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CLINICAL RESEARCH

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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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.[2,3] 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.[6] 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.[7] 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.[8] The protocol of the study has been prospectively registered and is publicly available (https://doi.org/10.17504/protocols.io.bvq7n5zn).

All patients were tested for ANCA by immunofluorescence or enzyme-linked immunosorbent assay[9] or both. Clinical phenotypes of pauci-immune vasculitis were assigned according to the Chapel Hill vasculitides nomenclature Consensus Conference.[10] 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.[1] Organ involvement was defined by previously described criteria.[6] 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 or 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.[11,12] 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[13]). 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 electronical 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 disagreements were resolved after reaching consensus.

Quality Assessment

The risk of bias of the included RCTs was evaluated with the Cochrane risk of bias (RoB-2) tool,[14] taking into consideration the domains of randomization, deviations from intended interventions, missing data, measurement of the outcome, and selection of the reported results. The credibility of evidence was appraised by implementing the CINeMA (Confidence In Network Meta-Analyses) approach,[15] which assesses within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. For the evaluation of imprecision, it was examined whether the estimated CIs crossed into the range of equivalence, which was defined as an OR or HR between 0.90 and 1.10. 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%. League tables were constructed to visualize the relative effects of interventions. *P*-scores were estimated to rank treatments, with higher *P*-scores indicating better interventions. A multiobjective approach was implemented aiming to identify the optimal intervention in terms of relapse-free survival and risk of serious adverse effects; to achieve this, the *P*-scores for relapse-free survival were plotted against their respective *P*-scores for serious adverse effects. The geometric distance of each treatment from the ideal point (x_0, y_0), with x_0 representing the global maximum of relapse-free survival *P*-scores and y_0 the global maximum of serious adverse effect *P*-scores, was estimated as follows:

$$d_i = \sqrt{(x_i - x_0)^2 + (y_i - y_0)^2} \quad (1)$$

The most suitable point was recognized by the minimization of d_i.[16]

Heterogeneity was quantified by the inconsistency index (I^2). The plausibility of the transitivity assumption was tested by examining the distribution of potential confounders (age, sex, clinical phenotype, ANCA positivity, and organ involvement) across different interventions. Consistency was assessed globally with the design-by-treatment interaction test[17] and locally with the SIDE (Separating Indirect from Direct Evidence) test,[18] in case closed loops were present.

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 jirovecii*, 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 and mycophenolate mofetil with azathioprine and low for the other comparisons. Ranking of treatments indicated rituximab as the best one (*P*-score: 0.864) and mycophenolate mofetil as the least effective one (*P*-score: 0.051).

Any Relapse

The comparisons of interventions regarding the occurrence of at least 1 relapse are presented in Supplementary Table S4 in Appendix 4. The relapse risk was estimated to be higher for azathioprine (OR: 2.15, 95% CI: 1.00–4.59) and mycophenolate mofetil (OR: 4.42, 95% CI: 1.63–11.94) than that for rituximab (Figure 3a and b). The credibility of evidence was 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 ($P\text{-score}_{efficacy}$: 0.864, $P\text{-score}_{safety}$: 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 (I^2: 0%–5.8%). The design-by-treatment interaction test indicated no evidence of inconsistency in all comparisons ($P > 0.05$)

Table 1. Methodologic characteristics of the included studies

Study	Country/design	Registration number	Interventions	Glucocorticoid dose[a]	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; Maritati	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
CYCAZAREM	Multinational, open-label	NA	Azathioprine vs. cyclophosphamide	10 mg/d	New-onset GPA, MPA, or renal-limited vasculitis; MPO/PR3-ANCA positivity or 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 or 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.
[a]At randomization.

