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Comparative Safety of bDMARDs and tsDMARDs for the Treatment of Rheumatoid arthritis: A Systematic Review and Network Meta-Analysis

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Abstract

To compare the relative clinical safety of biologic disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs) (adalimumab, infliximab, certolizumab pegol, golimumab, tocilizumab, sarilumab, tofacitinib, baricitinib, upadacitinib, peficitinib, filgotinib, abatacept, anakinra, rituximab) in patients with rheumatoid arthritis (RA) who had been treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) without adequate response by network meta-analysis. Eight databases include PubMed, The Cochrane library, Web of science, Embase, China National Knowledge Infrastructure (CNKI), Wanfang Database, VIP Database, and Chinese Biomedical Literature Database (CBM) were searched for randomized controlled trials (RCTs) of bDMARDs and tsDMARDs in the treatment of RA. The search period was established until February 18, 2023. The included RCTs were assessed for quality according to the bias risk assessment tool provided in the Cochrane Manual. The network meta-analysis based on the Bayesian framework was performed in R software (version 4.1.3) called the gemtc package (version 1.0-1) combined with the JAGS software, using the Markov chain Monte Carlo (MCMC) method. Safety outcomes included the incidence of adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs. The included 64 RCTs, totaling 30103 patients with RA were analyzed. There were 64, 53 and 52 studies reported the outcomes of AEs, SAEs, and discontinuations due to AEs respectively. In conclusion, peficitinib and sarilumab were ranked relatively worse than other interventions in the incidence of AEs. Regarding to the incidence of SAEs, the order of golimumab and certolizumab pegol was relatively lower than other interventions. Sarilumab and tocilizumab were ranked lower than other interventions in the incidence of discontinuations due to AEs. When patients treated with golimumab and certolizumab pegol, it was recommended that the signs of infection should be monitored in time.

Keywords

Biologic disease-modifying anti-rheumatic drugs; Targeted synthetic disease-modifying anti-rheumatic drugs; Network meta-analysis; Rheumatoid arthritis.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a common systemic, chronic and autoimmune disease mainly in inflammatory synovitis, which seriously affects the daily quality of life and work of patients [1]. Epidemiological surveys show that the global incidence of the disease is 0.5% ~ 1%, and it is

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easy to be high in the female population with a lifetime risk of RA in women of 3.6%, higher than that of men of 1.7% [2]. The age of onset of RA is not limited, which can occur at any age, and the peak incidence is 50 ~ 75 years old [3].

Currently, the first-line treatment drugs commonly recognized at home and abroad are conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), including methotrexate, leflunomide and so on [4]. The second-line drugs are biologic disease-modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs). The former are biologics that target cytokines and cell surface molecules, including tumor necrosis factor-α (TNF-α) inhibitors, interleukin-6 (IL-6) inhibitors, T-cell co-stimulation modulator, CD20 monoclonal antibodies, and interleukin-1 (IL-1) inhibitor. While the latter is a multi-target Janus kinase (JAK) inhibitor, which inhibits the inflammatory immune response by inhibiting JAK kinase to achieve the purpose of treating RA [5, 6].

2. MATERIALS AND METHODS

2.1. Retrieval strategy

Eight databases were searched, including PubMed, The Cochrane library, Web of science, Embase, China National Knowledge Infrastructure (CNKI), Wanfang Database, VIP Database and Chinese Biomedical Literature Database (CBM). Clinical randomized controlled trials (RCTs) related to the treatment of RA with bDMARDs and tsDMARDs were searched, and the reference lists of included studies were traced manually. The search terms included “rheumatoid arthritis”, “adalimumab”, “infliximab”, “certolizumab pegol”, “golimumab”, “etanercept”, “tocilizumab”, “sarilumab”, “tofacitinib”, “baricitinib”, “upadacitinib”, “peficitinib”, “filgotinib”, “abatacept”, “anakinra”, “rituximab”, “randomized controlled trial”, etc. The search period was established until February 18, 2023.

2.2. Literature inclusion and exclusion criteria

The literature inclusion criteria included: (1) Patients: adults who qualified the 1987 ACR revised criteria or the 2010 ACR and EULAR classification criteria [10, 11]; they had previously undergone treatment with csDMARDs without adequate response; they had not used bDMARDs or tsDMARDs, or had used them but discontinuations of drugs for reasons other than inadequate response. There are no restrictions on gender, nationality, race, or course of illness. (2) Interventions: the interventional group was csDMARDs in combination with any one of bDMARDs or tsDMARDs; the control group was csDMARDs in combination with placebo or the other one of bDMARDs or tsDMARDs. (3) Outcomes: the incidence of adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs. (4) Study: RCTs with or without blinding or allocation concealment in the studies, and the language of studies was limited to English or Chinese.

