A Meta-Analysis of the Safety and Efficacy of Maintenance Therapies for Antineutrophil Cytoplasmic Antibody Small-Vessel Vasculitis

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Introduction: To compare the efficacy and safety of different regimens used for maintenance of remission in patients with antineutrophil cytoplasmic antibody (ANCA) vasculitis.

Methods: This network meta-analysis studied adult patients with ANCA vasculitis in complete remission, who were maintained with various regimens, excluding patients with eosinophilic granulomatosis with polyangiitis (GPA) and those who have ended up in end-stage kidney disease. Outcomes of interest included relapse (any/major), relapse-free survival, and adverse effects. PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and Google Scholar were systematically searched from inception.

Results: Overall, the meta-analysis was based on 10 reports, describing the outcomes of 7 randomized controlled trials (RCTs) including 752 patients with ANCA vasculitis. Relapse-free survival was significantly worse with the use of azathioprine (hazard ratio [HR]: 2.11, 95% CI: 1.19–3.74), methotrexate (HR: 2.51, 95% CI: 1.24–5.08), and mycophenolate mofetil (HR: 3.57, 95% CI: 1.70–7.46) compared with the use of rituximab. Outcomes estimated for azathioprine (HR: 0.59, 95% CI: 0.37–0.94), cyclophosphamide (HR: 0.39, 95% CI: 0.20–0.75), and leflunomide (HR: 0.30, 95% CI: 0.11–0.84) were better than those for mycophenolate mofetil. When examining relapse-free survival, relapses were more likely with use of azathioprine (odds ratio [OR]: 2.15, 95% CI: 1.00–4.59) and mycophenolate mofetil (OR: 4.42, 95% CI: 1.63–11.94) compared with the use of rituximab. The risk of major relapse calculated for azathioprine (OR: 2.39, 95% CI: 1.10–5.19), methotrexate (OR: 3.18, 95% CI: 1.14–8.89), and mycophenolate mofetil (OR: 5.20, 95% CI: 1.65–16.37) was higher than that for rituximab. The rates of serious adverse effects did not differ significantly among interventions.

Conclusion: Rituximab appears predominant in maintaining remission in patients with ANCA vasculitis with no cost in adverse events.

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KEYWORDS: ANCA; immunosuppression; maintenance; relapse; remission; vasculitis

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ANCA vasculitis is a group of diseases characterized by inflammation of the blood vessels often leading to tissue destruction and organ failure.1 Timely diagnosis is essential to enable prompt treatment initiation and improve prognosis by limitation of irreversible organ damage. Induction of remission is achieved in the vast majority of patients by high-dose glucocorticoid therapy combined with cyclophosphamide or rituximab, followed by oral glucocorticoid tapering. Over the past 2 decades, considerable progress has been made in maintaining remission in patients with ANCA vasculitis using a variety of medications, including rituximab, azathioprine, mycophenolate, methotrexate, and glucocorticoids. However, although survival has improved dramatically over the last decades, relapse rates remain significant for certain patients, stressing the need for advocation of new therapeutic strategies.2–4 Factors that have been associated with increased risk of relapse include proteinase 3 (PR3)-ANCA seropositivity, lung or upper respiratory involvement, prior history of relapsing disease, persistence of elevated ANCA titers, particularly PR3-ANCA, and rising ANCA titers.4–6 Optimization of immunosuppressive regimens, used

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for remission maintenance, along with a personalized approach, based on patient-specific and disease-specific factors would balance the benefits of disease quiescence with the cost and morbidity of prolonged immunosuppression. This is particularly important given that most deaths occurring more than a year after the diagnosis of ANCA vasculitis are due to infection, malignancy, and cardiovascular disease rather than active vasculitis. The past 2 decades have greatly advanced the approach to maintenance of remission, with several effective agents and treatment strategies now in use.

The present network meta-analysis aimed to accumulate current literature knowledge and compare the efficacy and safety of different regimens used for maintenance of remission in patients with ANCA vasculitis.

**METHODS**

**Study Design and Definitions**

This network meta-analysis was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-analyses guidelines. The protocol of the study has been prospectively registered and is publicly available (https://doi.org/10.17504/protocols.io.bvq7m5zn).