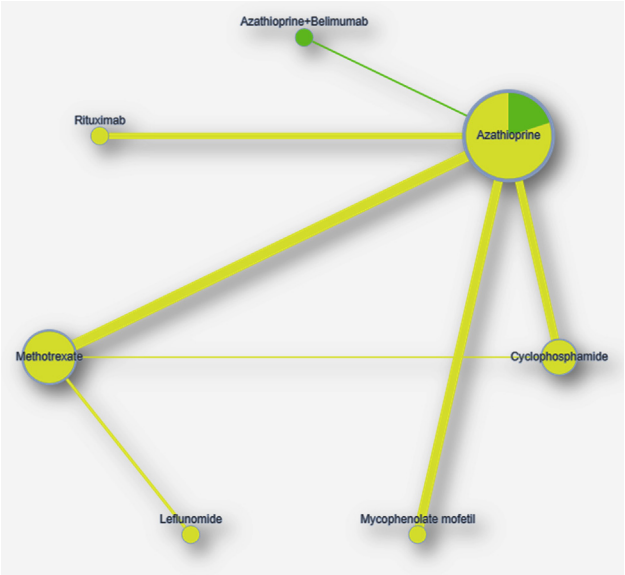

Figure 1. Network plot depicting the direct comparisons among interventions. Yellow color indicates some concerns of bias and green color low risk of bias. The size of circles reflects the number of studies including the intervention, and the thickness of lines is weighted according to the sample size of the respective comparison.

(Supplementary Table S6 in Appendix 6). 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

Relapse-free survival Serious adverse effects

Azathioprine	0.86 (0.38–1.96)	0.85 (0.39–1.85)	0.76 (0.18–3.22)	0.83 (0.43–1.62)	1.65 (0.64–4.24)	1.29 (0.61–2.70)
1.14 (0.37–3.45)	Azathioprine + Belimumab	0.98 (0.32–3.04)	0.88 (0.17–4.62)	0.97 (0.34–2.77)	1.91 (0.55–6.65)	1.49 (0.49–4.49)
1.52 (0.96–2.43)	1.34 (0.40–4.47)	Cyclophosphamide	0.89 (0.18–4.41)	0.98 (0.38–2.54)	1.94 (0.57–6.60)	1.52 (0.52–4.43)
1.96 (0.78–4.88)	1.72 (0.41–7.25)	1.28 (0.47–3.50)	Leflunomide	1.10 (0.30–3.97)	2.17 (0.39–12.21)	1.70 (0.33–8.60)
0.84 (0.56–1.27)	1.74 (0.23–2.42)	0.55 (0.31–0.99)	0.43 (0.19–0.97)	Methotrexate	1.98 (0.62–6.26)	1.54 (0.57–4.17)
0.59 (0.37–0.94)	0.52 (0.16–1.74)	0.39 (0.20–0.75)	0.30 (0.11–0.84)	0.70 (0.38–1.31)	Mycophenolate mofetil	0.78 (0.24–2.59)
2.11 (1.19–3.74)	1.86 (0.53–6.48)	1.38 (0.66–2.90)	1.08 (0.37–3.17)	2.51 (1.24–5.08)	3.57 (1.70–7.46)	Rituximab

Figure 2. 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.

