Efficacy and Safety of Biologics and Immunosuppressants in Maintenance Therapy for Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Network Meta-Analysis

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ABSTRACT

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a potentially life-threatening systemic autoimmune disease. This study aims to compare the effectiveness and safety of biologics and immunosuppressive agents in the maintenance treatment of AAV. A comprehensive search was conducted in Medline, PubMed, Embase, and the Cochrane Library databases to identify the relevant randomised controlled trials (RCTs). Nine RCTs involving 1,157 patients were included. For primary efficacy, rituximab had a lower relapse rate than azathioprine (AZA) and mycophenolate mofetil (MMF) (odds ratio (OR): 0.47, 95% confidence interval (CI): 0.26-0.84 and OR: 0.23, 95% CI: 0.08-0.68, respectively). Based on the result of the surface under the cumulative ranking curve (SUCRA), rituximab had the highest probability of reducing relapse (SUCRA = 86.6%), followed by cyclophosphamide (CYC), belimumab + AZA, methotrexate (MTX), AZA, and MMF. Regarding major relapse, rituximab also showed the highest probability (SUCRA = 93.6%). Concerning safety, there were no significant differences in the incidence of SAEs and serious infection among the different medicines. According to the SUCRA, MMF had the lowest probability of SAEs and serious infection. In conclusion, rituximab may be a treatment method for effectively reducing relapses in AAV patients during maintenance therapy among the medicines investigated. MMF has shown the lowest incidence of SAEs and serious infection.

Key Words: *Immunosuppressant, Rituximab, Meta-analysis*.

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INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare, heterogeneous, and potentially life-threatening systemic autoimmune disease that can affect various organs.[1,2] It encompasses different subtypes, including granulomatosis with polyangiitis (GPA), microscopic polyan-giitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[3,4] GPA and MPA are the two main subgroups within the AAV classification.[4,5] Without treatment, patients with AAV face a mortality rate of 93% within two years, primarily due to renal and respiratory failure.[6] The use of immunosuppressants and biologics has improved the survival rate of patients.[7] Rituximab is a commonly used biological preparation that has proven effective relief induction therapy in treating AAV.[8,9]

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Nevertheless, over 50% of patients experience relapse within five years of diagnosis, even after rituximab-induced remission, particularly those with a relapse history.[10,11] Contemporary therapeutic strategies for AAV encompass the utilisation of cyclophosphamide (CYC) or rituximab for remission induction, accompanied by less toxic immunosuppressive agents such as azathioprine (AZA), mycophenolate mofetil (MMF), or methotrexate (MTX) for maintenance therapy.[7] However, the potential drug toxicities associated with these treatments increase the risk of mortality and lead to serious side effects, including opportunistic infections, infertility, and malignancy, thereby presenting challenges for the long-term management of AAV in clinical practice.[5,12]

Rituximab is a B-cell depleting agent that effectively reduces the risk of recurrence of GPA and MPA, making it increasingly recognised as the standard therapy for inducing remission of AAV.[7,12] In terms of induction therapy, CYC shows efficacy comparable to rituximab.[13] Despite the use of the therapies above, relapse remains a major clinical challenge for AAV, leaving uncertainty about the optimal strategy for preventing relapse after remission. Biologics and immunosuppressants have demonstrated effectiveness as maintenance therapy in RCTs of AAV.[14-22] However, the evidence from various RCTs

comparing the relative efficacy and safety of rituximab, MMF, MTX, AZA, CYC, and belimumab as maintenance therapy for AAV remains inconclusive. There is limited evidence to recommend any specific agent as the best choice for AAV maintenance therapy. Therefore, the aim of this network meta-analysis was to evaluate the efficacy and safety of biologics and immunosuppressants as AAV maintenance therapy.

METHODOLOGY

This review adhered to the guidelines set forth by the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements.[23] The study protocol was duly registered with Prospero (CRD42023450314). Two authors systematically searched the literature for studies investigating the efficacy and safety of rituximab, MMF, MTX, CYC, belimumab, and AZA as maintenance therapy in patients with AAV.

