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Review Article

Comparative Efficacy and Safety of Biologic Treatments in Giant Cell Arteritis: A Network Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: The relative efficacy and safety of the biological therapies were compared by a network meta-analysis for giant cell arteritis (GCA).

Methods: We searched MEDLINE, EMBASE, and Cochrane databases to identify randomized controlled trials (RCTs) that assessed the efficacy and safety of tocilizumab, mavrilimumab, abatacept, and tumor necrosis factor (TNF) inhibitors for GCA treatment. The RoB 2.0 version of the Cochrane risk-of-bias instrument was used to assess the quality of the RCTs and a risk-of-bias and grading of recommendations assessment, development and evaluation (GRADE) were performed to ascertain the certainty of the evidence. The direct and indirect RCT findings were combined using a Bayesian network meta-analysis.

Results: A total of eight RCTs involving 533 patients were included. One RCTs had a high risk of bias, four had some concerns, and three had a low risk of bias. Except for one comparison, the overall certainty of the treatment effects was rated as moderate. Compared to TNF inhibitor and placebo, tocilizumab showed a greater rate of remission (odds ratio [OR], 5.68, 95% credible interval [CrI], 2.21-14.79; OR, 7.40, 95% Cr, 4.09-13.94). Tocilizumab had the best chance of being the best therapy based on the remission rate, followed by mavrilimumab, abatacept, TNF inhibitor, and placebo, according to the surface under the cumulative ranking curve (SUCRA)-based likelihood rating analysis. Tocilizumab demonstrated the highest probability of being a more effective relapse-based treatment than the other drugs, which were classified in decreasing order as follows: mavrilimumab, abatacept, TNF inhibitor, and placebo. The placebo was more likely to be the safest course of action, followed by mavrilimumab, abatacept, tocilizumab, and a TNF inhibitor.

Conclusion: Tocilizumab may be the most efficient remission-inducing and relapse-lowering biological agent for patients with GCA, and TNF inhibitors pose the highest risk of infection among the biologics studied.

Introduction

Giant cell arteritis (GCA) is a type of vasculitis that primarily affects the medium and large arteries of the head and neck. GCA may cause significant morbidity and death due to aortic aneurysms, stroke, and blindness.[1] Glucocorticoids are often administered as part of treatment because they are effective in causing remission of illness.[2,3] Significant negative consequences such as an increased risk of infection, osteoporosis, and diabetes are associated with long-term steroid use.[4-6]

In recent years, there has been an increased interest in the use of biological therapies for the treatment of GCA in patients who cannot tolerate years.[7] Several randomized controlled trials on biological treatments for GCA, including tocilizumab, mavrilimumab, abatacept, and tumor necrosis factor (TNF) inhibitors have been reported.[5,8-14] Interleukin-6 (IL-6) receptor antagonist tocilizumab prevents the production of IL-6, a crucial cytokine in the inflammatory response. Mavrilimumab is a human monoclonal antibody targeting the granulocyte-macrophage colony-stimulating factor receptor-α, while abatacept is a fusion protein that prevents the activation of T cells. TNF is a pro-inflammatory cytokine that is thought to be involved in the pathophysiology of GCA. TNF inhibitors, such as infliximab, adalimumab, and etanercept, block the action of TNF.

Although the use of biological agents for the treatment of GCA is increasing, there are currently no data comparing the efficacy and safety of these agents. Network meta-analysis is a statistical method that allows comparisons between several therapies that have not been directly tested in a clinical study.[15-18] By integrating data obtained from numerous RCTs, a network meta-analysis may provide estimates of treatment effects for treatments that

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have not been directly compared.[19,20] We aimed to compare the efficacy and safety of biological agents in the treatment of GCA using a network meta-analysis of RCTs.

Methods

Criteria for considering studies for review

We conducted a thorough search for studies examining the efficacy and safety of biological agent therapies for patients with GCA. MEDLINE, EMBASE, and the Cochrane Controlled Trials Register were used as databases in the literature review (as of April 2023).

Search methods for identification of studies

The following terms were used in the search strategy: "tocilizumab," "abatacept," "mavrilimumab," "etanercept," "adalimumab," "infliximab," "biologic agent," "giant cell arteritis," and "efficacy," and "safety" (Supplementary data). To identify papers that were not included in the electronic databases, further investigation was conducted on the references of the retrieved publications.

