Comparison of the efficacy and safety indicators of DMARDs for rheumatoid arthritis

A network meta-analysis

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Abstract
Objective: To compare efficacy and safety indicators of disease-modifying antirheumatic drugs, Sarilumab, Sirukumab, Baricitinib, Tocilizumab and Adalimumab in rheumatoid arthritis treatment by a network meta-analysis.

Methods: Medline, Embase, Web of Science, The Food and Drug Administration web site, and Cochrane library were searched from build to June 1, 2020. Clinical randomized controlled trails of these 5 drugs for rheumatoid arthritis were collected for network meta-analysis.

Results: A total of 4 randomized controlled trails with 2070 patients were obtained. The results of the network meta-analysis showed that:

(1) There was no significant difference between the 4 drugs (Sarilumab, Sirukumab, Adalimumab, and Tocilizumab) (P > .05) in terms of American College of Rheumatology 20.

(2) There was no significant difference between the 5 drugs in the aspect of the America College of Rheumatology 50% and 70% (American College of Rheumatology 50, American College of Rheumatology 70) (P > .05).

(3) There was no significant difference between the 3 drugs (Sarilumab, Sirukumab, Adalimumab) in terms of reducing disease activity score 28-erythrocyte sedimentation rate in patients (P > .05).

(4) No significant difference was observed among the 5 drugs in terms of incidence of adverse reactions, serious adverse reactions and withdrawal adverse reactions (P > .05).

The results of the ranked probability plot indicated that Tocilizumab and Sarilumab outperform other drugs in terms of efficacy and safety.

Conclusion: The results of the ranking of the 5 drugs showed that Tocilizumab and Sarilumab had the best efficacy and safety.

Abbreviations: ACR70 = American College of Rheumatology 70, DAS28-ESR = disease activity score 28-erythrocyte sedimentation rate, DMARDs = Disease-modifying anti-rheumatic drugs, IL-6 = Interleukin 6, JAK = the Janus kinase, RA = rheumatoid arthritis, RCTs = randomized controlled trials, TNF = tumour necrosis factor.

Keywords: adalimumab, baricitinib, disease-modifying anti-rheumatic drugs, network meta-analysis, rheumatoid arthritis, sarilumab, sirukumab, tocilizumab

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1. Introduction

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis. RA can lead to progressive joint disability, systemic inflammation, anemia and cardiovascular disease. The prevalence of RA ranges from 0.4% to 1.3% and is associated with gender (2–3 times higher in women than men) and region of population residence (higher in the north than in the south and higher in urban people than in rural areas). Currently, there are more biological disease-modifying anti-rheumatic drugs (DMARDs), but these drugs can only relieve the symptoms, not stop the progression of the disease, and have a high incidence of side effects. In the recent year, it has been shown that interleukin 6 (IL-6) and tumour necrosis factor (TNF) have an important role in the RA pathogenesis. TNF inhibitor (Adalimumab), IL-6 inhibitor (Sarilumab, Sirukumab, Tocilizumab) and the Janus kinase (JAK)1/2 inhibitor (Baricitinib) has been developed and used clinic.

Tocilizumab can be used in anti-RA resistant to methotrexate and TNF inhibitors with no difference in safety and efficiency compared to rituximab and abatacept. For refractory RA, rituximab and tocilizumab have better clinical outcomes than Abatacept. Sarilumab is the first humanized monoclonal antibody that directly binds to the alpha subunit of IL-6 receptor complex and blocks the cytokine-mediated inflammatory signaling cascade for use against RA. Adalimumab has been widely used worldwide as a TNF inhibitor against RA. Adalimumab and the biosimilar SB5 are safer and tolerated in terms of clinical efficiency, safety and immunogenicity of against RA.

Baricitinib is an oral reversible inhibitor of JAK1 and JAK2. It is more efficiency than Adalimumab for against RA. Sirukumab is a human anti-IL-6 monoclonal immunoglobulin G1 kappa antibody that inhibits IL-6-mediated effects. Some research has already shown the efficiency of Sirukumab against RA. However, these drugs have different clinical profiles. Tocilizumab and Adalimumab have been in clinical use for many years. The efficacy and safety of the other 3 drugs are unclear.