All patients were tested for ANCA by immunofluorescence or enzyme-linked immunosorbert assay or both. Clinical phenotypes of pauci-immune vasculitis were assigned according to the Chapel Hill vasculitides nomenclature Consensus Conference. Thus, a diagnosis of GPA was defined by the presence of necrotizing granulomatous inflammation in any tissue by histology, and/or imaging showing pulmonary nodules or cavities (noninfectious) and/or bony erosions, and/or subglottic stenosis in the upper respiratory tract. Eosinophilic GPA was defined by the presence of asthma, eosinophilia, and necrotizing granulomatous inflammation. Microscopic polyangiitis was defined by systemic necrotizing small-vessel vasculitis without evidence of granulomatous inflammation or asthma. Organ involvement was defined by previously described criteria. Outcomes of interest included relapse, relapse-free survival, major relapse, and serious adverse events. Remission, which followed response to immunosuppressive treatment, was defined as the stabilization or improvement of kidney function, as measured by serum creatinine levels, with resolution of hematuria in patients with kidney involvement or otherwise the absence of other manifestations of systemic vasculitis for >1 month. Persistent proteinuria with bland urine sediment was not considered indicative of active renal vasculitis. Relapse could only be recorded among patients who had achieved remission and was characterized by recurrent or new signs and symptoms of active vasculitis in any organ. Relapse-free survival was defined as the time from remission to the first relapse (major or any other), withdrawal, death or loss to follow-up, or the end of the follow-up period. Major relapse was defined as the new appearance of major organ involvement attributable to active vasculitis with a Birmingham Vasculitis Activity Score > 0. End-stage kidney disease was characterized by the initiation of chronic dialysis. Serious adverse events were defined as those that required hospitalization.

**Eligibility Criteria**

The target population of the study consisted of adult patients with ANCA vasculitis in complete remission including the clinical phenotypes of GPA, microscopic polyangiitis, and renal-limited disease. Patients with eosinophilic GPA, as well as those who have ended up in end-stage kidney disease and were on renal replacement therapies, were excluded. The following interventions for maintenance therapy were compared: azathioprine, cyclophosphamide, rituximab, methotrexate, mycophenolate mofetil, leflunomide, and belimumab with azathioprine. The primary outcome of interest was relapse-free survival, whereas the secondary ones included the occurrence of at least one relapse, the occurrence of at least one major relapse, as well as the rates of serious adverse effects, serious infections, and malignancies. Only RCTs were held eligible. Observational studies, in vitro studies, animal studies, and review articles were excluded.

**Search Strategy**

The literature search was performed by systematically searching PubMed, Scopus, Web of Science, CENTRAL, and ClinicalTrials.gov from inception. The Google Scholar database was also searched for gray literature coverage, whereas the full reference list of the included studies was screened to identify potential missing articles (“snowball” method). The date of the last search was set at June 15, 2021. The search strategy was based on a combination of Medical Subject Headings (MeSH) terms with a list of keywords of maintenance therapies. Specifically, the main algorithm was the following: (“Antibodies, Antineutrophil Cytoplasmic” [Mesh] or “Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis” [Mesh] or “Granulomatosis with Polyangiitis” [Mesh] or “Microscopic Polyangiitis” [Mesh] or ANCA or pauci-immune or “granulomatosis with polyangiitis” or “microscopic polyangiitis” or Wegener) and maintenance and (azathioprine or cyclophosphamide or rituximab or
methotrexate or mycophenolate mofetil or leflunomide or belimumab).”

Study Selection
The process of study selection followed 3 consecutive stages. At first, the titles and abstracts of all electronic records were screened to assess for potential eligibility. Of them, the articles that were presumed to meet the inclusion criteria of the meta-analysis were retrieved as full texts. Then, any study that did not report the outcomes of interest or met any of the exclusion criteria was excluded. Study selection was performed by 2 researchers, and any possible discrepancies were resolved through consensus.

Data Extraction
The following information was extracted: name of first author, year of publication, study design, eligibility criteria, dosing details, adjunct therapies, type of induction treatment, vasculitis clinical phenotype, myeloperoxidase/PR-3 ANCA positivity, patients’ number, sex, serum creatinine or estimated glomerular filtration rate, organ involvement, as well as the necessary data for outcomes of interest (relapse-free survival, rate of any/major relapse and serious adverse events). Data were extracted using prespecified forms by 2 researchers independently; any possible discrepancies were resolved after reaching consensus.