The literature exclusion criteria were as follows: (1) duplicate publications; (2) animal and cell experimental researches, etc.; (3) review literature, conference abstracts, etc.; (4) case reports, retrospective studies, real-world studies, etc.; (5) outcome measures were missing or unavailable even if authors were contacted; (6) lack of full text.

2.3. Data extraction and quality evaluation

Literature screening and data extraction were conducted independently by two review authors and cross-checked, with the assistance of a third investigator in case of discrepancy. Information extracted included first author, publication year, patient diagnostic criteria, interventions, sample size, age, gender, outcomes. The included RCTs were assessed for quality according to the bias risk assessment tool provided in the Cochrane Manual, including the following seven aspects: (1) whether the method of random sequence generation was

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appropriate; (2) whether the allocation scheme was concealed; (3) whether blinding was applied for patients and investigators; (4) whether the assessors of outcomes were blinded; (5) whether the result data was complete; (6) whether research results were reported selectively; (7) whether there were other sources of bias. These points were divided into three levels: low risk, unclear and high risk.

2.4. Statistical analysis

The network meta-analysis based on the Bayesian framework was performed in R software (version 4.1.3) called the gemtc package (version 1.0-1) combined with the JAGS software, using the Markov chain Monte Carlo (MCMC) method. Four Markov chains were adopted for simulation analysis. The initial value was 2.5; the iteration step was refined to 1; the number of pre-simulation iterations was 10000 for annealing, and the number of iterations was 40000 to achieve model convergence. When the potential scale reduction factors (PSRF) tend to 1, it indicates that the model convergence is satisfactory. Otherwise, the number of iterations would have to continue to increase. In this study, risk ratio (RR) was used as the effect quantity, and 95% credible interval (95% CrI) that does not include 1 was used as the standard for statistical difference. The analysis results included the network diagram, league table and surface under the cumulative ranking curve (SUCRA) of interventions in each outcome. The best and the worst of the interventions were ranked according to the SUCRA. The closer the SUCRA is to 100%, the better the intervention.

3. RESULTS

3.1. Literature retrieval results

10654 related records were obtained through databases and 5 additional records were obtained from other sources. 7727 records remained after duplicates were removed. Screening was performed according to the inclusion and exclusion criteria, and 64 articles [12-75] were finally included, with a total of 64 studies for the final quantitative analysis (Fig. 1).

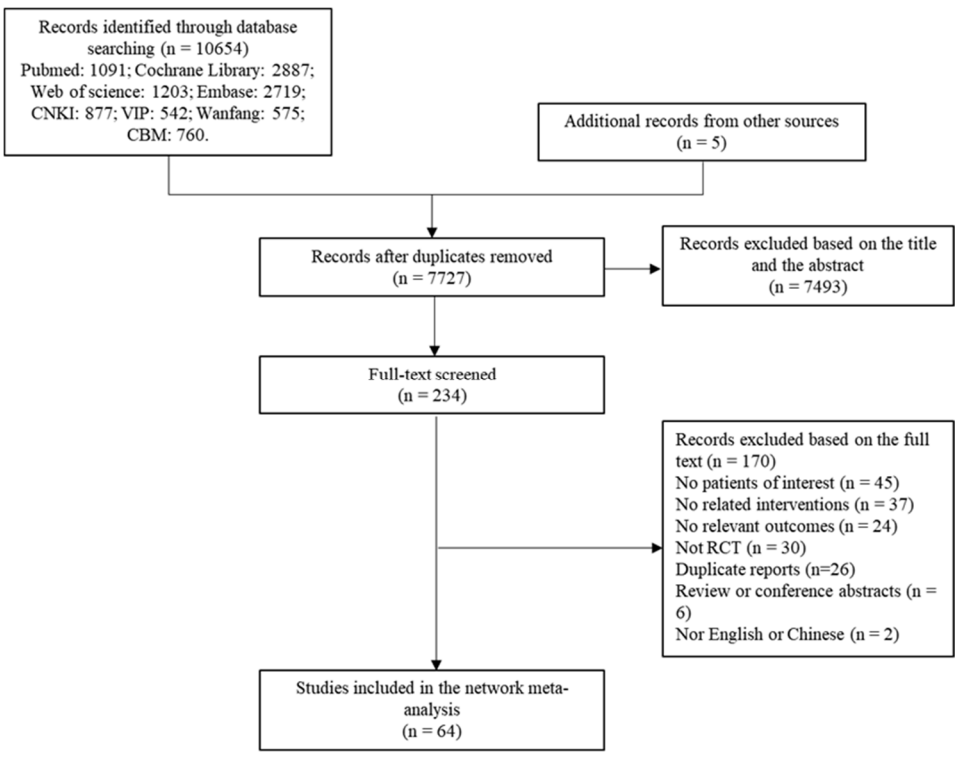

Figure 1. Flowchart of study selection process

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3.2. Basic characteristics and quality assessment

