-2014.10 | 4 | 26 | 53 | 0.3 | 144 | 171 | 334 | Placebo  
adalimumab 40mg eow+MTX  
adalimumab 20mg eow+MTX  
adalimumab 40mg eow+MTX  
adalimumab 80mg eow+MTX  
placebo  |
| Ducourau et al. (81) | NCT02889796 | 2016.8.30-2019.6.20 | 7 | 24 | 53 | 7.3 | 391 | 475 | 800 | Placebo  
adalimumab 40 mg bw+MTX  
adalimumab 20 mg bw+MTX  
adalimumab 40 mg bw+MTX  
adalimumab 80 mg bw+MTX  
placebo  |

(Continued)
### TABLE 1 | Continued

| Author, Year | Duration of trials (years) | Quality score | Follow-up time (Week) | Average age (years old) | Duration of rheumatoid arthritis (years) | Number of women (n) | Number of patients (n) | Total number of cases (n) | Intervention measures |
|--------------|-----------------------------|---------------|-----------------------|------------------------|------------------------------------------|---------------------|-----------------------|------------------------|----------------------|
| Fleischman et al. (77) | FAST4WARD 2003.6-2004.7 | 6 | 24 | 52.7 | 8.7 | 87 | 111 | 220 | certolizumab 400mg placebo |
| Smolen et al., 2009 | RAPID 2 2005.6-2006.9 | 4 | 24 | 51.9 | 6.5 | 192 | 246 | 619 | certolizumab 400mg + MTX placebo + MTX |
| Choy et al. (42) | NCT00544154 | 7 | 24 | 53 | 9.4 | 91 | 126 | 247 | certolizumab 400mg + MTX placebo |
| Weinblatt et al. (47) | REALISTIC (NCT00717236) | 7 | 12 | 55.4 | 8.6 | 660 | q | 1063 | certolizumab (certolizumab 400mg qw 0, 2 and 4, followed by certolizumab 200 mg eow) +DMARDs placebo + DMARDs |
| Schiff et al. | NCT01147341 | 4 | 52 | 56.1 | 12 | NR | 27 | 37 | certolizumab 400mg qw 0, 2 and 4, followed by 200mg eow) +DMARDs placebo |
| Yamamoto et al. (63) | J-RAPID 2008.11.19-2010.8.18 | 7 | 24 | 54.3 | 6.0 | 58 | 72 | 316 | certolizumab 100mg eow + MTX placebo + MTX |
| Furst et al. | DOSEFLEX 2011.10-2013.8 | 7 | 52 | 49.4 | 4.0 | 129 | 159 | 316 | certolizumab 400mg/200mg eow +MTX placebo + MTX |
| Smolen et al. | CERTAIN | 5 | 24 | 53.6 | 4.5 | 81 | 96 | 194 | certolizumab 200mg eow +MTX placebo + MTX |
| Atsumi et al. | C-OPERA (NCT01451203) | 2011.10-2013.8 | 7 | 52 | 49.1 | 4.7 | 75 | 98 | certolizumab 400mg/200mg eow +MTX placebo + MTX |
| Emery et al. (72) | C-EARLY (NCT01519791) | 2012.1-2015.9 | 6 | 52 | 50.4 | 0.24 | 497 | 660 | 879 | certolizumab 400mg/200mg eow +MTX placebo + MTX |
| Kang et al. (75) | NCT00999317 | 2009.12-2011.8 | 4 | 24 | 51.6 | 6.5 | 72 | 85 | 127 | certolizumab 400mg/200mg eow +MTX placebo + MTX |
| Bi et al. (76) | RAPID-C (NCT02151851) | 2014.7.23-2016.6.17 | 6 | 24 | 48.2 | 7.0 | 268 | 316 | 429 | certolizumab 200 mg eow (loading dose: 400 mg certolizumab qw 0, 2 and 4, followed by 200 mg certolizumab eow) +DMARDs placebo + DMARDs |
| Hetland et al. (79) | NCT01491815 | 2012.12.3-2018.12.11 | 6 | 24 | 47.1 | 6.6 | 95 | 113 | 399 | active conventional treatment certolizumab 200 mg qw (400 mg qw 0, 2, and 4) + MTX placebo + MTX |
| Genovese et al. (59) | 1997.5-1999.3 | 5 | 104 | 49 | 1 | 75 | 217 | 632 | three 2.5-mg MTX qw and placebo biw 10 mg of etanercept biw and three placebo tablets qw, 25 mg of etanercept biw and three placebo tablets qw certolizumab pegol (400 mg weeks 0, 2, 4, adalimumab (40 mg once qw) plus placebo 50 mg etanercept qw 25 mg etanercept biw |
| Smolen et al. (1) | 2011.12.14-2013.11.11 | 4 | 12 | 53 | 5.9 | 96 | 457 | 914 | certolizumab pegol (400 mg weeks 0, 2, 4, adalimumab (40 mg once qw) plus placebo |
| Keystone et al. (16) | N/A | 5 | 8 | 54 | 10.8 | 36 | 457 | 914 | certolizumab pegol (400 mg weeks 0, 2, 4, adalimumab (40 mg once qw) plus placebo |

