


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 trails, TNF = tumour necrosis factor.

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

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MH and SZ carried out the studies, participated in collecting data, and drafted the manuscript. HN and BY performed the statistical analysis and participated in its design. YH and XY helped to draft the manuscript. All authors read and approved the final manuscript.

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1. Introduction

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis.^[1] 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).^[2–6] Currently, there are more biological disease-modifying antirheumatic 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.^[7,8] 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.^[9,10]

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.^[11] For refractory RA, rituximab and tocilizumab have better clinical outcomes than Abatacept.^[12] 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.^[11] Adalimumab and the biosimilar SB5 are safer and tolerated in terms of clinical efficiency, safety and immunogenicity of against RA.^[13,14]

Baricitinib is an oral reversible inhibitor of JAK1 and JAK2. It is more efficiency than Adalimumab for against RA.^[15,16] Sirukumab is a human anti-IL-6 monoclonal immunoglobulin G 1 kappa antibody that inhibits IL-6-mediated effects.^[17] Some research has already shown the efficiency of Sirukumab against RA.^[18] However, these drugs have different clinical profiles. Tocilizumab and Adalimumab have been in clinical use for many years.^[19] The efficacy and safety of the other 3 drugs are unclear.^[20]

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 “rheumatic 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;

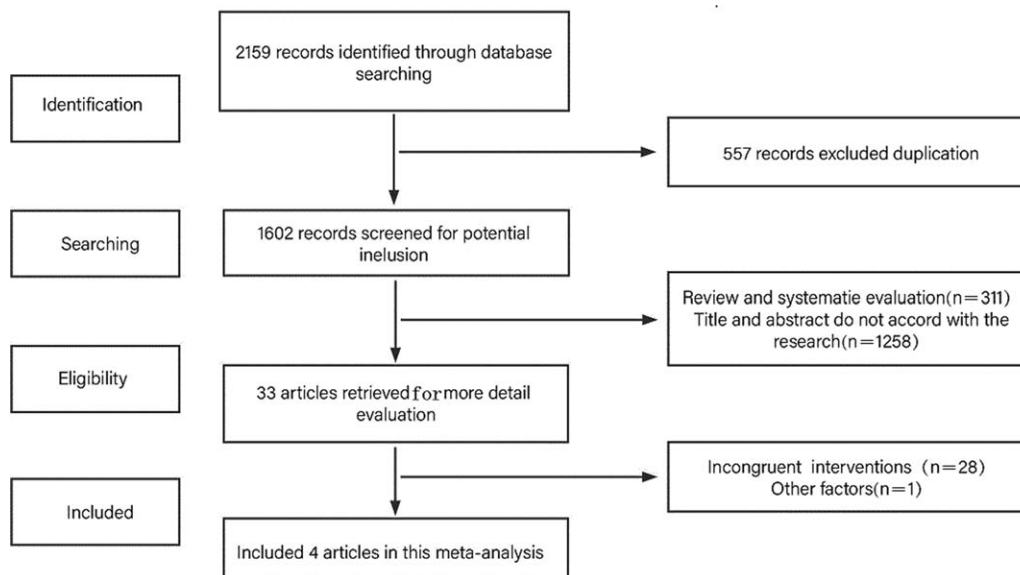


Figure 1. Flow diagram depicting the study selection process.

- (4) cases met the American Rheumatology Association 1987 criteria for RA diagnosis^[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^[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,^[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.^[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 $\alpha = 0.05$ 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^[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^[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^[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, ACR5,0 and ACR70

Three^[24,25,27] reported ACR20 before and after treatment, and 4^[24–27] reported ACR50 and ACR70 before and after treatment. Four of these drugs (Sarilumab, Sirukumab 50mg and 100mg, 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^[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^[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.^[28] The basic

Table 1
Characteristics of included individual studies.