Medline (from January 1, 1946), PubMed (from January 1, 1966), Embase (from January 1, 1974), and the Cochrane Library (from January 1, 1992) databases were searched to identify relevant RCTs up to May 2023. This search was limited to English language publications on human subjects. The authors adopted the following search terms: (Rituximab OR rituximab CD20 antibody OR mycophenolate mofetil OR mycophenolate sodium OR cyclophosphamide OR cytophosphane OR cyclophosphamide monohydrate OR belimumab OR methotrexate OR methotrexate sodium OR azathioprine OR azathioprine sodium sendoxan) AND (anti-neutrophil cytoplasmic antibody-associated vasculitis OR ANCA-associated vasculitis OR vasculitide, ANCA-associated). Additionally, the reference lists of the retrieved publications were manually screened to identify any additional relevant articles not captured by the electronic searches. Both authors performed the eligibility assessment independently, and disagreements were resolved through consensus-based discussions.

The criteria to include studies were RCTs. The study population had to consist of patients diagnosed with AAV, confirmed either by positive ANCA or histological verification and maintenance treatments for active AAV patients encompassed using rituximab, MMF, MTX, CYC, belimumab, or AZA (both as single entities and in combination). Exclusion criteria for study selection were non-RCTs; studies with insufficient data, duplicated publications, conference reports, and systematic reviews. Two researchers conducted independent literature screening based on pre-defined inclusion and exclusion criteria. They excluded irrelevant literature and carefully reviewed the full text of potentially eligible studies. Any discrepancies were resolved through discussions or consultations with a third researcher. The extracted data from the included studies consisted of the following information: First author, publication year, sample size, intervention measures, outcomes, quality assessment, and adverse reactions.

Based on the risk bias assessment tool from the systematic review provided by the Cochrane Collaboration network, the overall assessment was conducted using seven criteria categorised as high, moderate, or low risk of bias.[24,25] Two authors independently evaluated the risk of bias for each question. In the event of any disagreement, the study group held discussions to reach a consensus regarding the results.

After performing data extraction and conducting a quality assessment of the included studies, the authors used mvmeta and network packages in Stata 17.0 software and Review Manager (RevMan) version 5.4 to conduct a network meta-analysis.[26] The primary efficacy outcome was relapse, and the secondary outcome was major relapse. The primary safety outcome was serious adverse events (SAEs), and the secondary outcome was serious infection. Major relapse is defined as the reappearance or worsening of the disease characterised by a Birmingham vasculitis activity score (BVAS) greater than 0 and involvement of at least one major organ, a life-threatening manifestation, or both. SAEs are defined as adverse events greater than Grade III on any given scale or meet the criteria for serious adverse events defined by the U.S Food and Medicine Administration. The node-split model was employed to examine inconsistencies.[27] In cases where there was no statistically significant difference ($p > 0.05$), indicating minimal heterogeneity among the included studies, the consistency model was used for network meta-analysis. Alternatively, the inconsistency model was employed for network meta-analysis.[28,29] Meta-analysis was conducted using the frequentist random-effect model, and odds ratio (OR) with 95% confidence interval (CI) was obtained. If the 95% CI did not encompass 1 for OR, it indicated significant differences between interventions.[30,31] A two-tailed p-value of <0.05 was set for statistical significance. The surface under the cumulative ranking value (SUCRA) was used to rank the relative efficacy and safety of interventions, with higher SUCRA values indicating better intervention.[32]

RESULTS

The search yielded 11,550 articles, from which 164 potentially eligible articles were retrieved. Ultimately, nine articles involving 1,157 participants were included in the study. The selection process is illustrated in Figure 1. The Figure 2 shows the evaluation of the quality of RCTs in the study using the Cochrane risk of bias tool.