No studies on network meta-analysis of these 5 drugs for the treatment of RA have been reported. In this study, their effectiveness and safety of DMARDs for the treatment of RA were evaluated using a network meta-analysis of the clinical data (Fig. 1). The comparative study of DMARDs will not only help to increase the understanding of the efficacy and safety of new drugs, but also provide clinical evidence for clinicians to treat RA patients who are not responding to remitting antirheumatic drugs.

2. Methods

This manuscripts’ data is based on the studies of the published/publicly reported literature. Ethical approval (review) was not required by Ethics Committee of Affiliated Hospital of Southwest Medical University, China. The data used in this manuscript are all data involving secondary use, without any personal identifiers, and without access to signed informed consent.

2.1. Data sources and search strategy

Literatures published before June 1, 2020 were searched in Medline (via PubMed), Embase (via OVID), Web of Science, The Food and Drug Administration web site and Cochrane library. The search results were restricted to studies conducted in humans, regardless of language or ethnicity. The search terms used were “Sarilumab,” “Sirukumab,” “Baricitinib,” “Tocilizumab,” “Adalimumab,” “RA” and “rheumatoid arthritis,” and were adjusted to the relevant regulations of each database.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows:

1. randomized controlled trails (RCTs);
2. patients over 18 years of age diagnosed with RA;
3. complete experimental data;
4. 2159 records identified through database searching;
5. 1602 records screened for potential inclusion;
6. 33 articles retrieved for more detail evaluation;
7. Included 4 articles in this meta-analysis;
8. 557 records excluded duplication;
9. Review and systematic evaluation (n=311);
10. Title and abstract do not accord with the research (n=1256);
11. Incongruent interventions (n=28); Other factors (n=1).

Figure 1. Flow diagram depicting the study selection process.
(4) cases met the American Rheumatology Association 1987 criteria for RA diagnosis\textsuperscript{[21]};
(5) the study’s medication was in accordance with the medication guidelines.

The exclusion criteria were
(1) studies with unreliable literature based on the Jadad scoring\textsuperscript{[22]},
(2) studies with incomplete processes;
(3) retrospective studies;
(4) combination of medication;
(5) observation clinical trials;
(6) systematic reviews;
(7) literature duplication;
(8) animal experiment.

2.3. Data extraction
Data were abstracted independently by 2 reviewers, according to the inclusion and exclusion criteria, and checked by a third reviewer. For each study, the data extracted included study design, baseline characteristics, interventions, efficacy outcomes and safety.

2.4. Outcome indicators
Primary outcome indicators included American College of Rheumatology (ACR) 20, American College of Rheumatology 50 (ACR50), American College of Rheumatology 70 (ACR70); ACR criteria are commonly used to assess the improvement in tender or swollen joint counts, acute phase reactant, patient and physician global assessments, pain scale, and disability/functionality questionnaire. American College of Rheumatology 20 (ACR20), 50 and 70 indicated 20%, 50% and 70% improvement in ACR criteria. The secondary outcome indicators included disease activity score 28-erythrocyte sedimentation rate (DAS28-ESR), the incidence of adverse reactions, incidence of serious adverse reactions, and incidence of patients who withdraw from treatment due to adverse reactions.

2.5. Risk of bias
Two investigators assessed the quality of eligible studies using the scores\textsuperscript{[23]}, which ranges from 0–7 and which assesses random sequence generation, double-blinding, allocation concealment, patient dropout, and dropout rates. For studies with a Jadad scores of 4–7 the quality was classified as high, while studies with a score of 0–3 were classified as low.\textsuperscript{[22]}

2.6. Statistical analysis
Direct and indirect results were compared using R language and R studio 1.1.464 software, and the associated 95% confidence intervals were calculated for data analysis. The network drawing was carried out using Stata16.0 software, with each node representing the intervention, the size of the node representing the size of the sample size, and the thickness of the connecting line representing the number of studies included in the study. For continuous variables, the weighted mean difference was used as the effect size. For dichotomous variables, the odds ratio was used as the effect size, expressed as a 95% confidence intervals. The sorted probability plot was used to rank the efficacy of interventions, and α = 0.05 was set as the test level of significance.