Selection of studies

The following studies satisfied the inclusion criteria: (1) RCTs comparing biological agents with a placebo for the treatment of GCA, (2) studies providing endpoints for the clinical efficacy and safety of biological agents, and (3) studies including patients with GCA who complied with the standards outlined by the American College of Rheumatology in 1990.[21] The exclusion criteria were (1) redundant data, (2) insufficient data and (3) conference abstracts, unpublished data, and non-English papers. Two independent assessors (YH Lee and GG Song) selected studies in stages of this process (title, abstract and full-text) and a consensus was reached to settle the assessors' differences. Efficacy was defined as the number of patients who achieved remission and those who relapsed throughout the follow-up period.[22] The remission and relapse rates were determined using the criteria used in the first investigation. Safety was defined as the number of serious adverse events (SAEs) and frequency of infection.[23]

Data extraction

The following information was obtained from each investigation: efficacy and safety results, initial author, publication year, and features such as follow-up time. Two independent assessors extracted the data on the procedures and results. A consensus was reached to settle the assessors' differences.

Assessment of methodological quality

Two independent reviewers (YH Lee and GG Song) checked the methodological quality of studies. The RoB 2.0 version of the Cochrane risk-of-bias instrument was used to assess the quality of the RCTs, which covered 5 areas that pertain to the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported outcomes.[24] We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement while conducting our meta-analysis.[25]

Certainty assessment

Quality of evidence was evaluated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and divided into four categories: high, moderate, low and very low.[26]

Data analysis

The potential of the most effective agent was used to evaluate the efficacy and safety of the biological treatments for GCA. A Bayesian network meta-analysis with a fixed-effects model was performed using NetMetaXL[27] and the WinBUGS statistical analysis tool, version 1.4.3 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK). The Markov chain Monte Carlo approach was used to determine the magnitude of the aggregate effect. 10,000 burn-in cycles and 10,000 monitoring iterations were performed in each network. The probability of being the best, second best, etc. was calculated from the relative treatment efficacy data, and the rating for each treatment (known as the surface under the cumulative ranking curve [SUCRA]) was represented as a percentage,[28] with values ranging from 0 to 100 for treatments likely to be the best or worst, respectively. According to the SUCRA assessments of the outcomes, the treatments with the most noticeable effects were categorized and are shown as summary estimates in the league tables.[28] For trials with multiple arms, we documented pairwise odds ratios (ORs) and 95% credible intervals (CrI). If the 95% CrI was not equal to one, the combined findings were considered statistically significant. Inconsistency indicates the degree of discrepancy between the direct and indirect evidence.[29] A network meta-analysis must be conducted, and consistency must be quantified.[30] To evaluate the network inconsistency between direct and indirect estimates in each loop, the posterior mean deviation of the individual data points in the inconsistency model was compared with the posterior mean deviation in the consistency model.[31] A sensitivity test was performed by contrasting the random-effects and fixed-effects models. We looked at the funnel plot to see whether there was any publishing bias.

Results

Studies incorporated in the meta-analysis

A total of 656 papers were identified using computer or manual searches, and 12 were selected for full-text review based on the title and abstract. The fact that two studies lacked GCA data (other study)[32,33] and two were reviews[34,35] led to the exclusion of four of the 12 investigations. The inclusion criteria for the meta-analysis were fulfilled by eight RCTs (Figure 1).[8-14] Data from two independently treated groups were included in this qualifying studies.[13] Eight comparative studies including 533 individuals were