Primary study	Regimens	Male/ Female	Age (yr)	BMI (kg·m ⁻²)	DAS- 28CRP	DAS-28 ESR	Duration of RA (yr)	Study location	Study duration (wk)	Jadadscore
Burmeister 2017 ^[24]	Sarilumab 200 mg q2w	27/157	50.9±12.6	27.1±5.6	6.0±0.9	6.8±0.8	8.1±8.1	86 research sites in 7 countries	24	7
Cem 2013 ^[25]	Adalimumab 40 mg q2w	35/150	53.6±11.9	27.3±6.5	6.0±0.9	6.8±0.8	6.6±7.8	76 research sites in 15 countries	24	5
	Tocilizumab 8 mg/kg q4w	34/129	54.4±13.0	/	/	/	7.3±8.1			
Taylor 2017 ^[26]	Adalimumab 40 mg q2w	29/133	53.3±12.4	/	/	/	6.3±6.9	26 research sites in 281 countries	24,52	7
	Baricitinib 4 mg qd	112/375	54.0±2.0	/	5.8±0.9	6.5±0.9	10.0±9.0			
Taylor 2018 ^[27]	Adalimumab 40 mg qw	79/251	54.0±12.0	/	5.8±0.9	6.4±1.0	10.0±9.0	16 research sites in 109 countries	24	7
	Sirukumab 50 mg q4w	29/157	52.5±12.5	27.8±6.0	6.1±1.0	6.9±0.9	4.2 (1.6-9.5)			
	Sirukumab 100 mg q2w	33/154	49.8±12.3	27.6±6.5	6.1±1.0	6.9±0.9	4.6 (2.1-9.0)			
	Adalimumab 40 mg q2w	30/156	52.6±12.2	27.9±5.6	6.1±1.0	6.9±0.9	4.0 (1.4-8.4)			

pathological changes are synovial swelling, granulocyte infiltration in the acute phase and synovial hypertrophy in the chronic phase.^[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-