(Continued)
| Author, Year | Duration of trials (years) | Quality score | Follow-up time (Week) | Average age (years old) | Duration of rheumatoid arthritis (years) | Number of women (n) | Number of patients (n) | Total number of cases (n) | Intervention measures |
|-------------|---------------------------|---------------|-----------------------|-------------------------|------------------------------------------|---------------------|------------------------|-------------------------|------------------------|
| van der Heijde et al. (26) | TEMP0 2000.10-2001.7 | 6 | 104 | 52.5 | 6-8 | 171 | 231 | 682 | etanercept 25mg biw + MTX |
| Lan et al. (21) | | | | | | | | | etanercept 25mg biw + placebo |
| van Riel et al. (22) | ADORE 2003.3-2004.5 | 4 | 16 | 53 | 10 | 126 | 159 | 314 | etanercept 25 mg biw |
| Weissman et al. (27) | RA | 6 | 16 | 60.6 | 10.1 | 192 | 266 | 535 | etanercept 25mg biw |
| Emery et al. (28) | COMET | 2004.10-2006.2 | 7 | 52 | 50.5 | 8-8 | 196 | 274 | 542 | etanercept 50mg qw + MTX |
| Lan et al. (21) | | | | | | | | | placebo + MTX |
| van Riel et al. (22) | | | | | | | | | placebo + MTX |
| Kim et al. (44) | APPEAL | 2007.6-2009.3 | 6 | 16 | 48.4 | 6.5 | 17 | 197 | 300 | etanercept 25 mg biw+MTX |
| Takeuchi et al. (83) | NCT00445770 | NA | 6 | 52 | 51.8 | 3.0 | 145 | 182 | 550 | etanercept 25 mg biw |
| Emery et al. (56) | NCT00913458 | 2009.10-2012.12.17 | 5 | 39 | 49.6 | 0.54 | 47 | 63 | 193 | etanercept (25 mg)+MTX |
| Machado et al. (59) | NCT00848354 | 2009.6-2011.3 | 5 | 24 | 48.4 | 7.9 | 248 | 281 | 423 | etanercept(50 mg)+MTX |
| Nam et al. (60) | EMPIRE | 2006.10-2009.5 | 7 | 78 | 47.9 | 0.5 | 44 | 55 | 110 | etanercept(50 mg)+MTX |
| Smolens et al. (62) | PRESERVE (NCT00565409) | 3 | 52 | 46.4 | 6-4 | 157 | 202 | 34 | etanercept 25mg qw+MTX |
| Keystone et al. (67) | CAMEO (NCT00854368) | 2012.12 | 6 | 104 | 54.3 | 9.0 | 72 | 98 | 205 | etanercept 50 mg qw |
| van Vollenhovn et al. (70) | NR | 4 | 20 | 59.6 | 16.6 | 18 | 27 | 191 | etanercept 50 mg qw+MTX |
| Yamanaka et al. (71) | ENCOUREAGE (UMIN000002687) | 2009.8-2014.4 | 5 | 52 | 52.8 | 2.0 | 138 | 161 | 191 | toch 25 mg biw + MTX |
| Pavelka et al. (73) | NCT01578850 | 2012.7-2015.3 | 6 | 28 | 46.1 | 8.0 | 136 | 167 | 343 | etanercept 50mg qw +DMARDs |
| Curtis et al. (82) | SEAM-RA | 2015.2.20-2018.6.26 | 6 | 48 | 56.2 | 9.7 | 76 | 101 | 153 | placebo+MTX |
| Kay et al. (30) | | | | | | | | | etanercept |
| Emery et al. (34) | GO-BEFORE | 2005.12.12-2007.10.1 | 6 | 24 | 50.9 | 3.5 | 135 | 159 | 634 | etanercept 50mg qw +DMARDs |
| Keystone et al. (36) | GO-FORWARD | 20005.12.19-2007.9.17 | 5 | 16 | 52 | 4.5 | 72 | 89 | 444 | etanercept 50mg qw + Placebo |
| | | | | | | | | | Placebo+MTX |