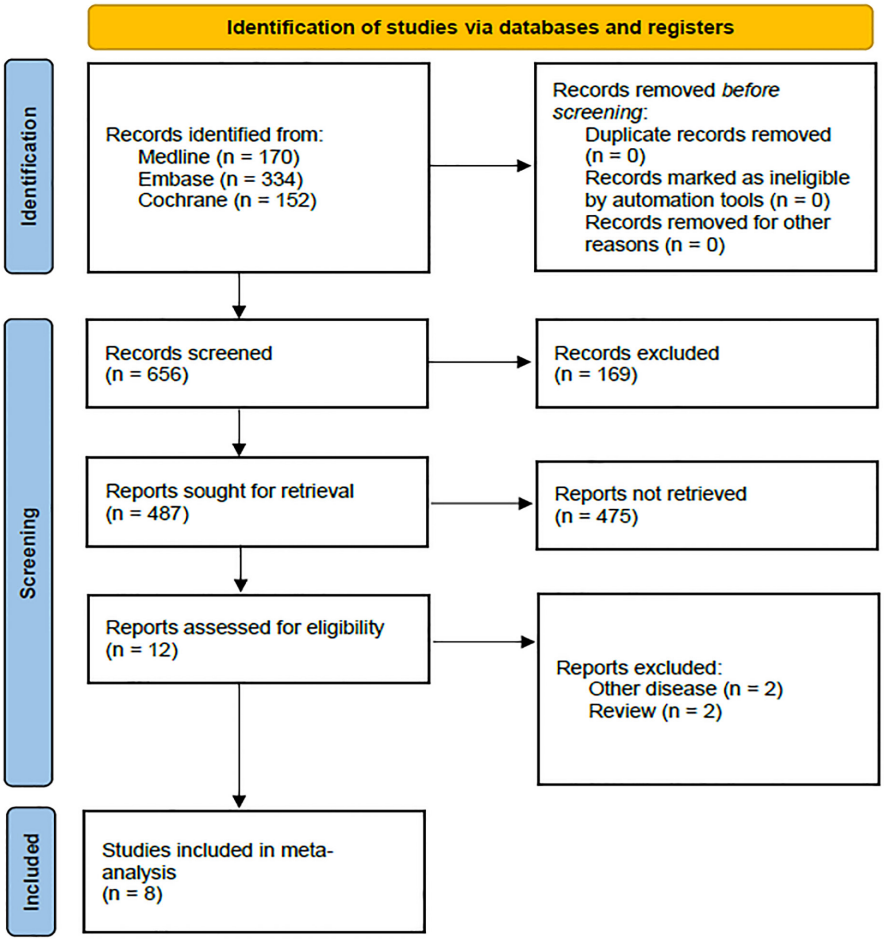

Figure 1. Flowchart displaying the method used to choose the study's articles.

included in the meta-analysis (Table 1). Tocilizumab was the subject of three trials; TNF inhibitors (etanercept, adalimumab, and infliximab) were assessed in three studies, mavrilimumab was examined in one study, and abatacept was examined in one study in both the GCA and control groups (Table 1). The combination of etanercept, adalimumab, and infliximab as a single intervention was sought after to evaluate the overall efficacy and safety of TNF inhibitors, because combining evidence of TNF inhibitors allows for comparisons with other classes of biologics used in similar disease settings. All trials supplied both efficacy and safety data, with the exception of one trial that did not offer information on SAE as a safety outcome for this network meta-analysis. One RCTs had a high risk of bias, four had some concerns, and three had a low risk of bias (Figure 2). Because all of the included studies were

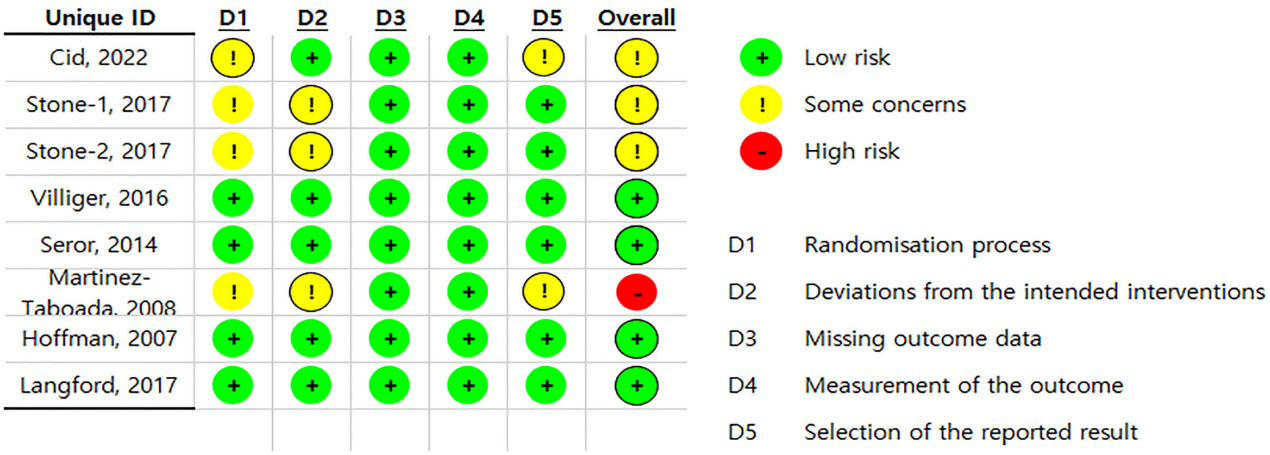

Figure 2. Methodological quality on risk of bias of randomized controlled trials.

Table 1. Characteristics of individual studies included in the meta-analysis.