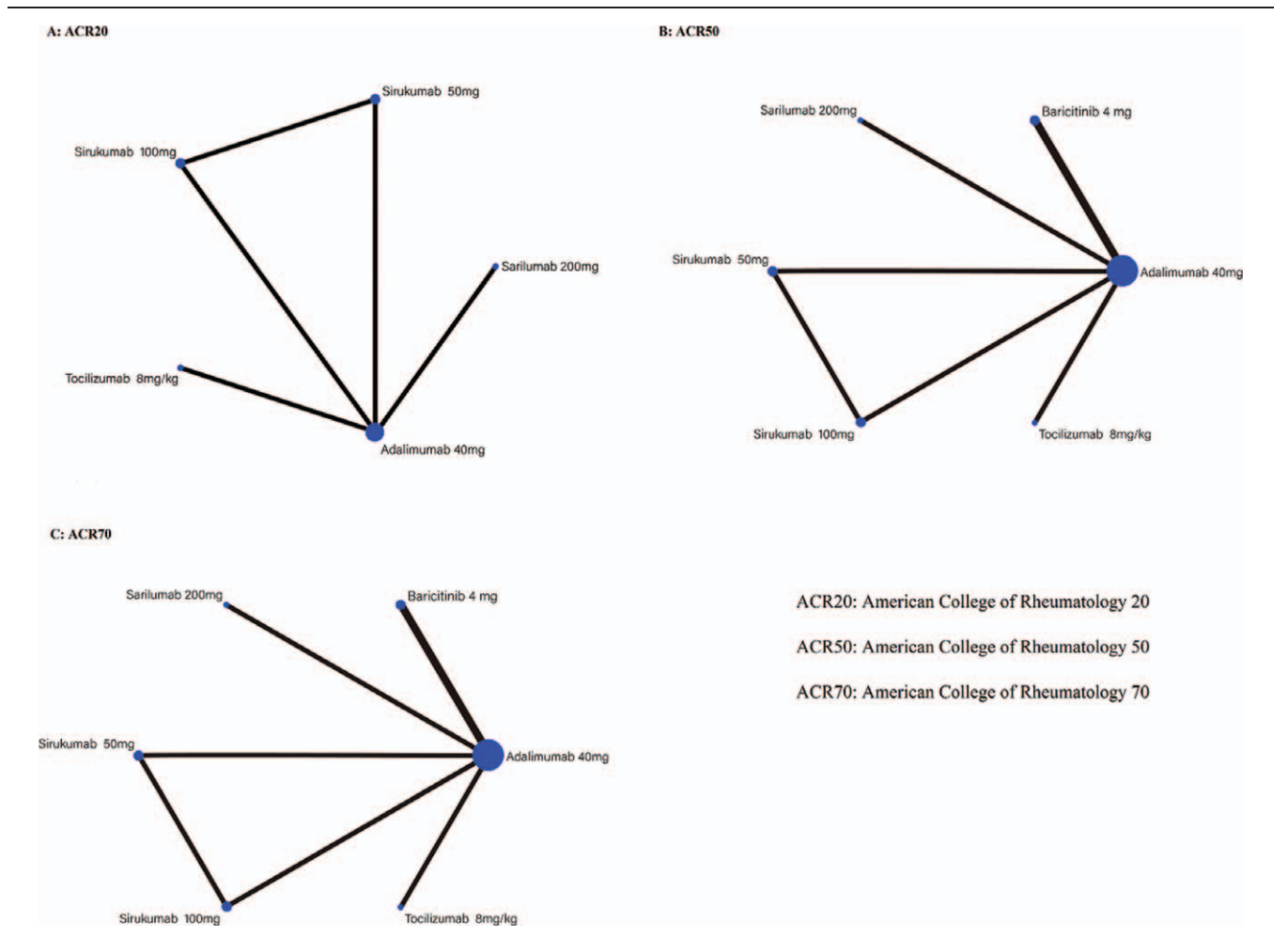


Figure 2. Network evidence diagram.

Table 2**ACR20 network meta-analysis results: ACR response rates (OR, 95% CI).**

Sarilumab 200mg	1.3(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 $\geq 20\%$ 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)	0.87 (0.69,1.10)	Adalimumab 40mg	0.76 (0.55,1.10)
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 $\geq 50\%$ ACR response. ACR50 = American College of Rheumatology 50, CI = confidence intervals, OR = odds ratio.

ing TNF- α production can inhibit the inflammatory response of RA and achieve the purpose of treating RA.^[30–33] Many cytokines involved in the pathogenesis of autoimmune and inflammatory diseases use JAK to transmit intracellular signals.^[34]

Mutations in JAK cause many immune defects that are associated with RA.^[35] IL-6 can promote synovial fibroblast proliferation and pannus formation and induce osteoclast formation.^[36] 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,^[37] 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 4**ACR70 network meta-analysis results: ACR response rates (OR, 95% CI).**

Sarilumab 200mg	2.10(0.68,6.50)	1.70(0.55,5.10)	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 (0.62,5.50)	1.50 (0.50,4.30)	1.40 (0.56,3.30)	1.80 (0.84,3.70)	Tocilizumab 8mg/kg

Achieving $\geq 70\%$ 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 (0.88,1.20)	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)	0.96 (0.89,1.00)	Adalimumab 40mg	1.00 (0.88,1.10)
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.