Quality Assessment
The risk of bias of the included RCTs was evaluated by 2 researchers independently; any possible discrepancies were resolved after reaching consensus. The risk of bias and quality of evidence judgments were performed by 2 authors, and final decisions were drawn after discussion of potential conflicting assessments.

Statistical Analysis
Statistical analysis was performed in R-4.0.5 (package “netmeta”15). A frequentist methodology was implemented by fitting random-effects models, assuming a common heterogeneity parameter across comparisons. The effect measure was HR for relapse-free survival and OR for the other outcomes. CIs were set at 95%.

RESULTS

Study Selection
The process of study selection is schematically depicted in the PRISMA flowchart (Supplementary Figure S1 in Appendix 1). Overall, literature search resulted in 1886 records. After deduplication and abstract screening, 13 articles were retrieved as potentially eligible. Of them, 3 studies were excluded, because 1 article evaluated only the duration of maintenance treatment,19 1 assessed the dosing schedule of rituximab,20 whereas in another 1 studying the add-on effects of etanercept, standard therapy with either cyclophosphamide or methotrexate was administered in both groups.21 As a result, the meta-analysis was based on 10 reports,21–32 describing the outcomes of 7 RCTs that comprised a total of 752 patients.

Included Studies
The main methodologic characteristics of the included studies are presented in Table 1. A total of 6 RCTs were open-label, whereas the BREVAS trial was a double-blinded, placebo-controlled one. Patients with other concomitant autoimmune diseases, active infections, or malignancies were excluded (Supplementary Table S1).
in Appendix 2). The majority of patients had received induction therapy with oral or pulse i.v. cyclophosphamide in conjunction with high-dose glucocorticoids, whereas rituximab was used in a minority of patients in 1 study. At randomization, all patients were treated with oral-tapering glucocorticoids. Most patients received also prophylaxis against Pneumocystis jiroveci, as well as gastroprotective and anti-osteoporotic therapy, as appropriate (Supplementary Table S2 in Appendix 2). The baseline patients’ characteristics are described in Supplementary Table S3 in Appendix 2. The median age of participants ranged from 52 to 59 years, whereas 50.8% of them were males. The most common diagnosis was GPA (76.8%), whereas renal involvement ranged from 17.3% to 95%.

Quality assessment indicated that some concerns of bias due to deviations from intended interventions were raised in the 6 open-label studies because blinding was not feasible, although the ascertainment of outcomes was performed using validated methods. No concerns of bias were raised in the domains of randomization, missing data, selective reporting, and measurement of outcomes (Supplementary Figure S2 in Appendix 3). The network plot of direct comparisons adjusted for risk of bias is illustrated in Figure 1.

Relapse-Free Survival
The outcomes of the network meta-analysis regarding relapse-free survival are depicted in a league table (Figure 2). Relapse-free survival was significantly worse with the use of azathioprine (HR: 2.11, 95% CI: 1.19–3.74), methotrexate (HR: 2.51, 95% CI: 1.24–5.08), and mycophenolate mofetil (HR: 3.57, 95% CI: 1.70–7.46) when compared with the use of rituximab. However, better outcomes were estimated for azathioprine (HR: 0.59, 95% CI: 0.37–0.94), cyclophosphamide (HR: 0.39, 95% CI: 0.20–0.75), and leflunomide (HR: 0.30, 95% CI: 0.11–0.84) than those for mycophenolate mofetil. Figure 3a–f illustrates in forest plots the credibility of evidence concerning the comparisons of all interventions with azathioprine. The quality of evidence was appraised as moderate for the comparisons of rituximab, cyclophosphamide, and mycophenolate mofetil and low for the remaining ones. Mycophenolate mofetil ranked as the least effective intervention with regard to any relapse occurrence (P-score: 0.015) (Figure 3).

Major Relapse
The results of major relapse are summarized in Supplementary Table S4 in Appendix 4. The risk of major relapse calculated for azathioprine (OR: 2.39, 95% CI: 1.10–5.19), methotrexate (OR: 3.18, 95% CI: 1.14–8.89), and mycophenolate mofetil (OR: 5.20, 95% CI: 1.65–16.37) was higher than that for rituximab. The quality of evidence was judged as moderate for the comparison of azathioprine with rituximab and mycophenolate mofetil, but low for the remaining comparisons (Figure 3). Ranking of interventions indicated leflunomide (P-score: 0.925) and rituximab (P-score: 0.832) as the best ones and mycophenolate mofetil (P-score: 0.164) as the worst one. Notably, the difference between leflunomide and azathioprine was not statistically significant.