A. Efficacy and safety

Authors (Ref)	Induction	Follow-up period	Number of Patients		Remission		Relapse		Serious adverse events		Infection	
			Biologic	Placebo	Biologic	Placebo	Biologic	Placebo	Biologic	Placebo	Biologic	Placebo
Cid, 2022[14]	Mavrilimumab	26 weeks	42	28	35	14	8	13	2	3	3	2
Stone-1, 2017[13]	Tocilizumab	52 weeks	100	51	56	9	23	25	15	13	75	33
Stone-2, 2017[13]	Tocilizumab	52 weeks	50	50	26	7	13	34	7	11	36	38
Villiger, 2016[11]	Tocilizumab	52 weeks	20	20	17	2	1	5	7	5	10	1
Seror, 2014[10]	Adalimumab	24 weeks	34	36	20	18	20	26	5	17	20	11
Martinez-Taboada, 2008[9]	Etanercept	12 months	8	9	4	2	4	7	3	3	4	4
Hoffman, 2007[8]	Infliximab	22 weeks	28	16	12	8	16	8	8	4	20	9
Langford, 2017[12]	Abatacept	12 months	20	21	10	7	10	14	10	8	na	na

B. Dosage of biological agents

Authors	Number of Patients		Biologics	Dose of biological	Efficacy
	Biologic	Placebo			
Cid, 2022[14]	42	28	Mavrilimumab	Mavrilimumab 150 mg or placebo injected subcutaneously every 2 weeks	Sustained remission at week 26 was 83% for mavrilimumab and 50% for placebo recipients (p=0.0038).
Stone-1, 2017[13]	100	51	Tocilizumab	Subcutaneous tocilizumab, at a dose of 162 mg, weekly	Sustained remission at week 52 occurred in 56% of the patients treated with tocilizumab, as compared with 14% of those in the placebo group ($P < 0{\cdot}001$).
Stone-2, 2017[13]	50	50	Tocilizumab	Subcutaneous tocilizumab, at a dose of 162 mg, every other week	Sustained remission at week 52 occurred in 53% of those treated with tocilizumab every other week, as compared with 14% of those in the placebo group ($P < 0{\cdot}001$).
Villiger, 2016[11]	20	20	Tocilizumab	Tocilizumab at 8 mg/kg every 4 weeks intravenously	Relapse-free survival was achieved in 17 (85%) patients in the tocilizumab group and 2 (20%) in the placebo group ($P = 0{\cdot}001$).
Seror, 2014[10]	34	36	Adalimumab	A 10-week subcutaneous treatment of adalimumab 40 mg every other week	The number of patients achieving remission was 20 (58.9%) and 18 (50.0%) in the adalimumab and placebo arm (P=0.46).
Martinez-Taboada, 2008[9]	8	9	Etanercept	Etanercept at 25 mg twice weekly (subcutaneous injection).	Fifty percent of the patients in the etanercept group and 22.2% in the placebo group were able to control the disease without corticosteroid therapy (NS).
Hoffman, 2007[8]	28	16	Infliximab	Infusions of infliximab, 5 mg/kg, or placebo at 0, 2, and 6 weeks and every 8 weeks thereafter.	Infliximab therapy did not increase the proportion of patients without relapse compared with placebo (43% vs.50%) (NS).
Langford, 2017[12]	20	21	Abatacept	Abatacept at a dose of 10 mg/kg (500 mg for 60 kg body weight, 750 mg for 60–100 kg, and 1,000 mg for .100 kg) by intravenous infusion on days 1, 15, 29 and week 8 and every 4 weeks thereafter.	The relapse-free survival rate at 12 months was 48% for those receiving abatacept and 31% for those receiving placebo ($P = 0.049$).

Table 1. Continued.

C. Study and patient numbers		
Treatment	**Study number**	**Patient number**
Placebo	8	221
Tocilizumab	3	170
TNF inhibitor	3	70
Abatacept	1	20
Mavrilimumab	1	42

NS: Not significant, NA: Not available

RCTs, the starting confidence of evidence was high. One of the eight studies included in the network meta-analysis exhibited a high risk of bias. Because of the nature of a network meta-analysis, this risk of bias may influence all network estimates across all comparisons. Except for one comparison, the overall certainty of the treatment effects was rated as moderate. Relevant details of the studies included in the meta-analysis are presented in Table 1.