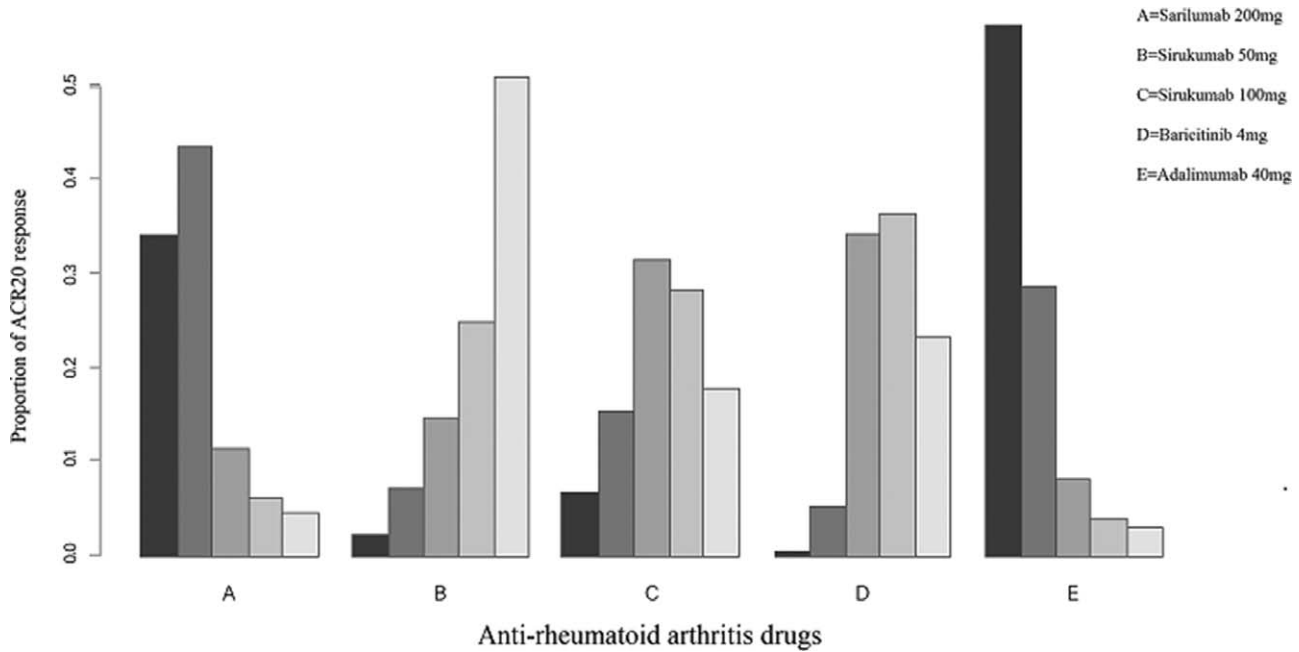


Figure 3. Proportion of ACR20 response treated by DMARDs: (The lighter the color, the higher the sorting, the better the treatment effect; A = Sarilumab 200 mg; B = Sirukumab 50 mg; C = Sirukumab 100 mg; D = Baricitinib 4 mg; E = Adalimumab 40 mg). DMARDs: disease-modifying antirheumatic drugs. ACR20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

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.

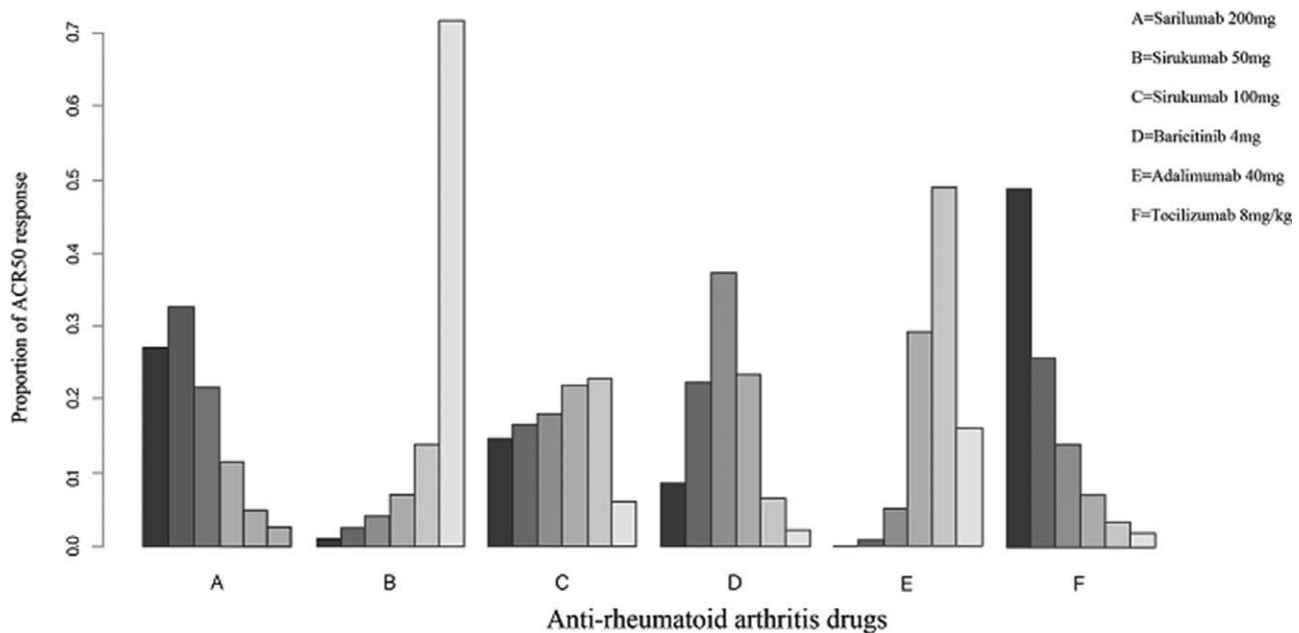


Figure 4. Proportion of ACR50 response treated by DMARDs: (The lighter the color, the higher the sorting, the better the treatment effect; A = Sarilumab 200 mg; B = Sirukumab 50 mg; C = Sirukumab 100 mg; D = Baricitinib 4 mg; E = Adalimumab 40 mg; F = Tocilizumab 8 mg/kg). DMARDs: disease-modifying antirheumatic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