Adverse Events
The rates of serious adverse events did not differ significantly among interventions (Figure 2). The quality of evidence was assessed to be low, whereas the highest P-score was estimated for mycophenolate mofetil (P-score: 0.816), followed by rituximab (P-score: 0.695). Similarly, no significant differences were observed in the outcomes of serious infection and cancer (Supplementary Table S5 in Appendix 4). The overall quality of evidence was low for both outcomes because of imprecision (Figure 3).

Multiobjective Evaluation
The relationship between the P-scores for relapse-free survival and serious adverse effect risk is depicted in a scatterplot (Figure 4). Rituximab (P-score efficacy: 0.864, P-score safety: 0.695) presented the minimum distance (d = 0.122) from the optimal point (0.864, 0.816). As a result, rituximab emerged as the best treatment with regard to efficacy and safety.

Transitivity and Consistency
No significant differences were noted in the distributions of the examined potential confounders (Supplementary Figures S3 to S6 in Appendix 5). Therefore, no threats to the transitivity assumption were identified. The overall heterogeneity was estimated to be low (I²: 0%–5.8%). The design-by-treatment interaction test indicated no evidence of inconsistency in all comparisons (P > 0.05).
| Study      | Country/design                  | Registration number | Interventions                                      | Glucocorticoid dose | Inclusion criteria                                                                 | Induction therapy                                                                 | Follow-up duration |
|-----------|----------------------------------|---------------------|---------------------------------------------------|---------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------|
| 2007; Metzler | Multicenter (Germany), open-label | NA                  | Leflunomide vs. methotrexate                      | ≤10 mg/d            | New-onset GPA                                                                    | Oral cyclophosphamide + high-dose glucocorticoids                               | 21 mo              |
| 2017; Mantatti | Italy, open-label                | NCT00751517         | Cyclophosphamide vs. methotrexate                 | 5 mg/d              | New-onset GPA or MPA                                                             | Oral cyclophosphamide + high-dose glucocorticoids                               | 24 mo              |
| BREVAS    | Multinational, double-blind      | NCT01663623         | Azathioprine vs. azathioprine + belimumab         | ≤10 mg/d            | New-onset/relapsing GPA or MPA; MPO/PR3-ANCA positivity                          | Rituximab + high-dose glucocorticoids; oral or pulse i.v. cyclophosphamide + high-dose glucocorticoids | 36 mo              |
| CYCAZREM  | Multinational, open-label        | NA                  | Azathioprine vs. cyclophosphamide                 | 10 mg/d             | New-onset GPA, MPA, or renal-limited vasculitis; MPO/PR3-ANCA positivity; histologic confirmation; renal involvement or threatened loss of vital organ function | Oral cyclophosphamide + high-dose glucocorticoids                               | 8.5 yr             |
| IMPROVE   | Multinational, open-label        | NCT00307645         | Azathioprine vs. mycophenolate mofetil            | 15 mg/d             | New-onset GPA or MPA; MPO/PR3-ANCA positivity                                    | Oral or pulse i.v. cyclophosphamide + high-dose glucocorticoids ± plasma exchange | 39 mo              |
| MAINRITSAN| France, open-label               | NCT00748644         | Azathioprine vs. rituximab                        | 20 mg/d             | New-onset/relapsing GPA, MPA or renal-limited vasculitis; MPO/PR3-ANCA positivity; histologic confirmation | Pulse i.v. cyclophosphamide + high-dose glucocorticoids                          | 28 mon             |
| WEGENT    | Multicenter (France/Belgium), open-label | NCT00349674       | Azathioprine vs. methotrexate                     | 15 mg/d             | New-onset GPA or MPA; MPO/PR3-ANCA positivity or histologic confirmation; renal involvement or involvement of ≥2 organs | Pulse i.v. cyclophosphamide + high-dose glucocorticoids                          | 11.9 yr            |

ANCA, antineutrophil cytoplasmic antibody; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; NA, not available; PR3: proteinase-3.*At randomization.
Similarly, the SIDE test indicated no significant inconsistency in the closed loop of azathioprine, cyclophosphamide, and methotrexate (Supplementary Table S7 in Appendix 6).