In the meta-analysis, nine studies were included, all of which reported both efficacy and safety outcomes.[14-22] Two studies solely focused on relapse data as the efficacy outcome for this particular analysis.[14,17] Additionally, one article specifically reported the combined usage of belimumab and AZA.[20] The primary characteristics encompassing these studies are displayed in Table I.

In evaluating the primary efficacy outcome, rituximab significantly reduced relapse rates more than AZA and MMF (OR: 0.47, 95% CI: 0.26-0.84 and OR: 0.23, 95% CI: 0.08-0.68, respectively). Furthermore, CYC demonstrated a lower relapse rate compared to MMF (OR: 0.31, 95% CI: 0.10-0.98, Figure 3).

Table I: Characteristics of included studies.

Studies	AAV type	Remission induction	Follow-up duration	Treatment arms	Number of patients	Relapse	Major relapse	SAEs	Serious infection
Terrier *et al.*[15] 2018	MPA 23, GPA 87, RLV 5	Rituximab	60 month	Rituximab/AZA	57/58	24/37	16/29	23/27	15/16
Guillevin *et al.*[22] 2014	MPA 23, GPA 87, RLV 5	Rituximab	28 month	Rituximab/AZA	57/58	9/26	3/17	45/44	11/8
Hiemstra *et al.*[21] 2010	MPA 100, GPA 56	CYC	4 year	MMF/AZA	76/80	42/30	18/10	8/13	3/8
Pagnoux *et al.*[17] 2008	MPA 30, GPA 96	CYC	36 month	MTX/ AZA	63/63	21/23	NA	11/5	5/1
Jayne *et al.*[19] 2003	MPA 60, GPA 95	CYC	18 month	CYC/AZA	79/76	10/11	5/5	7/8	3/4
Maritati *et al.*[18] 2017	GPA 27, MPA 14, EGPA 30	CYC	24 month	CYC/MTX	33/38	7/9	5/5	4/5	1/2
Walsh *et al.*[14] 2014	PR3-ANCA 110, others 34	CYC	10 year	CYC/AZA	73/71	26/37	NA	17/15	4/8
Jayne *et al.*[20] 2019	GPA 83, MPA22	CYC or Rituximab	3 year	Belimumab + AZA/AZA	53/52	6/8	1/0	18/16	4/4
Smith *et al.*[16] 2023	PR3-ANCA 123, MPO-ANCA 47	Rituximab	48 month	Rituximab/AZA	85/85	25/28	5/11	37/48	15/19

AAV: Antineutrophil cytoplasmic antibody-associated vasculitis; SAEs: Serious adverse events; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis; RLV: Renal-limited vasculitis; EGPA: Eosinophilic granulomatosis with polyangiitis; PR3: Proteinase 3; MPO: Myeloperoxidase; AZA: Azathioprine; MMF: Mycophenolate mofetil; MTX: Methotrexate; CYC: Cyclophosphamide; Mo: Months; Yr: Years; Na: Not available.