The network meta-analysis included 64 RCTs, totaling 30103 patients with RA. 64 RCTs, published from 1998 to 2021 were all randomized controlled trials. Among the 64 RCTs, 6 RCTs considered adalimumab as the study drug, accompanied with 6 RCTs for infliximab, 8 RCTs for certolizumab pegol, 6 RCTs for golimumab, 3 RCTs for etanercept, 5 RCTs for tocilizumab, 3 RCTs for sarilumab, 3 RCTs for tofacitinib, 4 RCTs for baricitinib, 5 RCTs for upadacitinib, 3 RCTs for peficitinib, 2 RCTs for filgotinib, 6 RCTs for abatacept, 2 RCTs for rituximab and 2 RCTs for anakinra. All patients with RA were diagnosed according to the 1987 ACR revised criteria or the 2010 ACR and EULAR classification criteria. Among the 64 RCTs, 38 and 21 RCTs had a low risk in random sequence generation and concealment of allocation, respectively. 63 RCTs performed blinding on the patients and research investigators; 25 RCTs performed blinding to the outcome indicators. There was a low risk of bias on incomplete outcome data and selective reporting in 64 and 59 RCTs respectively, and the risk of other bias was unclear.

3.3. Network meta-analysis results

3.3.1 AEs

The network meta-analysis was conducted on 64 RCTs, including 16 interventions and 27598 patients (Fig. 2A). The consistency of interventions explored by the node split model was relatively good, so the consistency model was applied. The PSRF value of the network meta-analysis was 1.02, indicating a good convergence. Among the fifteen drugs, adalimumab (RR: 1.08, 95% CrI: 1.03, 1.14), tocilizumab (RR: 1.20, 95% CrI: 1.11, 1.30), sarilumab (RR: 1.25, 95% CrI: 1.14, 1.37), baricitinib (RR: 1.09, 95% CrI: 1.01, 1.18), upadacitinib (RR: 1.20, 95% CrI: 1.12, 1.30), filgotinib (RR: 1.11, 95% CrI: 1.01, 1.22), and anakinra (RR: 1.11, 95% CrI: 1.01, 1.23) all had significant differences compared with placebo. There were significant differences between adalimumab and tocilizumab (RR: 0.90, 95% CrI: 0.82, 0.99), infliximab and tocilizumab (RR: 0.89, 95% CrI: 0.80, 0.98), certolizumab pegol and tocilizumab (RR: 0.88, 95% CrI: 0.79, 0.97), golimumab and tocilizumab (RR: 0.88, 95% CrI: 0.78, 0.98), adalimumab and sarilumab (RR: 0.87, 95% CrI: 0.78, 0.96), infliximab and sarilumab (RR: 0.85, 95% CrI: 0.76, 0.96), certolizumab pegol and sarilumab (RR: 0.85, 95% CrI: 0.75, 0.95), golimumab and sarilumab (RR: 0.84, 95% CrI: 0.75, 0.95), sarilumab and tofacitinib (RR: 1.19, 95% CrI: 1.02, 1.39), sarilumab and baricitinib (RR: 1.14, 95% CrI: 1.02, 1.30), adalimumab and upadacitinib (RR: 0.90, 95% CrI: 0.83, 0.98), infliximab and upadacitinib (RR: 0.88, 95% CrI: 0.81, 0.98) , certolizumab pegol and upadacitinib (RR: 0.88, 95% CrI: 0.79, 0.97), golimumab and upadacitinib (RR: 0.88, 95% CrI: 0.79, 0.97), sarilumab and abatacept (RR: 1.19, 95% CrI: 1.03, 1.36), upadacitinib and abatacept (RR: 1.14, 95% CrI: 1.01, 1.30), tocilizumab and rituximab (RR: 1.17, 95% CrI: 1.02, 1.34), sarilumab and rituximab (RR: 1.21, 95% CrI: 1.05, 1.40), upadacitinib and rituximab (RR: 1.17, 95% CrI: 1.02, 1.34) (Fig. 3). According to the SUCRA values, placebo (92.81%) had the highest probability of becoming the best treatment measure in AEs, followed by rituximab (75.75%) (Fig. 6).