Credibility of Evidence

The outcomes of the CINEMA evaluations are presented in Supplementary Figures S7 to S10 in Appendix 7. Some concerns of within-study bias were raised in most comparisons because of the nonblinded nature of the included trials. The main reason for downgrading was imprecision owing to the wide estimated CIs that extended in both sides of the equivalence range. No concerns were assigned in the domain of reporting bias as the risk of publication or time-lag bias was judged to be low owing to the prospective registration of RCTs in the field. In addition, the risk of bias due to heterogeneity and incoherence was assessed to be low owing to the methodologic similarity of trials and the lack of statistical inconsistency.

DISCUSSION

This study evaluated the risk of relapse among patients with ANCA vasculitis who had previously achieved remission, by receiving the standard of care, namely high-dose glucocorticoids with cyclophosphamide or rituximab. Final inclusion of 10 reports from 7 RCTs showed that the relapse-free survival was significantly longer in patients treated with rituximab, compared with patients receiving mycophenolate mofetil, or azathioprine, or methotrexate as maintenance therapy. The risk of experiencing any relapse was significantly lower in patients treated with rituximab than in those treated with azathioprine, or mycophenolate mofetil, whereas the risk of experiencing a major relapse was also significantly lower among patients treated with rituximab than among those treated with any of the other therapeutic options. Notably, the frequency of serious adverse events, including infections and malignancies, was found similar across treatment choices.

Clinical experience has shown that the frequency of relapses among patients with ANCA vasculitis varies, with reported rates being between 10% and 60%, whereas a proportion of them experience a recurrently relapsing course, despite immunosuppression. The

![Network plot depicting the direct comparisons among interventions. Yellow color indicates some concerns of bias and green color low risk of bias. The size of circles reflects the number of studies including the intervention, and the thickness of lines is weighted according to the sample size of the respective comparison.](image1.png)

![League table of the comparisons of interventions regarding relapse-free survival (lower half) and serious adverse effects (upper half). The outcome expresses the comparison of the column intervention with the respective row intervention. Highlighted cells indicate statistical significance.](image2.png)
The impact of relapses on quality of life and accumulation of disease burden and irreversible tissue damage is undoubtful. Several investigations have focused on the etiology of relapsing disease, including the detection of autoantibodies, which develop when self-reactive B cells escape the regulation that ensures self-tolerance. Bunch et al. in mice studies showed that tolerance to myeloperoxidase is maintained by central and peripheral deletion and that some myeloperoxidase-binding B cells are positively selected into the marginal zone and B-1 B-cell subsets. A defect in these regulatory pathways could result in autoimmune disease. Rituximab, by its B-cell-depleting properties, has been shown to be efficacious in treating ANCA vasculitis, suggesting B cells play an important role in the pathophysiology of this disease. Yet, the B-cell phenotype in these patients might be used as an indicator of disease activity, response to treatment, or future relapse. Specifically, the CD5⁺ B-cell subpopulation was identified as a potential immunologic marker of sustained remission when robust, or a harbinger of subsequent relapse when low or declining, offering a potentially useful clinical tool to modulate maintenance immunotherapy. In clinical practice, the use of rituximab for remission maintenance in patients with ANCA vasculitis was evaluated in the MAINRITSAN trial, which compared low-dose rituximab (500 mg on days 0 and 14, and then months 6, 12, and 18) with azathioprine (for 22 months) following initial therapy with cyclophosphamide. Rituximab was found to be more efficacious than azathioprine in maintaining remission at 28 months, but azathioprine was tapered earlier than is typical. Long-term follow-up showed higher relapse-free survival for the rituximab group at 60 months. Moreover, a comparison between rituximab and azathioprine in remission maintenance took place in the RITAZAREM trial, which enrolled patients who achieved remission with rituximab after experiencing a relapse. Patients received 1000 mg rituximab every 4 months for 5 doses, or 2 mg/kg per day of azathioprine for 24 months. With the final analyses of the maintenance phase pending, of 170 patients who were randomized, 18% of patients in the rituximab arm versus 38% in the azathioprine arm experienced a relapse. Importantly, fewer serious adverse events were recorded in the rituximab group. The optimal dose of rituximab was examined in the MAINRITSAN2 that evaluated dosing of rituximab for remission. Participants in remission either received a fixed 500 mg rituximab infusion on days 0 and 14, and then 6, 12, and 18 months, or tailored therapy on the basis of CD19⁺ B lymphocytes or ANCA titer. Relapses were similar in both groups at 28 months (17% vs. 10%), but the tailored group received fewer infusions. MAINRITSAN3, which studied the effect of extended maintenance rituximab therapy on relapse and death, reported that the number of serious adverse events was similar among patients who received placebo or rituximab for an additional 18 months. However, the mean γ-globulin was lower in the rituximab group, highlighting risk of hypogammaglobulinemia with long-term rituximab is a fact. Against the longer duration of maintenance therapy, especially with rituximab, is the argument that therapy with rituximab is aiming at reconstitution of B-cell repertoire, after
depletion to maintain tolerance, by bypassing the presumable “defect” that resulted in the production of ANCA antibodies. If so, even patients who have a high likelihood for relapse, that is, patients with PR3-ANCA and upper respiratory or lung involvement,⁴,⁵ might theoretically be able to achieve sustained remission through the depletion and reconstruction of the B-cell reservoir, following rituximab administration.