3. Results
3.1. Search and study characteristics
According to the searching strategy, 2159 relevant literatures, including 4 RCTs\textsuperscript{[24–27]} were initially obtained for a total of 2070 patients. The literatures were published from 2013 to 2020 for 5 interventions, with Sirukumab in 2 dose groups and the remaining drugs 1 dose group. The Jadad score included in the literature ranged from 5 to 7, and the overall literature quality was high. The flow chart of literature search was shown in Figure 1. The basic characteristics of the included literature and the literature quality evaluation were shown in Table 1.

3.2. Network diagram
A total of 4 RCTs\textsuperscript{[24–27]} and 5 interventions were included in this study including 3 two-arm studies and 1 three-arm study. The network was plotted with ACR20, ACR50, and ACR70 indicators, respectively. One study\textsuperscript{[26]} did not describe the changes in ACR20 in patients after treatment. Adalimumab had a large number of studies (Fig. 2).

3.3. Results of network meta-analysis of effect indices
ACR20, ACR50, and ACR70
Three\textsuperscript{[24,25,27]} reported ACR20 before and after treatment, and 4\textsuperscript{[24–27]} reported ACR50 and ACR70 before and after treatment. Four of these drugs (Sarilumab, Sirukumab 50 mg and 100 mg, Adalimumab, Tocilizumab) were not significantly different in reducing ACR20 (P > .05); there was no significant difference among the 5 drugs in ACR50 and ACR70 (P > .05, Tables 2–4).

3.4. DAS28-ESR
Only two literatures\textsuperscript{[24,27]} described the DAS28-ESR level in patients after treatment, and their network meta-analysis showed no significant difference between Sarilumab, Sirukumab, and Adalimumab in reducing DAS28-ESR (P > .05).

3.5. 4.5 Safety indicators
All included literature\textsuperscript{[24–27]} reported adverse reactions, serious adverse events, and patient’s withdrawal due to adverse reactions after drug administration. The side effects are mainly in the central nervous system, digestive system, cardiovascular system and urinary system, etc. The network meta-analysis results showed that the incidence of adverse reactions, serious adverse events, and patient withdrawal due to adverse reactions were not significantly different among the 5 drugs (P > .05). The results of the incidence of adverse reactions were shown in Table 5.

3.6. Ranking probability map
Tocilizumab and Sarilumab outperformed the other drugs in terms of efficacy and safety. Among them, the probability ranking plots for ACR20, ACR50 and ACR70 were shown in Figures 3–5, and the safety levels were shown in Table 6.

4. Discussion
RA is a highly disabling disease driven by multiple inflammatory cells and a complex network of cytokines.\textsuperscript{[28]} The basic
pathological changes are synovial swelling, granulocyte infiltration in the acute phase and synovial hypertrophy in the chronic phase.\cite{29} If the symptoms are severe, it can lead to the inability to take care of oneself, increasing the psychological burden of patients and their families, as well as increasing the financial burden of the family.

### 4.1. Cytokines of RA

The development of RA is mainly related to genetic factors, environmental factors and various cytokines in the body. Among the cytokines of RA, TNF-α, mainly produced by monocytes/macrophages, plays an extremely critical role. Therefore, block-
ing TNF-α production can inhibit the inflammatory response of RA and achieve the purpose of treating RA. Many cytokines involved in the pathogenesis of autoimmune and inflammatory diseases use JAK to transmit intracellular signals.

Mutations in JAK cause many immune defects that are associated with RA. IL-6 can promote synovial fibroblast proliferation and pannus formation and induce osteoclast formation. With the induction of various inflammatory factors, the IL-6 in the synovial fluid of the joints increases, and its levels correlated with the degree of disease activity and joint destruction, so the development of biological agents that block these factors would be an avenue for clinical treatment of RA. Meanwhile, given that the therapeutic effects of conventional drugs such as non-steroidal anti-inflammatory drugs, slow-acting antirheumatic drugs, glucocorticoids, and botanical drugs are still not very satisfactory.