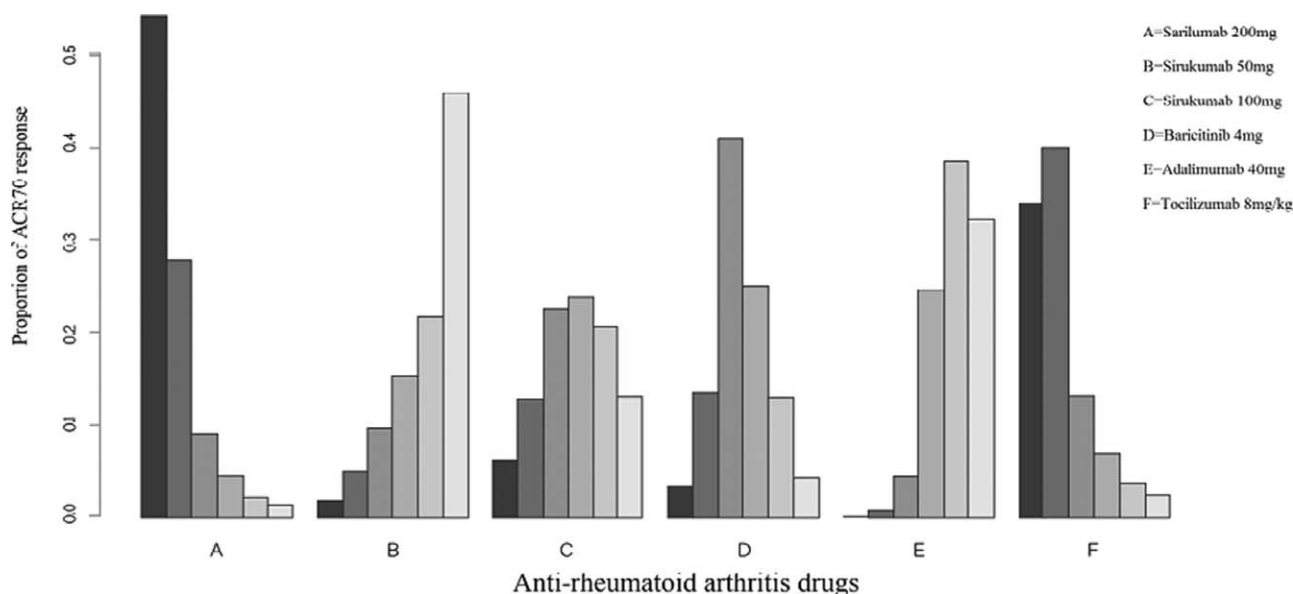


Figure 5. Proportion of ACR70 response treated by DMARDs (The lighter the color, the higher the sorting, the better the treatment effect; A = Sarilumab 200mg; B = Sirukumab 50mg; C = Sirukumab 100mg; D = Baricitinib 4mg; E = Adalimumab 40mg; F = Tocilizumab 8mg/kg). DMARDs: disease-modifying antirheumatic drugs. ACR70 = American College of Rheumatology 70.

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 and ranked 5th and 6th, suggesting 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^[38] et al. In this study, the evaluation results of adverse events were similar. Tocilizumab, a humanized monoclonal antibody,^[40] fights against RA by binding to IL-6 receptor and inhibiting downstream IL-6 signaling.^[41] Lee et al^[42] 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 G 1

monoclonal antibody.^[43] The results of this drug for treatment of RA are similar to those of Choy,^[44,45] who analysed Sarilumab’s treatment of RA. In addition, the safety of Sirukumab for RA is similar to the results of SIRROUND-D^[46] 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.^[47]

4.4. Study limitations

This study also has certain limitations:

- (1) among the included studies, only Taylor et al^[26] 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^[26] and no post-treatment disease activity score 28-C-reactive protein (DAS28-CRP) was reported in all included studies^[23-26];
- (3) The small number of included there may be a risk of publication bias.

Table 6
Probability ranking.

The sorting	Treatment measures	Rank probability ranking of the incidence of adverse reactions (%)	Treatment measures	Rank probability ranking of the incidence of serious adverse reactions (%)	Treatment measures	Rank probability ranking of patients withdrawing due to adverse reactions (%)
1	Sirukumab 50mg	40.43	Baricitinib 4mg	55.37	Baricitinib 4mg	50.61
2	Baricitinib 4mg	24.50	Sirukumab 50mg	38.36	Sirukumab 50mg	34.22
3	Sirukumab 100mg	17.34	Sirukumab 100mg	33.06	Sirukumab 100mg	29.07
4	Adalimumab 40mg	31.48	Adalimumab 40mg	33.38	Adalimumab 40mg	33.33
5	Tocilizumab 8mg/kg	19.27	Tocilizumab 8mg/kg	23.54	Sarilumab 200mg	23.08
6	Sarilumab 200mg	27.71	Sarilumab 200mg	49.22	Tocilizumab 8mg/kg	34.50

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.