Network meta-analysis of biological agent efficacy in RCTs

Tocilizumab is listed at the top left of the league table's diagonal (Tables 2 and 3). In comparison to TNF inhibitors, tocilizumab showed a greater rate of remission (OR, 5.68, 95% CrI, 2.21-14.79) (Table 2, Figure 3). Tocilizumab was most likely the best therapy based on the rate of remission, followed by mavrilimumab, abatacept, and TNF inhibitor, according to the ranking probability based on SUCRA (Table 3). Compared to TNF inhibitor, tocilizumab had a decreased recurrence rate (OR, 0.31, 95% CrI, 0.12-0.77) (Table 2, Figure 3). Tocilizumab was most likely a more effective relapse-based treatment than the other drugs, which were ordered, in decreasing order, as follows: mavrilimumab, abatacept, and TNF inhibitor (Table 3). This rating likelihood was based on the SUCRA.

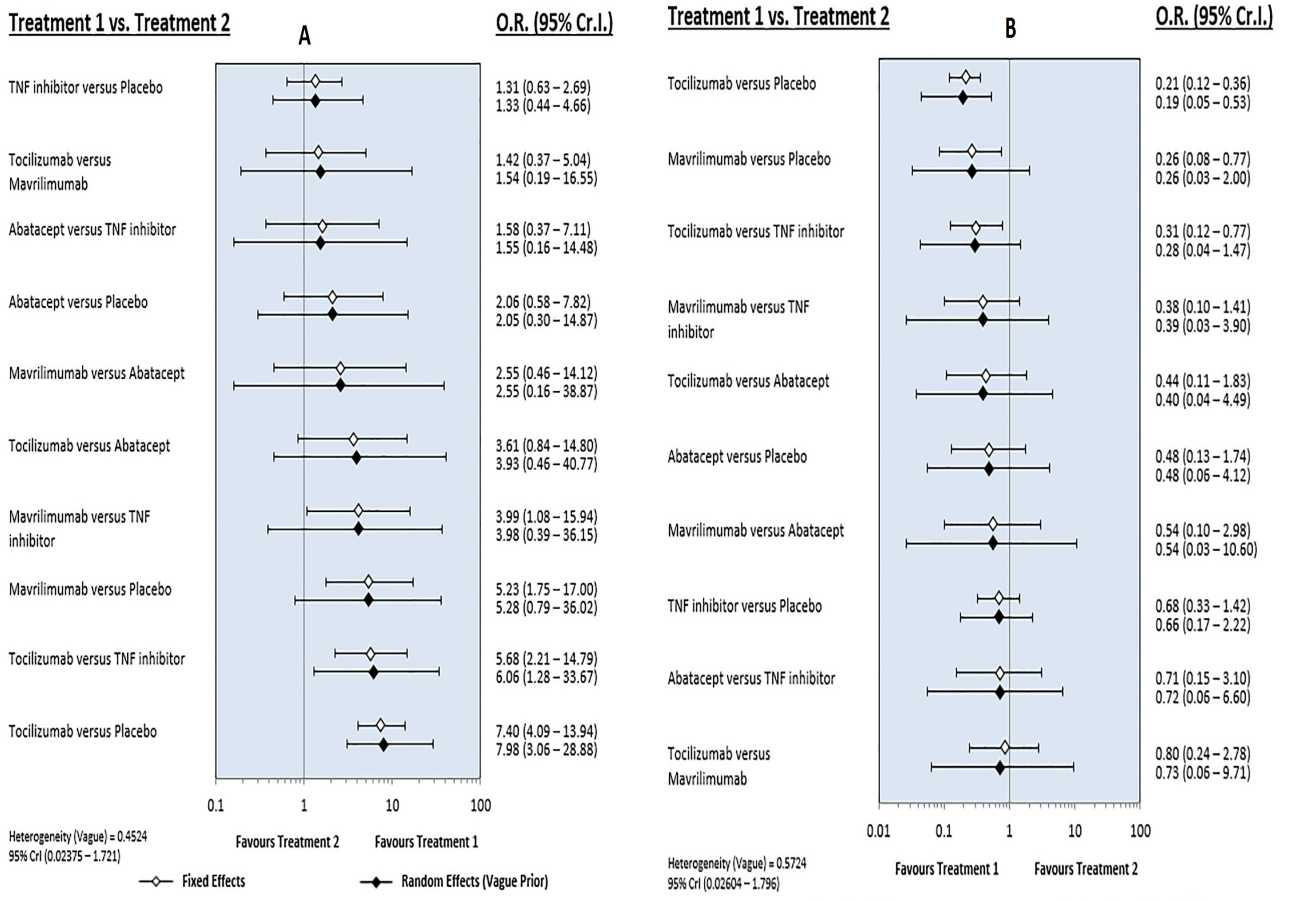

Figure 3. The comparative efficacy and safety of biologic treatments based on remission (a) and relapse (b), using Bayesian network meta-analysis of randomized controlled trials.