### 4.2. Disease-modifying antirheumatic drugs

DMARDs targeting these cytokines continue to be introduced. The TNF inhibitor Adalimumab has been widely used in clinic to replace conventional drugs in the treatment of RA. Tocilizumab was the first IL-6 antibody to be marketed. With the successful development of Tocilizumab, biological agents such as Sarilumab, Sirukumab and Baricitinib, which act on JAK1/2 have also been developed for RA treatment with good application prospects. There have been studies on the efficacy and safety of macromolecular biological agents, but most of them have focused on the efficacy and safety of a particular biological agent for the treatment of RA, or a combination of biological agents and biological agents. Compared to the efficacy and safety of conventional drugs for the treatment of RA and long-term safety research/systematic evaluation of macromolecular biological agents, there are few trials based on the efficacy evaluation of multiple biological agents for treatment of RA. Therefore, the aim

#### Table 2

ACR20 network meta-analysis results: ACR response rates (OR, 95% CI).

| Sarilumab 200mg | 1.30(0.77,2.20) | 1.20(0.71,2.00) | 1.20(0.85,1.80) | 0.94(0.55,1.60) |
|----------------|----------------|----------------|----------------|----------------|
| 0.77 (0.45,1.30) | Sirukumab 50mg | 0.92 (0.63,1.30) | 0.95 (0.65,1.40) | 0.72 (0.42,1.20) |
| 0.84 (0.49,1.40) | 1.10 (0.75,1.60) | Sirukumab 100mg | 1.00 (0.71,1.50) | 0.79 (0.46,1.30) |
| 0.81 (0.56,1.20) | 1.10 (0.73,1.50) | 0.97 (0.67,1.40) | Adalimumab 40mg | 0.76 (0.52,1.10) |
| 1.10 (0.63,1.80) | 1.40 (0.81,2.40) | 1.30 (0.74,2.20) | 1.30 (0.89,1.90) Tocilizumab 8mg/kg |

Achieving ≥20% ACR response. ACR20 = American College of Rheumatology 20, CI = confidence intervals, OR = odds ratio.

#### Table 3

ACR50 network meta-analysis results: ACR response rates (OR, 95% CI).

| Sarilumab 200mg | 1.40(0.85,2.40) | 1.10(0.68,1.80) | 1.10(0.73,1.60) | 1.20(0.90,1.70) | 0.94(0.60,1.50) |
|----------------|----------------|----------------|----------------|----------------|----------------|
| 0.70 (0.42,1.20) | Sirukumab 50mg | 0.78 (0.52,1.20) | 0.75 (0.47,1.20) | 0.86 (0.57,1.30) | 0.66 (0.39,1.10) |
| 0.90 (0.54,1.50) | 1.30 (0.86,1.90) | Sirukumab 100mg | 0.96 (0.61,1.50) | 1.10 (0.75,1.60) | 0.85 (0.51,1.40) |
| 0.94 (0.63,1.40) | 1.30 (0.84,2.10) | 1.00 (0.67,1.60) | Baricitinib 4mg | 1.20 (0.92,1.40) | 0.88 (0.59,1.30) |
| 0.81 (0.59,1.10) | 1.20 (0.77,1.70) | 0.90 (0.61,1.30) | Adalimumab 40mg | 0.76 (0.55,1.10) | 0.47 (0.15,1.50) |
| 1.10 (0.67,1.70) | 1.50 (0.89,2.60) | 1.20 (0.70,2.00) | 1.10 (0.76,1.70) | 1.30 (0.94,1.80) Tocilizumab 8mg/kg |

Achieving ≥50% ACR response. ACR50 = American College of Rheumatology 50, CI = confidence intervals, OR = odds ratio.