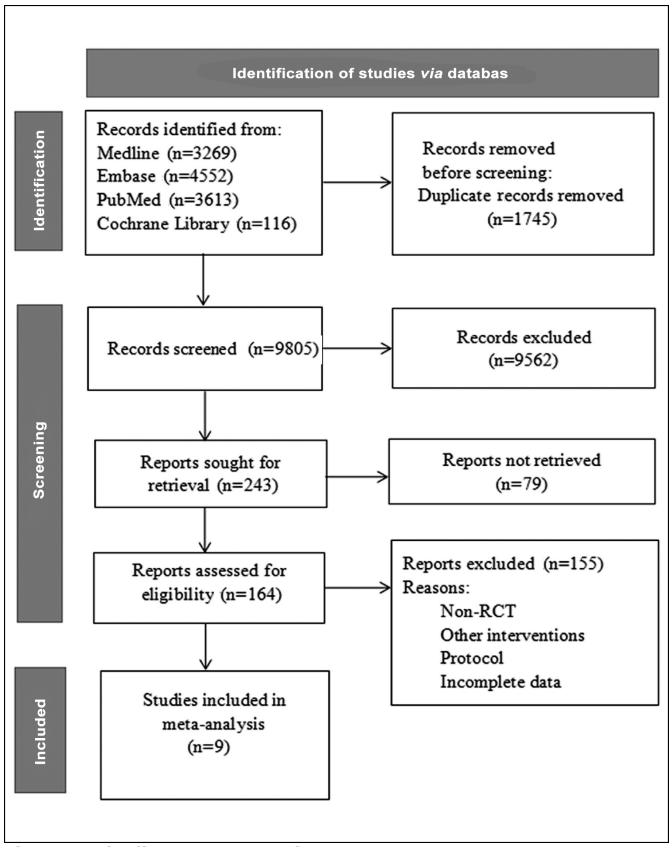

Figure 1: The literature screening process.

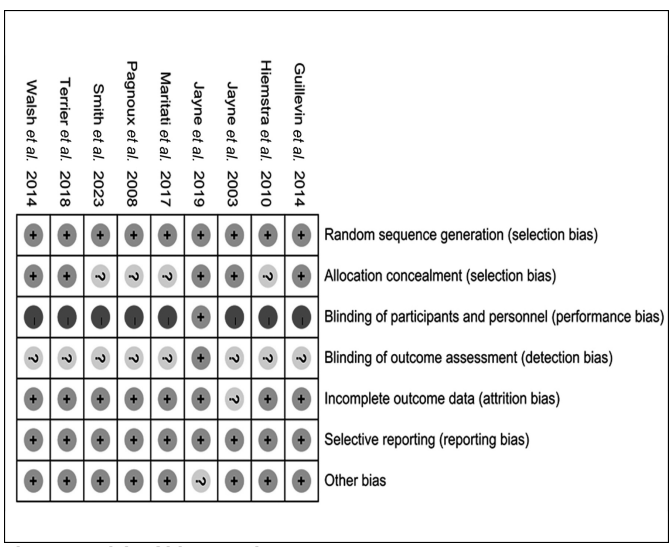

Figure 2: Risk of bias graph.

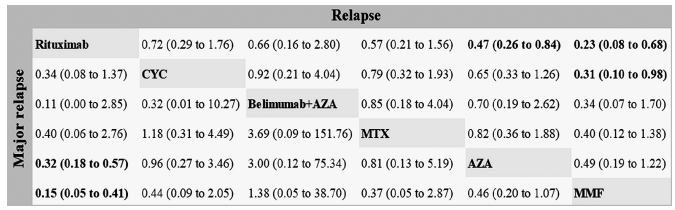

Figure 3: The network meta-analysis for the efficacy outcome.
AZA: Azathioprine; MMF: Mycophenolate mofetil; MTX: Methotrexate; CYC: Cyclophosphamide.

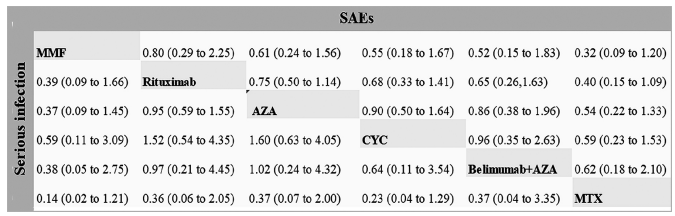

Figure 4: The network meta-analysis for the safety outcome.
AZA: Azathioprine; MMF: Mycophenolate mofetil; MTX: Methotrexate; CYC: Cyclophosphamide.