Table 2. League tables showing the results of the network meta-analyses comparing the effects of all drugs including ORs and 95% credible intervals.

A. Remission. OR > 1 means the treatment in the top left is better.				
Tocilizumab				
1.42 (0.37 – 5.04)	**Mavrilimumab**			
3.61 (0.84 – 14.80)	2.55 (0.46 – 14.12)	**Abatacept**		
5.68 (2.21 – 14.79)	3.99 (1.08 – 15.94)	1.58 (0.37 – 7.11)	**TNF inhibitor**	
7.40 (4.09 – 13.94)	5.23 (1.75 – 17.00)	2.06 (0.58 – 7.82)	1.31 (0.63 – 2.69)	**Placebo**
B. Relapse. OR < 1 means the treatment in the top left is better.				
Tocilizumab				
0.80 (0.24 – 2.78)	**Mavrilimumab**			
0.44 (0.11 – 1.83)	0.54 (0.10 – 2.98)	**Abatacept**		
0.31 (0.12 – 0.77)	0.38 (0.10 – 1.41)	0.71 (0.15 – 3.10)	**TNF inhibitor**	
0.21 (0.12 – 0.36)	0.26 (0.08 – 0.77)	0.48 (0.13 – 1.74)	0.68 (0.33 – 1.42)	**Placebo**
C. Serios adverse events. OR < 1 means the treatment in the top left is better.				
TNF inhibitor				
1.15 (0.14 – 11.89)	**Mavrilimumab**			
0.85 (0.31 – 2.25)	0.73 (0.08 – 5.80)	**Tocilizumab**		
0.45 (0.20 – 0.98)	0.39 (0.04 – 2.84)	0.53 (0.29 – 0.98)	**Placebo**	
0.27 (0.06 – 1.20)	0.23 (0.02 – 2.43)	0.32 (0.08 – 1.33)	0.60 (0.17 – 2.12)	**Abatacept**
D. Infection. OR < 1 means the treatment in the top left is better.				
Placebo				
0.96 (0.11 – 6.79)	**Mavrilimumab**			
1.08 (0.00 – 805.15)	1.16 (0.00 – 1203.00)	**Abatacept**		
0.68 (0.39 – 1.17)	0.71 (0.09 – 6.48)	0.63 (0.00 – 314.40)	**Tocilizumab**	
0.41 (0.19 – 0.84)	0.42 (0.05 – 4.21)	0.38 (0.00 – 197.50)	0.60 (0.24 – 1.49)	**TNF inhibitor**

RCT network meta-analysis of biological agent safety

Between the treatments, the number of SAEs did not substantially differ, except between the TNF inhibitor and placebo, and between mavrilimumab and placebo (Table 2, Figure 4). As it demonstrated a lower incidence of infection than the other treatments, placebo was more likely to be the safest option, followed by mavrilimumab, abatacept, tocilizumab, and a TNF inhibitor (Table 2). However, compared to TNF inhibitors, the probability of infection with placebo decreased (OR 0.41, 95% CrI, 0.19-0.84) (Table 2, Figure 4).

Inconsistency and Sensitivity

The possibility that these discrepancies had a substantial negative influence on how well the network meta-analysis performed was minimal according to the inconsistency diagrams analyzing network disparities between direct and indirect estimates. Additionally, the outcomes of the random- and fixed-effects models were comparable, demonstrating the validity of the NMA findings (Figure 2). The findings of the sensitivity analysis, which excluded the research with a high risk of bias, were similar to the overall results. The funnel plot demonstrated symmetry, suggesting evidence of no publication bias (Figure 5).

Table 3. Rank probability of efficacy and safety of biologic agents based on the remission, relapse, serious adverse events, and infection.

Treatment	SUCRA (Surface under the cumulative ranking curve)			
	Remission	Relapse	Serious adverse events	Infection
Tocilizumab	0.916	0.877	0.752	0.730
Mavrilimumab	0.784	0.760	0.723	0.593
Abatacept	0.444	0.477	0.670	0.562
TNF inhibitor	0.266	0.313	0.249	0.436
Placebo	0.091	0.072	0.107	0.179