3.3.2 SAEs

The network meta-analysis was conducted on 53 RCTs, including 16 interventions and 25329 patients (Fig. 2B). The consistency of interventions explored by the node split model was relatively good, so the consistency model was applied. The PSRF value of the network meta-analysis was 1, indicating a good convergence. Among the fifteen drugs, certolizumab pegol (RR: 2.01, 95% CrI: 1.19, 3.57) and golimumab (RR: 2.75, 95% CrI: 1.20, 7.04) had significant differences compared with placebo. When fifteen drugs compared to each other, there were significant differences between adalimumab and golimumab (RR: 0.37, 95% CrI: 0.13, 0.97), golimumab and filgotinib (RR: 3.34, 95% CrI: 1.04, 11.99) (Fig. 4). According to the SUCRA

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values, filgotinib (78.05%) had the highest probability to become the best treatment measure in SAEs, followed by placebo (71.06%) (Fig. 6).

3.3.3 Discontinuations due to AEs

The network meta-analysis was conducted on 52 RCTs, including 15 interventions and 25476 patients (Fig. 2C). The consistency of interventions explored by the node split model was relatively good, so the consistency model was applied. The PSRF value of the network meta-analysis was 1.01, indicating a good convergence. Among the fourteen drugs, adalimumab (RR: 1.45, 95% CrI: 1.03, 2.06), infliximab (RR: 1.92, 95% CrI: 1.14, 3.35), certolizumab pegol (RR: 1.64, 95% CrI: 1.08, 2.59), tocilizumab (RR: 2.25, 95% CrI: 1.18, 4.76), and sarilumab (RR: 2.75, 95% CrI: 1.56, 5.00) all had significant differences compared with placebo. There were significant differences between infliximab and abatacept (RR: 2.07, 95% CrI: 1.04, 4.22), tocilizumab and abatacept (RR: 2.44, 95% CrI: 1.06, 6.02), sarilumab and baricitinib (RR: 2.10, 95% CrI: 1.01, 4.63), sarilumab and filgotinib (RR: 3.00, 95% CrI: 1.24, 7.15), sarilumab and abatacept (RR: 2.98, 95% CrI: 1.38, 6.57) (Fig. 5). According to the SUCRA values, abatacept (83.35%) had the highest probability of becoming the best intervention in ACR70, followed by filgotinib (81.95%) (Fig. 6).

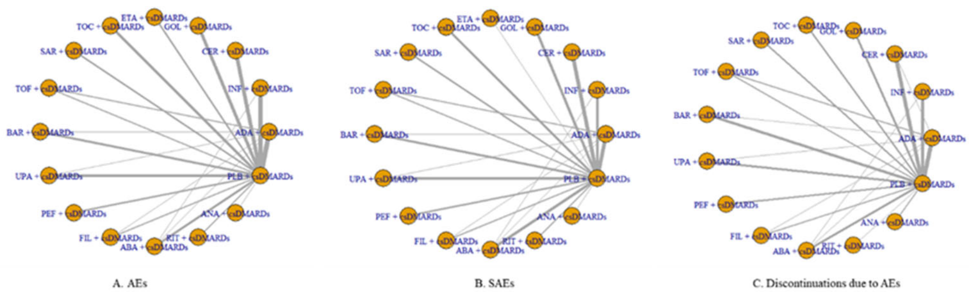

Figure 2. Network diagram of interventions

Each circle represents a drug. The connected circles represent the two drugs that have been compared in studies. The width of the lines is proportional to the number of trails.

Abbreviation: AEs, adverse events; SAEs, serious adverse events; ADA, adalimumab; INF, infliximab; CER, certolizumab pegol; GOL, golimumab; ETA, etanercept; TOC, tocilizumab; SAR, sarilumab; TOF, tofacitinib; BAR, baricitinib; UPA, upadacitinib; PEF, peficitinib; FIL, filgotinib; ABA, abatacept; RIT, rituximab; ANA, anakinra.