(Continued)
Malignant Tumors

32 articles (14–20, 23, 26, 27, 29–32, 34–39, 43, 47–49, 52, 57, 60, 65, 74, 75, 77, 79) reported the occurrence of malignant tumors, involving 16947 RA patients. The network of eligible comparisons was shown in the Supplementary Figure 7. Mesh meta-analysis showed that there was no statistically significant difference between 12 therapies (Supplementary Table 3).

We did the global consistency test. The test result p-value was 0.6219. We also made local consistency and the test result p-value was greater than 0.05, which was considered to be locally consistent. According to the SUCRA analysis (Supplementary Figure 8), golimumab had the highest risk to cause malignant tumors (SUCRA =0.778), while golimumab combined DMARDs had the lowest risk to cause malignant tumors (SUCRA = 0.285) compared with the other 11 therapies.

DISCUSSION

Based on the data and information of included RCTs, our study aims to evaluate the risk of adverse effects of 10 anti-TNF therapies in patients with rheumatoid arthritis. All available direct and indirect evidence of various treatment options was analyzed and compared simultaneously by network meta-

### TABLE 1 | Continued

| Author, Year | Duration of trials (years) | Quality score | Follow-up time (Week) | Average age (years old) | Duration of rheumatoid arthritis (years) | Number of women (n) | Number of patients (n) | Total number of cases (n) | Intervention measures |
|--------------|-----------------------------|---------------|-----------------------|-------------------------|------------------------------------------|---------------------|------------------------|------------------------|----------------------|
| Smolen et al. (38) GO-AFTER (NCT00299546) | 2006.2.21-2007.9.26 | 7 | 16 | 55 | 9.6 | 113 | 153 | 461 | Golimumab 50 mg q4w |
|               | 2006.2.21-2007.9.26 | 55 | 8.7 | 122 | 153 | Placebo |
| Kremer et al. (40) NCT00361335 | 2006.8.24-2008.8.25 | 6 | 16 | 49.9 | 7.4 | 21 | 128 | 643 | Golimumab 2mg/kg q12w |
|               | 2006.8.24-2008.8.25 | 48.4 | 8.4 | 10 | 129 | Placebo |
| Tanaka et al. (45) GO-FORTH | 2008.5-2009.11 | 5 | 16 | 50.4 | 8.8 | 15 | 86 | 261 | Golimumab 50 mg q4w+MTX |
|               | 2008.5-2009.11 | 50 | 8.1 | 78 | 87 | Placebo+MTX |
| Takeuchi et al. (53) GO-MONO NA | 2010.8-2011.10 | 4 | 16 | 52.9 | 8.1 | 81 | 101 | 308 | Golimumab 50 mg q4w |
| Li et al. (68) NCT01248780 | 2010.8-2011.10 | 51.1 | 8.7 | 73 | 88 | Placebo+MTX |
| Maini et al. (17) | 2008.5-2009.11 | 51.6 | 9.4 | 85 | 102 | Placebo+MTX |
| St. Clair et al. (18) START | 2009.7-2010.1 | 7 | 54 | 51 | 0.9 | 255 | 359 | 1004 | Placebo+MTX |