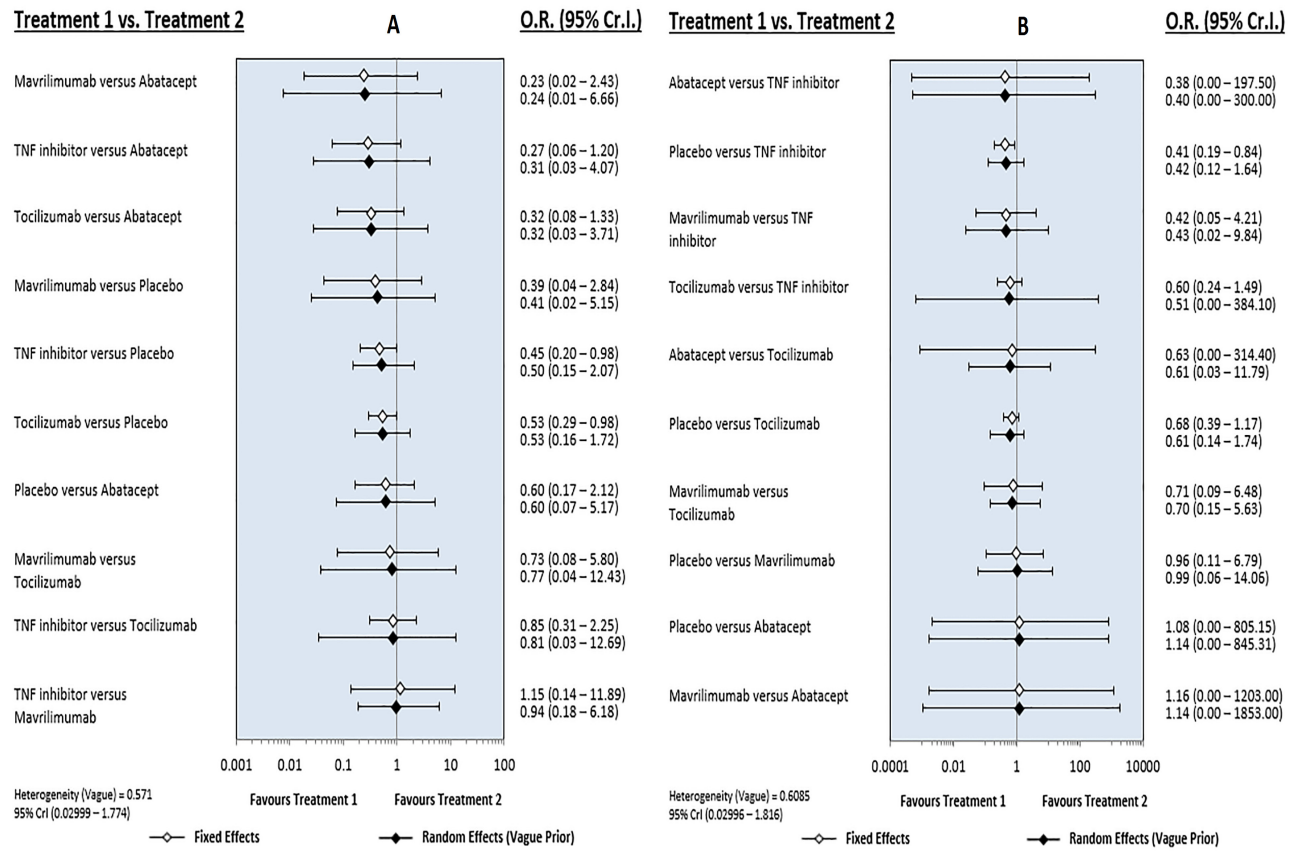

Figure 4. The comparative efficacy and safety of biologic treatments based on serious adverse events (a) and infection (b) using Bayesian network meta-analysis of randomized controlled trials.

Discussion

This network meta-analysis showed that tocilizumab was more effective in creating remission than TNF inhibitors and placebo, with a greater incidence of remission observed in individuals with GCA receiving tocilizumab. Tocilizumab was the most successful medication for lowering the risk of recurrence because it had a lower relapse rate than TNF inhibitors. According to the SUCRA rating, tocilizumab was the most successful therapy for remission and relapse prevention, followed by mavrilimumab, abatacept, and TNF inhibitors. The placebo was most likely the safest medication, followed by mavrilimumab, abatacept, tocilizumab, and TNF inhibitors, according to the SUCRA ranking.