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References

- [1] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011;365:2205–19.
- [2] Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet* 2016;388:2023–38.
- [3] Littlejohn Emily A, Monrad Seetha U. Early diagnosis and treatment of rheumatoid arthritis. *Prim Care* 2018;45:237–55.
- [4] Sacks JJ, Luo YH, Helmick CG. Prevalence of specific types of arthritis and other rheumatic conditions in the ambulatory health care system in the United States, 2001–2005. *Arthritis Care Res (Hoboken)* 2010;62:460–4.
- [5] Anić B. Epidemiology of inflammatory rheumatic diseases. *Reumatizam* 2014;61:13–8.
- [6] Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising? : results from Olmsted County, Minnesota, 1955–2007. *Arthritis Rheum* 2010;62:1576–82.
- [7] Smolen Smolen JS, Aletaha D, Redlich K. The pathogenesis of rheumatoid arthritis: new insights from old clinical data? *Nat Rev Rheumatol* 2012;8:235–43.
- [8] Lv H, Li Z, Xie Z, et al. Innovated formulation of TCM pangolin scales to develop a nova therapy of rheumatoid arthritis. *Biomed Pharmacother* 2020;126:109872.
- [9] Raimondo MG, Biggioggero M, Crotti C, Becciolini A, Favalli EG. Profile of sarilumab and its potential in the treatment of rheumatoid arthritis. *Drug Des Devel Ther* 2017;11:1593–603.
- [10] Tanaka Y, Fautrel B, Keystone EC, et al. Clinical outcomes in patients switched from adalimumab to baricitinib due to non-response and/or study design: phase III data in patients with rheumatoid arthritis. *Ann Rheum Dis* 2019;78:890–8.
- [11] Biggioggero M, Crotti C, Becciolini A, Favalli EG. Tocilizumab in the treatment of rheumatoid arthritis: an evidence-based review and patient selection. *Drug Des Devel Ther* 2018;13:57–70.
- [12] Gottenberg JE, Morel J, Perrodeau E, et al. French Society of Rheumatology and the investigators participating in AIR, ORA, and REGATE registries. Comparative effectiveness of rituximab, abatacept, and tocilizumab in adults with rheumatoid arthritis and inadequate response to TNF inhibitors: prospective cohort study. *BMJ* 2019;364:l67.
- [13] Burmester GR, Landewé R, Genovese MC, et al. Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis* 2017;76:414–7.
- [14] Weinblatt ME, Baranaukaite A, Niebrzydowski J, et al. Phase III randomized study of SB5, an adalimumab biosimilar, versus reference adalimumab in patients with moderate-to-severe rheumatoid arthritis. *Arthritis Rheumatol* 2018;70:40–8.
- [15] Keystone EC, Taylor PC, Tanaka Y, et al. Patient-reported outcomes from a phase 3 study of baricitinib versus placebo or adalimumab in rheumatoid arthritis: secondary analyses from the RA-BEAM study. *Ann Rheum Dis* 2017;76:1853–61.
- [16] Baricitinib for rheumatoid arthritis. *Aust Prescr*. 2019;42:34–5.
- [17] Zhuang Y, Xu Z, de Vries DE, et al. Pharmacokinetics and safety of sirukumab following a single subcutaneous administration to healthy Japanese and Caucasian subjects. *Int J Clin Pharmacol Ther* 2013;51:187–99.
- [18] Thanarajasingam U, Niewold TB. Sirukumab: a novel therapy for lupus nephritis. *Exp Opin Investig Drugs* 2014;23:1449–55.
- [19] Rubbert-Roth A, Furst DE, Nebesky JM, Jin A, Berber E. A review of recent advances using tocilizumab in the treatment of rheumatic diseases. *Rheumatol Ther* 2018;5:21–42.
- [20] Choy E, Freemantle N, Proudfoot C, et al. Evaluation of the efficacy and safety of sarilumab combination therapy in patients with rheumatoid arthritis with inadequate response to conventional disease-modifying antirheumatic drugs or tumour necrosis factor α inhibitors: systematic literature review and network meta-analyses. *RMD Open* 2019;5:e000798.
- [21] Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
- [22] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
- [23] Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- [24] Burmester GR, Lin Y, Patel R, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis* 2017; 76:840–7.
- [25] Gabay C, Emery P, van Vollenhoven R, et al. ADACTA Study Investigators. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013;381:1541–50.
- [26] Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. *N Engl J Med* 2017;376:652–62.
- [27] Taylor PC, Schiff MH, Wang Q, et al. Efficacy and safety of monotherapy with sirukumab compared with adalimumab monotherapy in biologic-naïve patients with active rheumatoid arthritis (SIRROUND-H): a randomised, double-blind, parallel-group, multinational, 52-week, phase 3 study. *Ann Rheum Dis* 2018;77:658–66.
- [28] Zhang JM, An J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin* 2007;45:27–37.
- [29] Guo Q, Wang Y, Xu D, Nossent J, Pavlos NJ, Xu J. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res* 2018;6:15.