| Aire et al. (12) | 2010.8-2011.10 | 50 | 0.9 | 247 | 363 | Placebo+MTX |
| Westhoven et al. (23) | 2010.8-2011.10 | 50 | 0.9 | 212 | 282 | Placebo+MTX |
| Zhang et al. (24) | 2010.8-2011.10 | 50 | 0.9 | 40 | 49 | Placebo+MTX |
| Schiff et al. (32) ATTEST | 2006.2-2007.2 | 6 | 28 | 48.9 | 7.3 | 13 | 86 | 275 | Placebo+MTX |
| Kim et al. (50) NCT00020852 | 2006.6-2007.2 | 6 | 28 | 49.1 | 7.3 | 136 | 165 | 275 | Placebo+MTX |
| Lannirai (51) NCT00020852 | 2006.6-2007.2 | 6 | 28 | 49.4 | 8.4 | 96 | 110 | 138 | Placebo+MTX |
| Repo et al. (51) NCT00020852 | 2006.6-2007.2 | 6 | 28 | 49.3 | 7.4 | 64 | 89 | 138 | Placebo+MTX |

biw, twice a week; qw, weekly; eow, every two weeks; q4w, every four weeks; q8w, every 8 weeks; q12w, every 12 weeks; MTX, methotrexate; DMARD, disease-modifying anti-rheumatic drugs; NA, not re.
analysis, which has a great advantage over traditional meta-analysis and makes up for the lack of head-to-head comparisons (83). To comprehensively assess the safety of anti-TNF therapies in RA patients, we also pay attention to detailed AEs like infections, serious infections, malignant tumors. What’s more, our meta-analysis included all RCTs with medium or high quality more recent studies to August 2021, which avoided the deficiency of observational studies and low-quality studies.

![Figure 2](image-url)  
**FIGURE 2** | Network of treatment comparisons for adverse events. The size of the circles corresponds to the total number of people. Direct comparable treatments are connected with a line. ADA, adalimumab; + D, plus DMARD; CZP, certolizumab; ETA, etanercept; GOL, golimumab; INF, infliximab; PBO, placebo; DMARD, disease-modifying anti-rheumatic drugs.

![Figure 3](image-url)  
**FIGURE 3** | The analysis SUCRA of adverse events for 12 therapies. ADA, adalimumab; + D, plus DMARD; CZP, certolizumab; ETA, etanercept; GOL, golimumab; INF, infliximab; PBO, placebo; DMARD, disease-modifying anti-rheumatic drugs.

### Table 2 OR of adverse events for 12 therapies.

| Treatmen-t | SUCRA | PrBest | MeanRank |
|------------|-------|--------|----------|
| ADA        | 33.5  | 0.2    | 8.3      |
| ADA+D      | 74.0  | 5.5    | 3.0      |
| CZP        | 90.6  | 70.7   | 2.0      |
| CZP+D      | 76.1  | 3.6    | 7.9      |
| ETA        | 37.1  | 0.2    | 7.9      |
| ETA+D      | 27.2  | 0.0    | 3.0      |
| GOL        | 53.5  | 4.5    | 6.1      |
| GOL+D      | 59.1  | 1.7    | 5.5      |
| INF        | 51.8  | 1.8    | 6.4      |
| INF+D      | 59.9  | 4.2    | 6.3      |
| PBO        | 6.6   | 11.3   | 11.3     |
| DMARD      | 38.7  | 2.6    | 8.6      |