The SUCRA values indicated that rituximab was the most probable treatment to decrease relapses (SUCRA = 86.6%), followed by CYC (SUCRA = 67.2%), belimumab + AZA (SUCRA = 58.6%), MTX (SUCRA = 49.0%). MMF and AZA had the lowest efficacy (SUCRA = 5.2% and 33.4%, respectively, Figure 4). In terms of major relapse, rituximab exhibited a significantly lower relapse rate compared to AZA and MMF (OR: 0.32, 95% CI: 0.18-0.57 and OR: 0.15, 95% CI: 0.05-0.41, respectively, Figure 3). According to the SUCRA values, rituximab demonstrated the highest probability of being the superior therapy for major relapse compared to other agents (SUCRA = 93.6%). The subsequent order of therapies based on their potential for reducing major relapse was MTX (SUCRA = 58.7%), AZA (SUCRA = 52%), CYC (SUCRA = 51.8%), belimumab + AZA (SUCRA = 24.9%), and MMF (SUCRA = 19.0%, Figure 4).

For safety outcomes, there was no significant difference in the incidence of SAEs and serious infections between medicines (Figure 5). Based on the SUCRA values, MMF appears to be the most favourable treatment option regarding safety, exhibiting a lower incidence of SAEs and serious infections than other medicines (Figure 4).

There is no evidence to suggest statistically significant inconsistency in relapse, major relapse, SAEs, and serious infection.

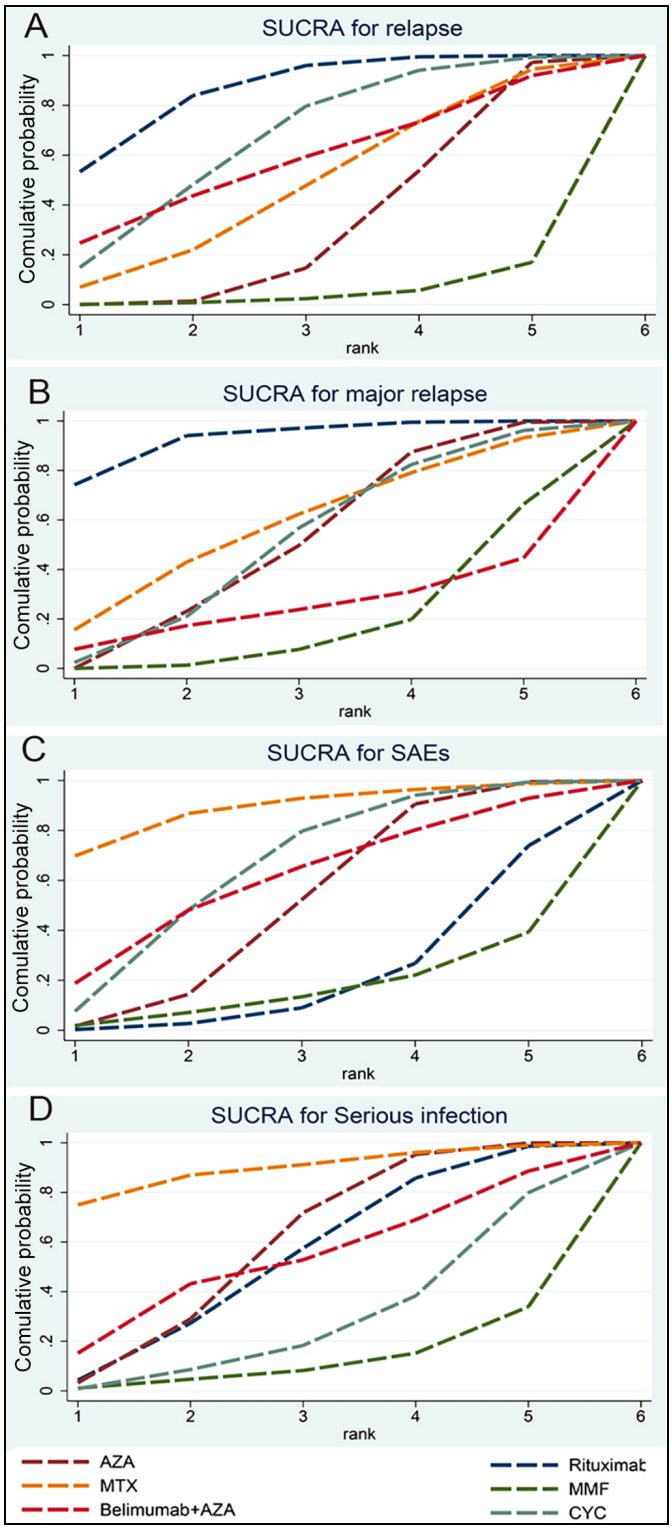

Figure 5: The surface under the cumulative ranking and probability.
AZA: Azathioprine; MMF: Mycophenolate mofetil; MTX: Methotrexate; CYC: Cyclophosphamide.