ADA	0.98 (0.91, 1.07)	0.98 (0.89, 1.06)	0.97 (0.89, 1.07)	1.09 (0.91, 1.31)	**1.11 (1.01, 1.22)**	**1.15 (1.04, 1.29)**	0.97 (0.86, 1.09)	1.01 (0.92, 1.09)	**1.11 (1.02, 1.21)**	1.07 (0.90, 1.32)	1.03 (0.93, 1.13)	0.97 (0.87, 1.09)	0.95 (0.84, 1.07)	1.03 (0.92, 1.15)	**0.92 (0.88, 0.97)**
1.02 (0.93, 1.10)	INF	0.99 (0.90, 1.09)	0.99 (0.89, 1.09)	1.11 (0.92, 1.34)	**1.13 (1.02, 1.25)**	**1.17 (1.04, 1.31)**	0.98 (0.85, 1.13)	1.02 (0.92, 1.13)	**1.13 (1.02, 1.24)**	1.08 (0.90, 1.35)	1.04 (0.92, 1.16)	0.99 (0.87, 1.11)	0.97 (0.85, 1.09)	1.04 (0.92, 1.17)	**0.94 (0.87, 1.00)**
1.03 (0.94, 1.12)	1.01 (0.92, 1.12)	CER	1 (0.90, 1.11)	1.12 (0.93, 1.36)	**1.14 (1.03, 1.27)**	**1.18 (1.05, 1.33)**	0.99 (0.86, 1.15)	1.03 (0.93, 1.15)	**1.14 (1.03, 1.27)**	1.09 (0.91, 1.37)	1.05 (0.93, 1.18)	1.00 (0.88, 1.14)	0.97 (0.85, 1.11)	1.05 (0.93, 1.19)	0.95 (0.88, 1.02)
1.03 (0.93, 1.13)	1.01 (0.92, 1.12)	1.00 (0.90, 1.12)	GOL	1.12 (0.93, 1.36)	**1.14 (1.02, 1.27)**	**1.18 (1.05, 1.34)**	0.99 (0.85, 1.16)	1.03 (0.92, 1.15)	**1.14 (1.03, 1.27)**	1.09 (0.91, 1.37)	1.05 (0.93, 1.19)	1.00 (0.87, 1.14)	0.98 (0.85, 1.11)	1.06 (0.93, 1.20)	0.95 (0.87, 1.03)
0.92 (0.76, 1.10)	0.90 (0.75, 1.09)	0.89 (0.73, 1.08)	0.89 (0.73, 1.08)	ETA	1.02 (0.84, 1.24)	1.06 (0.86, 1.29)	0.89 (0.71, 1.11)	0.92 (0.76, 1.12)	1.02 (0.84, 1.23)	0.98 (0.76, 1.29)	0.94 (0.77, 1.15)	0.89 (0.72, 1.10)	0.87 (0.70, 1.08)	0.94 (0.76, 1.15)	0.85 (0.71, 1.01)
0.90 (0.82, 0.99)	**0.89 (0.80, 0.98)**	**0.88 (0.79, 0.97)**	**0.88 (0.78, 0.98)**	0.98 (0.81, 1.20)	TOC	1.04 (0.92, 1.18)	0.87 (0.75, 1.01)	0.91 (0.81, 1.01)	1.00 (0.90, 1.11)	0.96 (0.80, 1.21)	0.92 (0.81, 1.04)	**0.88 (0.77, 1.00)**	**0.86 (0.75, 0.98)**	0.93 (0.81, 1.05)	**0.83 (0.77, 0.90)**
0.87 (0.78, 0.96)	**0.85 (0.76, 0.96)**	**0.85 (0.75, 0.95)**	**0.84 (0.75, 0.95)**	0.95 (0.77, 1.16)	0.96 (0.85, 1.09)	SAR	**0.84 (0.72, 0.98)**	**0.87 (0.77, 0.98)**	0.97 (0.85, 1.09)	0.92 (0.76, 1.16)	0.89 (0.78, 1.01)	**0.84 (0.73, 0.97)**	**0.82 (0.72, 0.95)**	0.89 (0.78, 1.02)	**0.80 (0.73, 0.88)**
1.03 (0.91, 1.17)	1.02 (0.89, 1.18)	1.01 (0.87, 1.16)	1.01 (0.86, 1.17)	1.13 (0.90, 1.41)	1.15 (0.99, 1.34)	**1.19 (1.02, 1.39)**	TOF	1.04 (0.90, 1.20)	1.15 (0.99, 1.33)	1.10 (0.89, 1.40)	1.06 (0.91, 1.24)	1.00 (0.85, 1.18)	0.98 (0.83, 1.16)	1.06 (0.90, 1.24)	0.96 (0.84, 1.08)