Results below the diagonal are the rate ratios with 95% confidence intervals from the network meta-analysis of direct and indirect comparisons between the row-defining treatment and the column-defining treatment. Numbers in red highlight statistically significant results. ADA, adalimumab; + D, plus DMARD; CZP, certolizumab; ETA, etanercept; GOL, golimumab; INF, infliximab; PBO, placebo; DMARD, disease-modifying anti-rheumatic drugs.
Therefore, our studies are much more reliable than the other meta-analyses or network meta-analyses.

After analysis of 10 therapies for patients with RA from 72 RCTs, we found golimumab monotherapy, in
tifl iximab monotherapy, etanercept monotherapy, adalimumab monotherapy, and etanercept+DMARDs therapy are the safer treatments when the
efficacies are similar, they did not increase the risk of all analyzed safety indexes. A comprehensive analysis of the results of network meta-analysis and SUCRA sequencing diagram of adverse reactions showed that etanercept monotherapy is the safest therapy of the 10 therapies was etanercept monotherapy. Etanercept monotherapy was recommended as an alternative treatment due to its good safety outcomes. Certolizumab+DMARDs was considered the worst therapy, so it was necessary to avoid using this therapy. Besides, etanercept may be able to reduce the expression and production of vascular endothelial growth factor, NO, and inducible NO synthase and contribute to having a beneficial effect upon the progression of atherosclerosis, reducing the risk of acute cardiovascular and/or cerebrovascular events (84). This is further demonstrated that etanercept therapy is safer. In 2014, Murdaca et al. investigated the role of single-nucleotide polymorphisms (SNPs) at positions -238, -308, and +489 of the TNF-α gene in the response to TNF-α inhibitors (adalimumab, etanercept, or in
tifl iximab) and found that the SNP +489 G allele may promote the response to etanercept. Thus, genetic polymorphisms could be performed before treatment to determine suitability for the etanercept monotherapy (85).

After head-to-head comparisons for the effects of these 10 anti-TNF therapies on the risk of serious infections, malignant tumors, we found no difference of 10 therapies. And compared with PBO therapy or DMARDS therapy, these 10 anti-TNF therapies did not affect the risk of serious infections, malignant tumors, and tuberculosis infection. This may be indicated that these 10 anti-TNF therapies are safe for serious infections, malignant tumors, and tuberculosis infection.

Interestingly, among these 10 anti-TNF therapies, five are TNF-α inhibitor monotherapies and another five are TNF-α inhibitors combinations of DMARDs. It was easy to find that in most cases the safety of TNF-α inhibitor monotherapy was superior to the corresponding TNF-α inhibitors combinations.
### TABLE 3 | OR of serious adverse events of 12 therapies.