This study has several strengths. A comprehensive literature search was ensured by screening 6 databases, without applying any date restrictions. Only RCTs were included, whereas network meta-analytical models were implemented, exploiting both direct and indirect evidence. In addition, a multiobjective analysis was performed to enable decision-making, indicating the optimal intervention with regard to both efficacy and safety. The credibility of the existing evidence was appraised following the CINeMA approach, providing a realistic framework for the interpretation of outcomes. In this context, the quality of evidence was judged to range from low to moderate because of concerns of imprecision, reflecting the small number of the available trials. Some concerns of study limitations were also raised because of the nonblinded nature of the treatments’ comparisons. Hence, future real-world studies are warranted to verify the clinical effects of treatments, especially rituximab and the azathioprine-belimumab combination.

No threats to the transitivity assumption were revealed, although the statistical assessment of consistency was limited by the absence of closed loops, with the exception of the azathioprine, cyclophosphamide, and methotrexate triangle. It should be also stated that the majority of cases were PR3 positive, whereas taking into account PR3/myeloperoxidase status was not feasible owing to the lack of individual participant data; therefore, whether the effects of rituximab differ depending on ANCA type remains unclear. Moreover, it is important to note that the vast majority of patients had received cyclophosphamide for remission induction; hence, the optimal maintenance regimen among those receiving rituximab as induction therapy needs further investigation.

Future directions pertain to questions regarding therapy for maintenance of remission in patients with ANCA vasculitis, including its optimal duration and the appropriate dosage scheme of rituximab. Yet, refining of therapy is also required for particular groups of patients including the elderly, who might need a milder and/or shorter scheme and those with particular characteristics, such as low serum complement levels at diagnosis,⁴⁹ who might require targeted therapies to be enquired for a certain period of time or even indefinitely, under specific circumstances. In the meanwhile, rituximab seems to be the preferable choice of maintenance therapy for patients with ANCA vasculitis who have achieved remission.

**DISCLOSURE**

All the authors declared no competing interests.

**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

Appendix 1. PRISMA flowchart.
Appendix 2. Study characteristics.
Appendix 3. Quality assessment.
Appendix 4. League tables.
Appendix 5. Transitivity assessment.
Appendix 6. Consistency assessment.

Appendix 7. Confidence IN Network Meta-Analyses (CINeMA).

Appendix 8. PRISMA checklist.

REFERENCES

1. Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med. 1997;20:1512–1523. doi:10.1056/NEJM19971120372106

2. Rhee RL, Hogan SL, Poulton CJ, et al. Trends in long-term outcomes among patients with antineutrophil cytoplasmic antibody-associated vasculitis with renal disease. Arthritis Rheumatol. 2016;68:1711–1720. https://doi.org/10.1002/art.39614

3. Iudici M, Pagnoux C, Courvoisier DS, et al. Granulomatosis with polyangiitis: study of 795 patients from the French Vasculitis Study Group registry. Semin Arthritis Rheum. 2021;51:339–346. https://doi.org/10.1016/j.semarthrit.2021.02.002

4. Hogan SL, Falk RJ, Chin H, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. Ann Intern Med. 2006;143:621–631. https://doi.org/10.7326/0003-4819-143-9-200601100-00005

5. Göçeroglu A, Berden AE, Fiocco M, et al. European vasculitis society (EUVAS). ANCA-associated glomerulonephritis: risk factors for renal relapse. PLoS One. 2016, 14;11:e0165402. https://doi.org/10.1371/journal.pone.0165402