Tocilizumab, abatacept, and mavrilimumab were shown to be effective in the treatment of GCA, however TNF inhibitors were not. The network meta-analysis conducted in this study has shed light on the comparative efficacy and safety of biological agents in the treatment of GCA. Our findings reveal several important insights that merit further exploration. First and foremost, our analysis suggests that tocilizumab emerges as a promising frontrunner in the treatment of GCA. Tocilizumab's superior efficacy in inducing remission compared to TNF inhibitors and

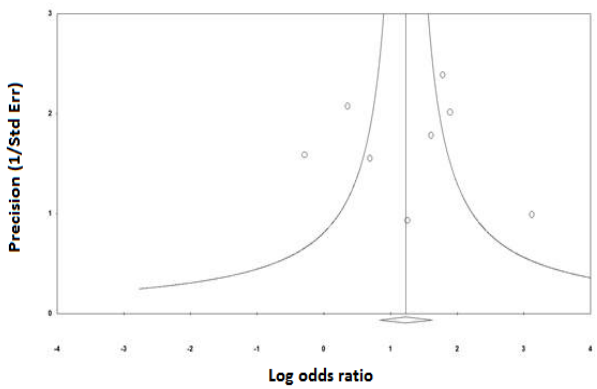

Figure 5. Funnel plot of studies that examined remission in network meta-analysis

placebo, as well as its ability to significantly lower the risk of recurrence, underscores its potential as a first-line therapy for this challenging condition. The mechanism of action of tocilizumab, targeting the IL-6 receptor and blocking TNF-α, appears to be particularly well-suited to reduce inflammation in GCA patients.[36] This suggests a mechanistic advantage over TNF inhibitors, which solely target TNF-α.[37] Furthermore, the ranking based on the Surface Under the Cumulative Ranking (SUCRA) method consistently places tocilizumab at the top in terms of both remission induction and relapse prevention, followed by mavrilimumab and abatacept, which are viable alternative options. TNF inhibitors, while ranking lower, may still have a role to play in specific cases. These rankings should inform clinical decision-making and guide the selection of the most appropriate biological agent for individual GCA patients. However, it is essential to acknowledge the complex nature of GCA treatment and the various factors contributing to the observed differences in efficacy and safety among these biological agents. Patient-specific characteristics, such as disease duration, disease activity, and previous treatment history, likely influence treatment outcomes. A more personalized approach to GCA management, considering these factors, may yield even better results. Future research should delve deeper into patient subgroups to identify which individuals are most likely to benefit from each treatment option.

The observed variations in the efficacy and safety of biological agents for the treatment of GCA may be attributed to several variables. First, the mechanism of action of each biological agent may be unique, leading to varying degrees of success in causing remission and avoiding recurrence. Tocilizumab, which targets the IL-6 receptor and blocks TNF-α, may be more efficient in reducing inflammation in patients with GCA than TNF inhibitors, which block TNF-α. Second, the observed discrepancies in treatment results may be attributed to variances in patient characteristics and illness severity. Individuals in the included trials may have had different illness durations, activity levels, and past treatment histories, which may have affected how well they responded to therapy. Third, the observed discrepancies in treatment results may have been influenced by variances in the research design and methodological quality of the included studies. The reliability and generalizability of the findings may have been affected by smaller sample sizes, shorter follow-up periods, and increased risk of bias. Overall, it is important to consider these possible confounding factors when evaluating the study results, and future research should focus on comparing the efficacy and safety of biological treatments for GCA. The network meta-analysis findings highlight tocilizumab as the top choice for GCA treatment, excelling in remission induction and relapse prevention, and mavrilimumab and abatacept are viable alternatives. Although TNF inhibitors rank lower, they remain options in specific cases. To advance GCA treatment, future research should delve into long-term safety and efficacy, patient subgroups, combination therapies, safety profiles, quality of life outcomes, cost-efficacy, and biosimilar options, providing a more comprehensive and personalized approach for GCA management.

However, there are limitations to this research that need to be considered. First, the RCT number included in this NMA was only eight RCTs. The ability to perform subgroup analysis based on patient characteristics or illness severity was hampered. Second, the follow-up periods in the included studies differed, which may have affected the accuracy of the relapse rate. In addition, the analysis did not include data from observational studies or from the actual world. Third, it was better to include comparative studies between two biological treatments, too. However, there were no such studies.

Conclusion

The findings of this study suggest that tocilizumab may be the best treatment for patients with GCA in terms of generating remission and lowering the risk of recurrence. This study also highlights the need to consider the higher risk of infection caused by TNF inhibitors when deciding on the best course of action for patients with GCA. The results of this study need to be confirmed by other studies with larger sample sizes and longer follow-up periods to provide more convincing evidence of the relative efficacy and safety of biological agents for treating GCA.

Author Contributions

Young Ho Lee: Conceptualization, Investigation, Formal Analysis, Writing - Original Draft. Gwan Gyu Song: Conceptualization, Investigation, Formal Analysis, Writing - Review & Editing.

Conflict of Interest

The authors have no conflicts of interest to declare.

Supplementary Data

Supplementary data, search strategy, are available at https://doi. org/10.34172/PS.2023.26.

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