|  | ADA | 2.05 | (0.94, 4.49) | 4.27 | (0.94, 19.46) | 2.57 | (1.95, 5.66) | 1.80 | (0.97, 3.42) | 1.96 | (0.97, 3.97) | 0.96 | (0.36, 2.60) | 5.08 | (1.68, 15.30) | 0.78 | (0.24, 2.49) | 2.20 | (1.00, 4.81) | 1.55 | (0.94, 2.56) | 1.88 | (0.93, 3.80) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0.49 | ADA | 2.08 | (0.22, 1.07) | 1.25 | (0.40, 10.71) | 0.88 | (0.78, 2.02) | 0.95 | (0.44, 1.75) | 0.47 | (0.59, 1.54) | 2.48 | (0.15, 1.52) | 0.38 | (0.99, 6.22) | 1.07 | (0.10, 1.42) | 0.76 | (0.65, 1.75) | 0.92 | (0.34, 1.68) |
| 0.23 | CZP | 0.60 | (0.05, 1.07) | 0.42 | (0.09, 2.47) | 0.46 | (0.12, 3.08) | 0.23 | (0.09, 1.99) | 1.19 | (0.09, 2.27) | 0.38 | (0.04, 1.20) | 0.18 | (0.19, 7.30) | 0.51 | (0.03, 1.08) | 0.44 | (0.10, 2.65) | 0.36 | (0.09, 1.53) |
| 0.39 | CZP | 0.70 | (0.18, 0.84) | 0.76 | (0.49, 1.29) | 0.38 | (0.48, 1.21) | 0.76 | (0.12, 1.20) | 1.98 | (0.79, 4.92) | 0.30 | (0.08, 1.12) | 0.61 | (0.53, 1.38) | 0.73 | (0.28, 1.32) | 0.73 | (0.53, 1.02) | 1.05 | (0.87, 1.22) |
| 0.56 | ETA | 1.09 | (0.29, 1.06) | 0.54 | (0.57, 2.29) | 2.83 | (0.50, 11.25) | 0.43 | (0.72, 83.2) | 0.43 | (0.62, 1.91) | 0.43 | (0.19, 1.53) | 0.43 | (1.00, 8.02) | 0.43 | (0.13, 1.45) | 0.43 | (0.61, 2.45) | 0.43 | (0.47, 1.58) |
| 0.51 | ETA | 0.92 | (0.25, 1.04) | 0.92 | (0.65, 1.69) | 1.31 | (0.44, 10.77) | 0.92 | (0.52, 1.61) | 0.40 | (1.04, 1.65) | 0.40 | (0.14, 1.50) | 0.40 | (0.12, 0.80) | 0.79 | (0.11, 1.41) | 0.96 | (0.69, 1.82) | 0.96 | (0.39, 1.61) |
| 1.04 | GOF | 2.03 | (0.38, 2.80) | 1.68 | (0.14, 3.23) | 0.96 | (0.06, 8.68) | 0.81 | (0.83, 23.50) | 5.26 | (0.67, 6.15) | 0.81 | (1.29, 21.45) | 2.28 | (0.21, 1.33) | 1.61 | (0.70, 7.36) | 1.95 | (0.68, 3.80) | 0.31 | (0.64, 5.97) |
| 0.20 | GOF | 0.39 | (0.03, 0.59) | 0.39 | (0.40, 1.01) | 0.19 | (0.14, 5.15) | 0.39 | (0.20, 1.26) | 0.19 | (0.12, 1.00) | 0.39 | (0.15, 0.96) | 0.19 | (0.05, 0.77) | 0.39 | (0.03, 0.71) | 0.37 | (0.10, 1.09) | 0.37 | (0.16, 0.87) |
| 1.28 | INF | 2.51 | (0.40, 4.08) | 1.24 | (0.71, 9.76) | 2.30 | (0.93, 32.24) | 1.24 | (0.89, 12.15) | 6.50 | (0.71, 8.70) | 1.24 | (0.32, 4.79) | 6.50 | (1.41, 29.90) | 1.24 | (0.76, 10.45) | 2.41 | (0.70, 5.67) | 2.41 | (0.68, 8.55) |
| 0.46 | INF | 0.82 | (0.21, 1.00) | 0.82 | (0.57, 1.53) | 0.82 | (0.38, 10.02) | 0.82 | (0.72, 1.89) | 2.31 | (0.41, 1.64) | 0.82 | (0.55, 1.45) | 2.31 | (0.14, 1.42) | 0.36 | (0.92, 5.79) | 0.86 | (0.10, 1.32) | 0.86 | (0.61, 1.21) |
| 0.64 | INF | 0.62 | (0.39, 1.06) | 1.26 | (0.60, 2.92) | 1.65 | (0.65, 11.51) | 1.26 | (0.76, 3.61) | 3.27 | (0.62, 2.55) | 1.26 | (0.62, 2.55) | 1.26 | (0.26, 14.6) | 1.19 | (1.08, 9.92) | 0.86 | (0.18, 1.43) | 0.86 | (0.64, 3.13) |
| 0.53 | INF | 0.51 | (0.26, 1.07) | 1.41 | (0.77, 1.55) | 0.96 | (0.46, 11.25) | 1.41 | (0.98, 1.93) | 2.70 | (0.52, 1.74) | 0.96 | (0.75, 1.45) | 2.70 | (0.17, 1.57) | 0.83 | (1.12, 1.47) | 0.83 | (0.83, 1.65) | 0.83 | (0.59, 2.47) |
| 0.53 | PBO | 0.70 | (0.15, 5.62) | 0.41 | (0.26, 1.07) | 0.17 | (0.77, 1.55) | 0.17 | (0.98, 1.93) | 0.17 | (0.52, 1.74) | 0.17 | (0.75, 1.45) | 0.17 | (1.15, 6.32) | 0.17 | (0.12, 1.47) | 0.17 | (0.83, 1.65) | 0.17 | (0.40, 1.69) |