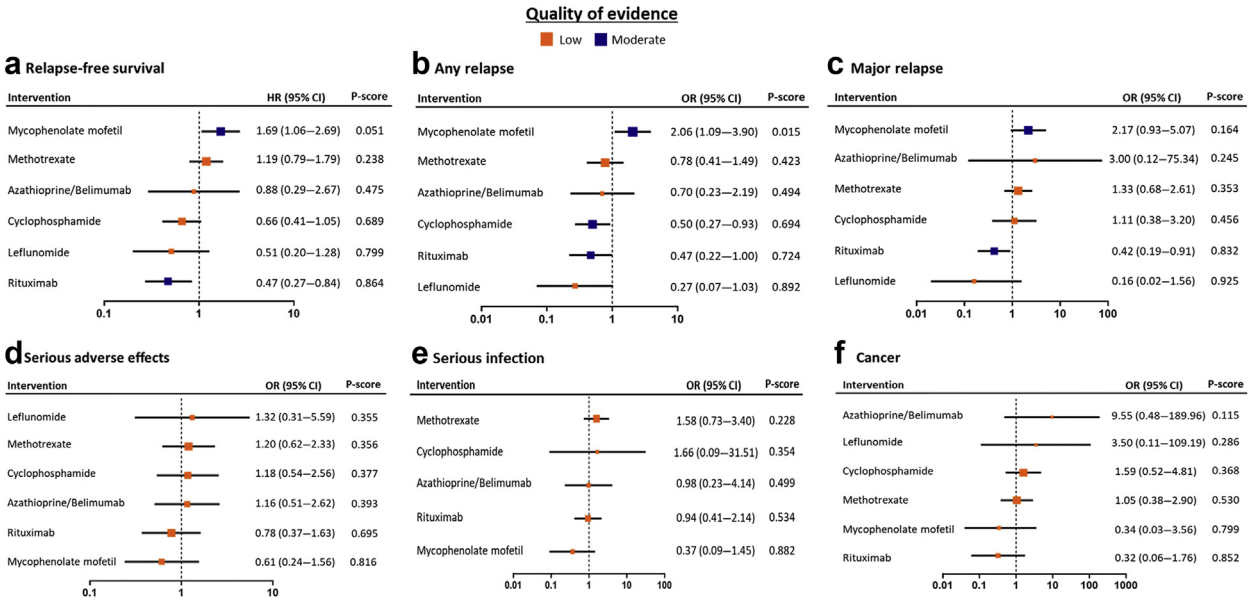

Figure 3. (a–f) Forest plots comparing the effects of interventions with azathioprine in primary and secondary outcomes namely relapse-free survival, any relpase, major relapse, serious adverse events, serious infections and cancer were created. Orange color indicates low quality of evidence and blue color moderate quality of evidence. HR, hazard ratio; OR, odds ratio.

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.*[32,33] 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.[34,35] Yet, the B-cell phenotype in these patients might be used as an indicator of disease activity, response to treatment, or future relapse.[36–40] 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.[41,42] 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.[20] Long-term follow-up showed higher relapse-free survival for the rituximab group at 60 months.[19] 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.[43] 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.[44] 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.[20] Relapses were similar in both groups at 28 months (17% vs. 10%), but the tailored group received fewer infusions.[20] MAINRITSAN3, which studied the effect of extended maintenance rituximab therapy on relapse and death,[45] reported that the number of serious adverse events was similar among patients who received placebo or rituximab for an additional 18 months.[36] However, the mean γ-globulin was lower in the rituximab group,[45] highlighting risk of hypogammaglobulinemia with long-term rituximab is a fact.[46–48] 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

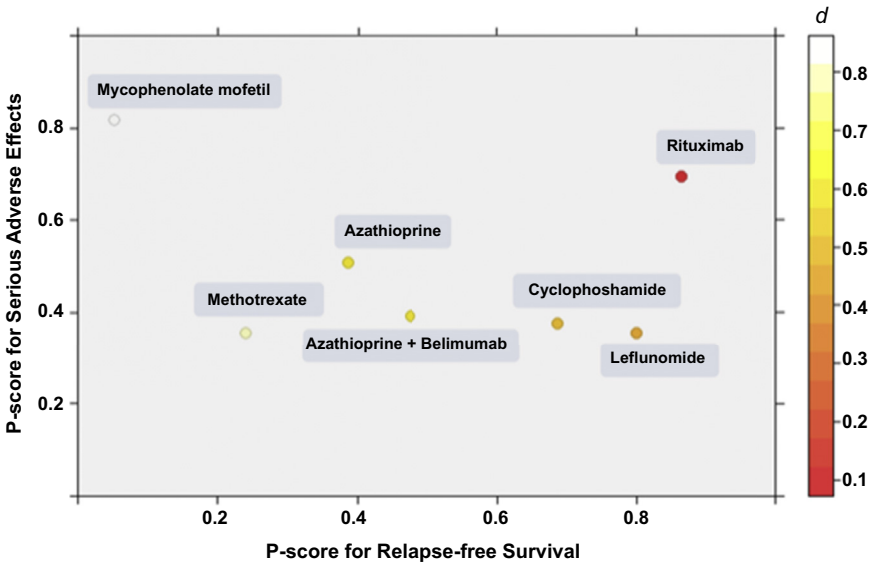

Figure 4. Scatterplot of interventions showing the association of *P*-scores for relapse-free survival and serious adverse effects. Interventions are colored depending on their distance (*d*) from the optimal point. Rituximab emerged as the best intervention.

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[50] 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.

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