6. Lionaki S, Blyth ER, Hogan SL, et al. Classification of anti-neutrophil cytoplasmic autoantibody vasculitides: the role of anti-neutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum. 2012;64:3452–3462. https://doi.org/10.1002/art.34562

7. Little MA, Nightingale P, Verbrugh CA, et al. European vasculitis study (EUVAS) group. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis. 2010;69:1036–1043. https://doi.org/10.1136/ard.2009.109389

8. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162:777–784. https://doi.org/10.7326/M14-2385

9. Hagen EC, Daha MR, Hermans J, et al. Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. Kidney Int. 1998;53:743–753. https://doi.org/10.1046/j.1523-1755.1998.00807.x

10. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1–11. https://doi.org/10.1002/art.37715

11. Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. J Am Soc Nephrol. 1996;7:33–39. https://doi.org/10.1681/ASN.V7133

12. Hogan SL, Nachman PH, Wilkman AS, et al. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. J Am Soc Nephrol. 1996;7:23–32. i:10.1681/ASN.V7123

13. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. BMJ. 2005;331:1064–1065. https://doi.org/10.1136/bmj.38636.593461.68

14. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:i4898. https://doi.org/10.1136/bmj.i4898

15. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINEMA: an approach for assessing confidence in the results of a network meta-analysis. PLOS Med. 2020;17:e1003082. https://doi.org/10.1371/journal.pmed.1003082

16. Chiangussi G, Codegone M, Ferrero S, Varessio FE. Comparison of multi-objective optimization methodologies for engineering applications. Comput Math Appl. 2012;63:912–942.

17. Jackson D, Boddington P, White IR. The design-by-treatment interaction model: a unifying framework for modelling loop inconsistency in network meta-analysis. Res Synth Methods. 2016;7:329–332. https://doi.org/10.1002/jrsm.11188

18. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010;29:932–944. https://doi.org/10.1002/sim.3767

19. Karras A, Pagnoux C, Haubitz M, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. Ann Rheum Dis. 2017;76:1662–1668. https://doi.org/10.1136/annrheumdis-2017-211123

20. Charles P, Terrier B, Perreodue É, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAIN-RITSAN2) [published correction appears in Ann Rheum Dis. 2019;78:e101]. Ann Rheum Dis. 2018;77:1144–1150. https://doi.org/10.1136/annrheumdis-2017-212878

21. Grou T, Wget R. Etanercept plus standard therapy for Wegener’s granulomatosis. N Engl J Med. 2005;352:351–361. https://doi.org/10.1056/NEJMoa041884

22. Puéchal X, Pagnoux C, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008;359:2790–2803. https://doi.org/10.1056/NEJMo0802311

23. Guillemin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis. N Engl J Med. 2018;379:1771–1780. https://doi.org/10.1056/NEJMo1404231

24. Terrier B, Pagnoux C, Perreodue É, et al. Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. Ann Rheum Dis. 2018;77:1151–1156. https://doi.org/10.1136/annrheumdis-2017-212768

25. Guillemin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med. 2014;371:1771–1780. https://doi.org/10.1056/NEJMo1404231

26. Hiemstra TF, Walsh M, Marh A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. JAMA. 2010;304:2381–2388. https://doi.org/10.1001/jama.2010.1658
27. Walsh M, Faurschou M, Berden A, et al. Long-term follow-up of cyclophosphamide compared with azathioprine for initial maintenance therapy in ANCA-associated vasculitis. *Clin J Am Soc Nephrol*. 2014;9:1571–1576. https://doi.org/10.2215/CJN.00100114

28. Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with anti-neutrophil cytoplasmic autoantibodies. *N Engl J Med*. 2003;349:36–44. https://doi.org/10.1056/NEJMoa020286

29. Jayne D, Blockmans D, Luqmani R, et al. Efficacy and safety of belimumab and azathioprine for maintenance of remission in antineutrophil cytoplasmic antibody–associated vasculitis: a randomized controlled study. *Arthritis Rheumatol*. 2019;71:952–963. https://doi.org/10.1002/art.40802

30. Maritati F, Alberici F, Oliva E, et al. Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: a randomized trial. *PLoS One*. 2017;12:e0185880. https://doi.org/10.1371/journal.pone.0185880