DISCUSSION

There have been significant improvements in managing patients with AAV. However, there are still challenges to overcome, especially concerning late relapses, reduction of glucocorticoid use, and the handling of treatment-related side effects and comorbidities.[33,34] High-quality RCTs have confirmed that rituximab effectively reduces relapse rates and has a safety profile similar to AZA.[15,16,22] Incorporating belimumab into the AZA regimen did not significantly decrease the risk of relapse in AAV maintenance.[20] CYC and MTX effectively maintained remission, with the CYC group experiencing five major and two minor relapses, while the MTX group had five major and four minor relapses.[18] MTX, MMF, and CYC were all shown to prevent relapse and were comparable to AZA in effectiveness.[14,18,19,21] However, there is still uncertainty regarding the best medicine selection for maintenance therapy in AAV.

This network meta-analysis included nine RCTs, with sample sizes ranging from 71 to 170, totalling 1,157 patients with AAV. This study compared the effectiveness and safety of rituximab, MMF, MTX, CYC, belimumab + AZA, and AZA as maintenance therapies for AAV patients. Specifically, among the nine studies considered, eight directly compared the efficacy of these maintenance drugs with AZA. The authors ranked the effectiveness and safety of biologics and immunosuppressive agents used in the maintenance treatment of patients with AAV. Rituximab is a potentially superior choice for remission maintenance therapy, showing better effectiveness compared to AZA, MMF, MTX, CYC, and the combination of belimumab with AZA.

CYC has been associated with potential risks such as diminished ovarian reserve, premature ovarian failure, male infertility, bladder cancer, myelodysplastic syndrome, and other malignancies.[34,35] Consequently, the long-term safety of CYC has garnered widespread attention and concern. Rituximab, MTX, and AZA offer the possibility of diminishing patients' exposure to CYC-related toxicity without increasing the relapse rate.[13,36] The safety analysis reveals no significant difference in severe adverse reactions and infections among all medicines. However, MMF appears to be the safest option compared to other medications. This network meta-analysis indicates that despite showing variations in treatment effectiveness in reducing relapse, additional studies are necessary to determine the best induction therapy, the ideal duration, and the dosage for maintenance therapy. A meta-analysis presented data from five randomised controlled trials, demonstrating the advantages of rituximab treatment in reducing relapses, similar to this research finding.[37] However, this study did not find substantial differences in terms of safety.

This study delivers more dependable results due to its inclusion of the latest trials and an RCT involving combination therapy. This meta-analysis has limitations such as variability in patient populations, baseline clinical characteristics, medicine dosages, and treatment durations among the included RCTs. Additionally, some treatment comparisons are indirect, which may be subject to additional confounding

covariates. Ultimately, only one study was included that investigated the combination of AZA with belimumab. The conclusions drawn from this singular study should be interpreted with caution. This finding underscores the need for more extensive trials to validate these results and explore potential combination therapies involving belimumab further.

CONCLUSION

The authors recommend rituximab as the preferred option for the maintenance therapy of AAV patients. Among the alternatives, it is worth noting that MMF carries the lowest risk of SAEs and serious infections. However, additional long-term head-to-head controlled trials are required to evaluate maintenance therapy medicines' relative efficacy and safety in patients with AAV.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
LZ, MG, XC: Conceived and designed the study and wrote the manuscript's first draft.
MG, SG, KL, YF, XC: Selected the articles, extracted and interpreted the data, and wrote the manuscript's final version.
All authors approved the final version of the manuscript to be published.

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