0.99 (0.91, 1.09)	0.98 (0.89, 1.09)	0.97 (0.87, 1.08)	0.97 (0.87, 1.08)	1.08 (0.89, 1.32)	1.10 (0.99, 1.24)	**1.14 (1.02, 1.30)**	0.96 (0.83, 1.11)	BAR	1.10 (0.99, 1.24)	1.06 (0.88, 1.33)	1.02 (0.90, 1.15)	0.96 (0.85, 1.10)	0.94 (0.83, 1.08)	1.02 (0.90, 1.16)	**0.92 (0.85, 0.99)**
0.90 (0.83, 0.98)	**0.88 (0.81, 0.98)**	**0.88 (0.79, 0.97)**	**0.88 (0.79, 0.97)**	0.98 (0.81, 1.20)	1.00 (0.90, 1.11)	1.04 (0.92, 1.17)	0.87 (0.75, 1.01)	0.91 (0.81, 1.01)	UPA	0.96 (0.80, 1.20)	0.92 (0.81, 1.04)	**0.87 (0.77, 0.99)**	**0.86 (0.75, 0.98)**	0.93 (0.81, 1.05)	**0.83 (0.77, 0.89)**
0.94 (0.76, 1.11)	0.92 (0.74, 1.10)	0.92 (0.73, 1.09)	0.91 (0.73, 1.10)	1.02 (0.78, 1.31)	1.04 (0.83, 1.25)	1.08 (0.86, 1.31)	0.91 (0.71, 1.12)	0.94 (0.75, 1.13)	1.04 (0.83, 1.25)	PEF	0.96 (0.76, 1.16)	0.91 (0.73, 1.11)	0.89 (0.71, 1.08)	0.96 (0.77, 1.17)	0.87 (0.70, 1.02)
0.97 (0.89, 1.08)	0.96 (0.86, 1.09)	0.95 (0.85, 1.07)	0.95 (0.84, 1.08)	1.07 (0.87, 1.31)	1.08 (0.96, 1.23)	1.12 (0.99, 1.29)	0.94 (0.81, 1.10)	0.98 (0.87, 1.11)	1.08 (0.96, 1.23)	1.04 (0.86, 1.31)	FIL	0.95 (0.82, 1.09)	0.93 (0.80, 1.07)	1.00 (0.87, 1.15)	**0.90 (0.82, 0.99)**
1.03 (0.92, 1.15)	1.01 (0.90, 1.15)	1.00 (0.88, 1.14)	1.00 (0.88, 1.15)	1.12 (0.91, 1.39)	1.14 (1.00, 1.31)	**1.19 (1.03, 1.36)**	1.00 (0.85, 1.17)	1.04 (0.91, 1.18)	**1.14 (1.01, 1.30)**	1.10 (0.90, 1.38)	1.06 (0.91, 1.21)	ABA	0.98 (0.84, 1.15)	1.06 (0.91, 1.22)	0.95 (0.85, 1.06)
1.05 (0.93, 1.19)	1.04 (0.92, 1.18)	1.03 (0.90, 1.17)	1.03 (0.90, 1.17)	1.15 (0.93, 1.42)	**1.17 (1.02, 1.34)**	**1.21 (1.05, 1.40)**	1.02 (0.86, 1.20)	1.06 (0.92, 1.21)	**1.17 (1.02, 1.34)**	1.12 (0.92, 1.42)	1.08 (0.93, 1.25)	1.02 (0.87, 1.19)	RIT	1.08 (0.93, 1.26)	0.97 (0.87, 1.08)
0.97 (0.87, 1.09)	0.96 (0.85, 1.09)	0.95 (0.84, 1.08)	0.95 (0.83, 1.08)	1.06 (0.87, 1.31)	1.08 (0.95, 1.23)	1.12 (0.98, 1.29)	0.94 (0.80, 1.11)	0.98 (0.86, 1.11)	1.08 (0.96, 1.23)	1.04 (0.86, 1.31)	1.00 (0.87, 1.15)	0.94 (0.82, 1.10)	0.92 (0.80, 1.07)	ANA	**0.90 (0.81, 0.99)**
1.08 (1.03, 1.14)	**1.07 (1.00, 1.14)**	1.06 (0.98, 1.14)	1.05 (0.98, 1.14)	1.18 (0.99, 1.42)	**1.20 (1.11, 1.30)**	**1.25 (1.14, 1.37)**	1.05 (0.92, 1.19)	**1.09 (1.01, 1.18)**	**1.20 (1.12, 1.30)**	1.15 (0.98, 1.42)	**1.11 (1.01, 1.22)**	1.05 (0.94, 1.18)	1.03 (0.92, 1.15)	**1.11 (1.01, 1.23)**	PLB