#### Table 4

ACR70 network meta-analysis results: ACR response rates (OR, 95% CI).

| Sarilumab 200mg | 2.10(0.68,6.50) | 1.70(0.55,1.10) | 1.60(0.62,3.90) | 2.00(0.93,4.40) | 1.10(0.39,3.40) |
|----------------|----------------|----------------|----------------|----------------|----------------|
| 0.47 (0.15,1.50) | Sirukumab 50mg | 0.79 (0.36,1.80) | 0.74 (0.29,1.90) | 0.96 (0.43,2.20) | 0.53 (0.18,1.60) |
| 0.59 (0.20,1.80) | 1.30 (0.56,2.80) | Sirukumab 100mg | 0.93 (0.37,2.40) | 1.20 (0.55,2.70) | 0.67 (0.23,2.00) |
| 0.64 (0.26,1.60) | 1.40 (0.52,3.40) | 1.10 (0.43,2.70) | Baricitinib 4mg | 1.30 (0.82,2.10) | 0.72 (0.31,1.80) |
| 0.49 (0.23,1.10) | 1.00 (0.46,2.30) | 0.83 (0.37,1.80) | 0.78 (0.47,1.30) | Adalimumab 40mg | 0.56 (0.27,1.20) |
| 0.89 (0.30,2.60) | 1.90 (0.82,5.50) | 1.50 (0.50,4.30) | 1.40 (0.56,3.30) | 1.80 (0.84,3.70) Tocilizumab 8mg/kg |

Achieving ≥70% ACR response. ACR70 = American College of Rheumatology 70, CI = confidence intervals, OR = odds ratio.

#### Table 5

The incidence of adverse reactions network meta-analysis results (OR, 95% CI).

| Sarilumab 200mg | 0.95(0.76,1.20) | 0.99(0.79,1.20) | 0.98(0.81,1.20) | 1.00(0.86,1.20) | 1.00(0.82,1.30) |
|----------------|----------------|----------------|----------------|----------------|----------------|
| 1.10 (0.85,1.30) | Sirukumab 50mg | 1.00 (0.91,1.20) | 1.00 (0.87,1.20) | 1.10 (0.93,1.20) | 1.10 (0.89,1.30) |
| 1.00 (0.81,1.30) | 0.96 (0.83,1.10) | Sirukumab 100mg | 0.99 (0.83,1.20) | 1.00 (0.88,1.10) | 1.00 (0.85,1.30) |
| 1.00 (0.85,1.20) | 0.97 (0.82,1.10) | 1.00 (0.85,1.20) | Baricitinib 4mg | 1.00 (0.96,1.10) | 1.00 (0.90,1.20) |
| 0.98 (0.83,1.20) | 0.93 (0.81,1.10) | 0.98 (0.83,1.10) | Adalimumab 40mg | 1.00 (0.88,1.10) | 0.98 (0.81,1.10) |
| 0.98 (0.80,1.20) | 0.93 (0.77,1.10) | 0.98 (0.80,1.20) | 0.96 (0.83,1.10) | 1.00 (0.88,1.10) Tocilizumab 8mg/kg |

CI = confidence intervals, OR = odds ratio.
The aim of this study was to compare the efficacy and safety of these 5 anti-rheumatic biologics for treatment of RA based on the existing trials with available metrics.

In terms of effectiveness, the efficacy of 5 anti-RA drugs was analyzed by online meta-analysis. Four of them (Sarilumab, Sirukumab, Adalimumab, Tocilizumab) did not differ significantly in reducing ACR20 ($P > .05$). There was no significant difference in reducing ACR50 and ACR70 ($P > .05$). These 5 biological agents have good effect in the treatment of RA, which is generally consistent with the findings of Bae$^{[38]}$ and Lee$^{[39]}$.

There was no significant difference in DAS28-ESR levels of 3 drugs, Sarilumab, Sirukumab and Adalimumab in this study. In terms of safety, there were no significant differences among the 5 anti-RA drugs, indicating that they have similar safety profiles.

Figure 3. Proportion of ACR20 response treated by DMARDs: (The lighter the color, the higher the sorting, the better the treatment effect; A = Sarilumab 200 mg; B = Sirukumab 50 mg; C = Sirukumab 100 mg; D = Baricitinib 4 mg; E = Adalimumab 40 mg). DMARDs: disease-modifying antirheumatic drugs. ACR20 = American College of Rheumatology 20.