31. Metzler C, Miehle N, Manger K, et al. Elevated relapse rate under oral methotrexate versus lefunomide for maintenance of remission in Wegener’s granulomatosis. *Rheumatology (Oxford)*. 2007;46:1087–1091. https://doi.org/10.1093/rheumatology/kem029

32. Bunch DQ, Silver JS, Majure MC, et al. Maintenance of tolerance by regulation of anti-myeloperoxidase B cells. *J Am Soc Nephrol*. 2008;19:1763–1773. https://doi.org/10.1681/ASN.2007030382

33. Aybar LT, McGregor JG, Hogan SL, et al. Reduced CD5(+) CD24(hi) CD38(hi) and interleukin-10(+) regulatory B cells in active anti-neutrophil cytoplasmic autoantibody-associated vasculitis permit increased circulating autoantibodies. *Clin Exp Immunol*. 2015;180:178–188. https://doi.org/10.1111/cei.12483

34. Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med*. 2010;363:221–232. https://doi.org/10.1056/NEJMoa0909905

35. Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med*. 2010;363:211–220. https://doi.org/10.1056/NEJMoa0909169

36. Berland R, Wortis HH. Origins and functions of B-1 cells with notes on the role of CD5. *Annu Rev Immunol*. 2002;20:253–300. https://doi.org/10.1146/annurev.immunol.20.100301.06483

37. Soldevila G, Raman C, Lozano F. The immunomodulatory properties of the CD5 lymphocyte receptor in health and disease. *Curr Opin Immunol*. 2011;23:310–318. https://doi.org/10.1016/j.coi.2011.03.003

38. Youinou P, Renaudineau Y. The antiphospholipid syndrome as a model for B cell-induced autoimmune diseases. *Thromb Res.* 2004;114:363–369. https://doi.org/10.1016/j.thromres.2004.06.019

39. Youinou P, Devauchelle V, Hutin P, et al. A conspicuous role for B cells in Sjögren’s syndrome. *Clin Rev Allergy Immunol*. 2007;32:231–237. https://doi.org/10.1007/s12016-007-8000-y

40. Hippen KL, Tze LE, Behrens TW. CD5 maintains tolerance in anergic B cells. *J Exp Med*. 2000;191:883–890. https://doi.org/10.1084/jem.191.5.883

41. Blair PA, Noreña LY, Flores-Borja F, et al. CD19(+)CD24(hi) CD38(hi) B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic lupus erythematosus patients. *Immunity*. 2010;32:129–140. https://doi.org/10.1016/j.immuni.2009.11.009

42. Iwata E, Ikeda S, Matsunaga S, et al. GIGAS CELL1, a novel negative regulator of the anaphase-promoting complex/cyclosome, is required for proper mitotic progression and cell fate determination in Arabidopsis. *Plant Cell*. 2011;23:4382–4393. https://doi.org/10.1105/tpc.111.092049

43. Gopaluni S, Smith RM, Lewin M, et al. Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis (RITA-ZAREM): study protocol for a randomized controlled trial. *Trials*. 2017;18:112. https://doi.org/10.1186/s13063-017-1857-z

44. Smith R, Jayne D, Merkel PA. OP0026 A randomized, controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients with ANCA-associated vasculitis and relapsing disease. *Ann Rheum Dis*. 2020;79:19–20.

45. Charles P, Perrodeau É, Samson M, et al. Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med*. 2020;173:179–187. https://doi.org/10.7326/M19-3827

46. Besada E, Koldingsnes W, Nossent JC. Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis. *Rheumatol (Oxford)*. 2014;53:1818–1824. https://doi.org/10.1093/rheumatology/keu194

47. Besada E, Koldingsnes W, Nossent JC. Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre. *Rheumatol (Oxford)*. 2013;52:2041–2047. https://doi.org/10.1093/rheumatology/ket257

48. Roberts DM, Jones RB, Smith RM, et al. Rituximab-associated hypogammaglobulinemia: incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun*. 2015;57:60–65. https://doi.org/10.1016/j.jaut.2014.11.009

49. Lionaki S, Marinaki S, Liapis G, et al. Hypocomplementemia in patients with Sjögren’s syndrome. *Clin Rev Allergy Immunol*. 2014;47:177–187. https://doi.org/10.1007/s12016-014-8270-8

50. Roth AJ, Ooi JD, Hess JJ, et al. Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis. *J Clin Invest*. 2013;123:1773–1783. https://doi.org/10.1172/JCI65292