Figure 3. Comparisons for AEs of the network meta-analysis

Abbreviation: ADA, adalimumab; INF, infliximab; CER, certolizumab pegol; GOL, golimumab; ETA, etanercept; TOC, tocilizumab; SAR, sarilumab; TOF, tofacitinib; BAR, baricitinib; UPA, upadacitinib; PEF, peficitinib; FIL, filgotinib; ABA, abatacept; RIT, rituximab; ANA, anakinra.

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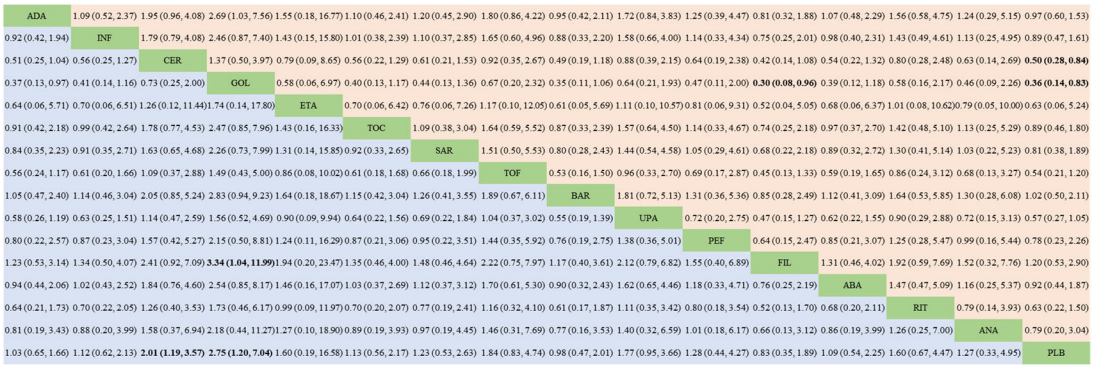

Figure 4. Comparisons for SAEs of the network meta-analysis

Abbreviation: ADA, adalimumab; INF, infliximab; CER, certolizumab pegol; GOL, golimumab; ETA, etanercept; TOC, tocilizumab; SAR, sarilumab; TOF, tofacitinib; BAR, baricitinib; UPA, upadacitinib; PEF, peficitinib; FIL, filgotinib; ABA, abatacept; RIT, rituximab; ANA, anakinra.

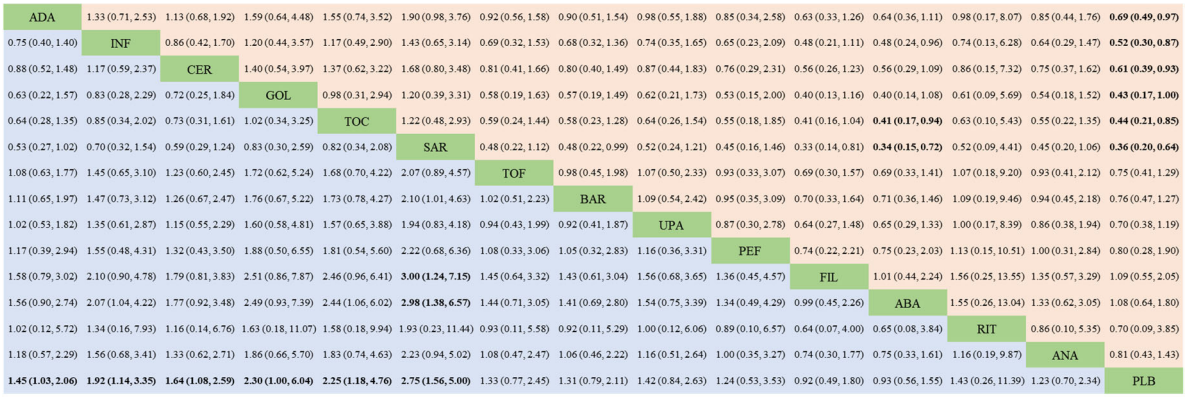

Figure 5. Comparisons for discontinuations due to AEs of the network meta-analysis

Abbreviation: ADA, adalimumab; INF, infliximab; CER, certolizumab pegol; GOL, golimumab; TOC, tocilizumab; SAR, sarilumab; TOF, tofacitinib; BAR, baricitinib; UPA, upadacitinib; PEF, peficitinib; FIL, filgotinib; ABA, abatacept; RIT, rituximab; ANA, anakinra.