Figure 4. Proportion of ACR50 response treated by DMARDs: (The lighter the color, the higher the sorting, the better the treatment effect; A = Sarilumab 200 mg; B = Sirukumab 50 mg; C = Sirukumab 100 mg; D = Baricitinib 4 mg; E = Adalimumab 40 mg; F = Tocilizumab 8 mg/kg). DMARDs: disease-modifying antirheumatic drugs. ACR50 = American College of Rheumatology 50.
4.3. Disease-modifying antirheumatic drugs probability ranking

In the probability ranking, Tocilizumab ranked first in ACR20 and ACR50 with 56.41% and 48.92%, Sarilumab ranked second with 43.44% and 32.57%. However, in ACR70, Tocilizumab was ranked second (40.03%) and Sarilumab was ranked first (54.29%). In the incidence of adverse reactions, Sirukumab ranked first with 40.43%, suggesting a higher risk of adverse events with this drug; Tocilizumab and Sarilumab are superior to the other 3 drugs (Sirukumab, Adalimumab, and Baricitinib) in terms of efficacy and safety. This is in agreement with Tocilizumab, Sarilumab and Sirukumab by Bae et al. In this study, the evaluation results of adverse events were similar. Tocilizumab, a humanized monoclonal antibody, fights against RA by binding to IL-6 receptor and inhibiting downstream IL-6 signaling. Lee et al. conducted a meta-analysis of the Tocilizumab, Rituximab, Abatacept and Tofacitinib networks and found that Tocilizumab to be relatively safe, similar to this study. Sarilumab is a human Immunoglobulin G1 monoclonal antibody. The results of this drug for treatment of RA are similar to those of Choy, who analysed Sarilumab’s treatment of RA. In addition, the safety of Sirukumab for RA is similar to the results of SIRROUND-D and others. When using this drug, special attention should be paid to its adverse effects. Further rigorous genetic and molecular studies will improve our understanding of the problem in order to update therapeutic approaches.

4.4. Study limitations

This study also has certain limitations:

1. Among the included studies, only Taylor et al. had 2 courses of treatment and the rest had 1 course of treatment;
2. The literature was incomplete, for example, no post-treatment ACR20 was reported in Taylor et al. and no post-treatment disease activity score 28-C-reactive protein (DAS28-CRP) was reported in all included studies;
3. The small number of included studies may be a risk of publication bias.

### Table 6

| The sorting (Rank) | Treatment measures | Rank probability ranking of the incidence of adverse reactions (%) | Rank probability ranking of the incidence of serious adverse reactions (%) | Rank probability ranking of patients withdrawing due to adverse reactions (%) |
|--------------------|--------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| 1                  | Sirukumab 50mg     | 40.43                                                        | Baricitinib 4mg                                                | 55.37                                                        | Baricitinib 4mg                                                |
| 2                  | Baricitinib 4mg    | 24.50                                                        | Sirukumab 50mg                                                | 38.36                                                        | Sirukumab 50mg                                                |
| 3                  | Sirukumab 100mg    | 17.34                                                        | Sirukumab 100mg                                               | 33.06                                                        | Sirukumab 100mg                                               |
| 4                  | Adalimumab 40mg    | 31.48                                                        | Adalimumab 40mg                                               | 33.38                                                        | Adalimumab 40mg                                               |
| 5                  | Tocilizumab 8mg/kg | 19.27                                                        | Tocilizumab 8mg/kg                                            | 23.54                                                        | Sarilumab 200mg                                               |
| 6                  | Sarilumab 200mg    | 27.71                                                        | Sarilumab 200mg                                               | 49.22                                                        | Tocilizumab 8mg/kg                                            |

The lower the ranking, the safer.
5. Conclusions

Our study found that Tocilizumab ranked first and Sarilumab ranked second in response to ACR20 and ACR50. While for ACR70 treatment response, Tocilizumab ranked second and Sarilumab ranked first. The incidence of adverse reactions was most prominent with Sirukumab and lowest with Tocilizumab and Sarilumab, suggesting that Tocilizumab and Sarilumab were superior to Sirukumab, Adalimumab and Baricitinib in terms of efficacy and safety. Overall, of the DMARDs studied, Tocilizumab and Sarilumab are the most prominent. However, due to the small amount of literature included in the network meta-analysis, the conclusions of this study need to be further validated by high-quality, long-term follow-up randomized controlled study.

Author contributions

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