- [30] Parameswaran N, Patial S. Tumor necrosis factor- α signaling in macrophages. *Crit Rev Eukaryot Gene Expr* 2010;20:87–103.
- [31] Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med* 2001;344:907–16.
- [32] Nesbitt A, Fossati G, Bergin M, et al. Mechanism of action of certolizumab pegol (CDP870): in vitro comparison with other anti-tumor necrosis factor alpha agents. *Inflamm Bowel Dis* 2007;13:1323–32.
- [33] Ohta S, Harigai M, Tanaka M, et al. Tumor necrosis factor-alpha (TNF-alpha) converting enzyme contributes to production of TNF-alpha in synovial tissues from patients with rheumatoid arthritis. *J Rheumatol* 2001;28:1756–63.
- [34] Banerjee S, Biehl A, Gadina M, et al. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs* 2017;77:521–46.
- [35] Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: current and future prospects. *Drugs* 2017;77:521–46.
- [36] Kotake S, Sato K, Kim KJ, et al. Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation. *J Bone Miner Res* 1996;11:88–95.
- [37] Madhok R, Crilly A, Watson J, Capell HA. Serum interleukin 6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. *Ann Rheum Dis* 1993;52:232–4.
- [38] Bae SC, Lee YH. Comparison of the efficacy and tolerability of tocilizumab, sarilumab, and sirukumab in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Clinical Rheumatol* 2018;37:1471–9.
- [39] Lee YH, Song GG. Comparison of the efficacy and safety of tofacitinib and filgotinib in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Z Rheumatol*. Accessed 2019 Nov 28. English.
- [40] Strand V, Burmester GR, Ogale S, Devenport J, John A, Emery P. Improvements in health-related quality of life after treatment with tocilizumab inpatients with rheumatoid arthritis refractory to tumor necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. *Rheumatology* 2012;51:1860–9.
- [41] Jordan N, Lutalo PM, D'Cruz DP. Novel therapeutic agents in clinical development for systemic lupus erythematosus. *BMC Med* 2013;11:120.
- [42] Lee YH, Bae SC. Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled trials. *Int J Rheum Dis* 2016;19:1103–11.
- [43] June RR, Olsen NJ. Room for more IL-6 blockade? Sarilumab for the treatment of rheumatoid arthritis. *Expert Opin Biol Ther* 2016;16:1303–9.
- [44] Choy E, Freemantle N, Proudfoot C, et al. Evaluation of the efficacy and safety of sarilumab combination therapy in patients with rheumatoid arthritis with inadequate response to conventional disease-modifying antirheumatic drugs or tumour necrosis factor (inhibitors: systematic literature review and network meta-analyses. *RMD Open* 2019;5:e000798.
- [45] Pelechas E, Voulgari PV, Drosos AA. Clinical evaluation of the safety, efficacy and tolerability of sarilumab in the treatment of moderate to severe rheumatoid arthritis. *Ther Clin Risk Manag* 2019;15:1073–9.
- [46] Takeuchi T, Thorne C, Karpouzas G, et al. Sirukumab for rheumatoid arthritis: the phase III SIRROUND-D study. *Ann Rheum Dis* 2017;76:2001–8.
- [47] Parvez MK, Niyazi S. The Genomic and Structural Organization of SARS-CoV-2: a mutational perspective. *Sci Medicine Journal* 2021;3:59–65.