Interventions	AEs		SAEs		Discontinuations due to AEs	
	SUCRA (%)	RANK	SUCRA (%)	RANK	SUCRA (%)	RANK
adalimumab	55.29	8	67.82	4	48.08	10
infliximab	62.88	7	60.57	6	28.15	12
certolizumab pegol	66.73	6	22.11	15	38.34	11
golimumab	69.22	5	12.46	16	21.88	13
etanercept	25.94	13	43.47	11	-	-
tocilizumab	16.07	14	60.09	7	20.52	14
sarilumab	8.18	16	54.14	8	10.64	15
tofacitinib	70.88	3	28.42	14	55.71	7
baricitinib	51.00	9	69.40	3	57.61	6
upadacitinib	15.37	15	29.53	13	50.12	9
peficitinib	32.18	12	51.25	10	59.50	5
filgotinib	43.78	10	78.05	1	81.95	2
abatacept	70.46	4	62.01	5	83.35	1
rituximab	75.75	2	37.69	12	50.75	8
anakinra	43.45	11	51.94	9	61.74	4
placebo	92.81	1	71.06	2	81.66	3

Figure 6. The relative ranking of interventions based on SUCRA

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Abbreviation: AEs, adverse events; SAEs, serious adverse events; SUCRA, surface under the cumulative ranking curve.

4. DISCUSSION

The study included 30103 patients of 64 RCTs used a network meta-analysis to investigate the comparative safety of bDMARDs and tsDMARDs for the treatment of RA patients who had been treated with csDMARDs without adequate response. The quality of included studies was generally high. Sixteen interventions, including placebo, were included in the incidence of AEs and SAEs. Regarding to the discontinuations due to AEs, except for etanercept, other fifteen interventions were included in the analysis.

In terms of safety, peficitinib was ranked relatively worse than other interventions in the incidence of AEs. The study showed that AEs occurring in $\geqslant$2% of patients who had been treated with peficitinib were urinary tract infection, upper respiratory tract infection, diarrhea, nasopharyngitis, and headache. The majority of AEs (97%) were mild or moderate in severity. Besides, there was no significant difference between peficitinib and placebo, so the safety of peficitinib in the incidence of AEs was probably acceptable [64]. The most common adverse event was infection in patients treated with sarilumab, and the severity was mild or moderate [46, 48]. Regarding to the incidence of SAEs, the order of golimumab and certolizumab pegol was relatively lower than other interventions. It was reported that patients treated with golimumab were at high risk of hospitalization or even death because of serious infections, especially in patients with a combination of immunosuppressive agents such as methotrexate and glucocorticoids. The common serious infections in patients treated with golimumab were lung infection, pneumonia, respiratory infection, and active tuberculosis [33]. Serious infections were also the common serious adverse events in patients treated with certolizumab pegol, and they included erysipelas, disseminated tuberculosis, peritoneal tuberculosis, pulmonary tuberculosis, and gastroenteritis [27]. Therefore, it was recommended that the signs of infection should be monitored in patients were treated with golimumab and certolizumab pegol. Sarilumab and tocilizumab were ranked lower than other interventions in the incidence of discontinuations due to AEs. The discontinuations of sarilumab were generally attributable to infections, neutropenia, and increased transaminase levels [46]. The common adverse events of discontinuations in patients treated with tocilizumab were marked but irreversible elevated aminotransferase levels, infusion reactions, and neutropenia [42].

The safety of the combination csDMARDs with bDMARDs or tsDMARDs was comprehensively evaluated in this study. It was the first network meta-analysis involved a total of fifteen drugs and three outcomes of safety. However, there were some limitations which should be mentioned in this study. Firstly, the language of included studies was English or Chinese, which may have potential selective bias. Secondly, there was some heterogeneity in the duration of drug maintenance and time point of outcome assessment. Finally, the duration of measurement for these outcomes ranged from 12 to 54 weeks, but RA is the disease with a long chronic course, and the shorter duration of measurement of the outcomes may have bias on the results of safety.

5. CONCLUSION

In conclusion, peficitinib and sarilumab were ranked relatively worse than other interventions in the incidence of AEs. Regarding to the incidence of SAEs, the order of golimumab and certolizumab pegol was relatively lower than other interventions. Sarilumab and tocilizumab were ranked lower than other interventions in the incidence of discontinuations due to AEs. When patients treated with golimumab and certolizumab pegol, it was recommended that the signs of infection should be monitored in time.

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