Results below the diagonal are the rate ratios with 95% confidence intervals from the network meta-analysis of direct and indirect comparisons between the row-defining treatment and the column-defining treatment. Numbers in red highlight statistically significant results. ADA, adalimumab; + D, plus DMARD; CZP, certolizumab; ETA, etanercept; GOL, golimumab; INF, infliximab; PBO, placebo; DMARD, disease-modifying anti-rheumatic drug.
of DMARDs. For example, the SUCRAs of safety outcomes for golimumab+ DMARDs are as follows: 59.1% (AEs), 94.0% (SAEs), and 57.5% (serious infections). By contrast, golimumab monotherapy was safer with corresponding SUCRAs of 53.5%, 16.7%, and 31.8%. Previous researchers have also conducted comparisons between TNF-\(\alpha\) inhibitor monotherapy and TNF-\(\alpha\) inhibitor combined with MTX. For instance, Breedveld et al. demonstrated that the proportions of RA patients inducing AEs and serious infections were higher under the treatment of adalimumab + DMARDs than the adalimumab monotherapy, which was in line with our results. However, some studies published before also presented no difference between the two kinds of treatment groups (86). Patients with RA treated with etanercept and those treated with etanercept + DMARDs were similar. Thus, further research should be conducted to estimate whether TNF-\(\alpha\) inhibitor combined with DMARDs therapy benefits TNF-\(\alpha\) inhibitor monotherapy or not.

Although we have made the study as comprehensive as possible, there are still some limitations. Firstly, even though the included trials were all RCTs, the results of safety comparisons among 10 drug therapies still showed some statistical inconsistency. Perhaps the RCTs with contradictions between direct and indirect evidence should be reconsidered. Secondly, 22 trials only had a follow-up time of fewer than 20 weeks. A short duration was not enough to judge the safety of treatment. Thirdly, medication dose, treatment cost, patient compliance, and other influential factors also affected trial homogeneity. Last but not least, different RCTs included in our research had different definitions of safety outcomes. There was still a shortage of clear definitions of AEs and SAEs.

In conclusion, we regard etanercept monotherapy as the optimal choice for RA patients in clinical practice when the efficacy was similar. Conversely, certolizumab+DMARDs therapy was not recommended. It was necessary to conduct long-term studies on patients with RA to provide a more complete assessment of diverse treatments and make a more judicious choice in clinical practice. All efforts should be made to improve the life quality and health standards for patients with RA.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

W-xP, YL, and BH conceived this meta-analysis. YL and XC extracted data. H-rX provided statistical advice and Q-zZ did all statistical analyses. YL, BH, and W-wL contributed to data interpretation. YL, BH, and JH drafted the report. H-rX, XC, and JH critically reviewed the article. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2022.814429/full#supplementary-material
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