Neurol Ther
https://doi.org/10.1007/s40120-026-00989-x

SYSTEMATIC REVIEW

Comparative Evaluation of Rituximab Versus Approved Therapies in Aquaporin-4-IgG-Positive Neuromyelitis Optica Spectrum Disorder: A Systematic Review and Network Meta-analysis

Mahdi Barzegar · Sara Samadzadeh · Bertrand Audoin · Achim Berthele · Ayse Altintas · Barbara Willekens · Sini Laakso · Shima Jahani · Viktoria Papp · Clarissa Zappe · Antonia Lefter · Aksel Siva · Alireza Afshari-Safavi · Sören Möller · Beatrijs Wokke · Rosa Cortese · Zsolt Illes · Saif Huda · Rommer Paulus · Silvia Messina · Nicolas Collongues · Marius Ringelstein · Álvaro Cobo-Calvo · Yael Hacohen · Georgina Arrambide · Jacqueline Palace · Sara Mariotto · Romain Marignier · Ruth Geraldes · Friedemann Paul · Nasrin Asgari · MEDEN study group

Received: March 5, 2026 / Accepted: June 15, 2026

ABSTRACT

***Introduction*:** Neuromyelitis optica spectrum disorder (NMOSD) is a rare antibody-mediated neuro-autoimmune disease. Monoclonal antibodies targeting B cell antigens CD19 and CD20, the interleukin-6 receptor, or the complement cascade are used as preventive therapies to reduce relapse rates. We conducted a network meta-analysis (NMA) to compare the effect of rituximab on time to first relapse with ravulizumab, eculizumab, inebilizumab, and satralizumab in patients with NMOSD who are aquaporin-4 (AQP4)-IgG-positive.

***Methods*:** A systematic search was conducted in PubMed, Scopus, CINAHL, EMBASE, Web of

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-026-00989-x.

M. Barzegar
Department of Neurology, Toledo University, Toledo, OH, USA

S. Samadzadeh · F. Paul
Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine and Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität Zu Berlin, Berlin, Germany

S. Samadzadeh · S. Jahani · A. Afshari-Safavi · N. Asgari
Institute of Regional Health Research & Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark

S. Samadzadeh · S. Jahani · A. Afshari-Safavi · N. Asgari
Department of Neurology, Slagelse Hospitals, Slagelse, Denmark

B. Audoin
APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques, Service de Neurologie, Marseille, France

B. Audoin
Department of Neurology, University Hospital of Marseille, Aix-Marseille University, CNRS, CRMBM, Marseille, France

A. Berthele · C. Zappe
Department of Neurology, School of Medicine and Health, Technical University Munich, Klinikum Rechts der Isar, Munich, Germany

A. Altintas
Neurology Department, School of Medicine, Koç University, Istanbul, Turkey

A. Altintas
Koç University Research Center for Translational Medicine (KUTTAM), Istanbul, Turkey

B. Willekens · A. Lefter
Department of Neurology, Antwerp University Hospital, University of Antwerp, Edegem, Belgium

Published online: 16 July 2026

Science, the Cochrane Library, and gray literature sources up to October 31, 2024, and updated on November 1, 2025, following PRISMA guidelines. A network meta-analysis of randomized and open-label trials was conducted to compare time to first relapse between rituximab and other monoclonal antibody therapies.

B. Willekens · A. Lefter
Translational Sciences Research Group, Faculty of Medicine and Health Sciences, University of Antwerp, Wilrijk, Belgium

B. Willekens
Laboratory of Experimental Haematology, VAXINFECTIO, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

S. Laakso
Neurocenter, Helsinki University Hospital, Helsinki, Finland

S. Laakso
Translational Immunology Research Program, University of Helsinki, Helsinki, Finland

V. Papp
Department of Neurology, Danish Multiple Sclerosis Center, Copenhagen University Hospital-Rigshospitalet, 2600 Glostrup, Denmark

A. Lefter · S. Messina · J. Palace · R. Geraldes
Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, Oxford, UK

A. Siva
Department of Neurology, Istanbul University-Cerrahpaşa Faculty of Medicine, Istanbul, Turkey

S. Möller
Open Patient Data Explorative Network, Odense University Hospital, University of Southern Denmark, Odense, Denmark

B. Wokke
Department of Neurology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

R. Cortese
Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

Z. Illes
Department of Neurology, Odense University Hospital, Odense, Denmark

S. Huda
Department of Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, UK

S. Huda
Department of Neurology, The Walton Centre NHS Foundation Trust, Liverpool, UK

R. Paulus
Department of Neurology, Medical University of Vienna, Vienna, Austria

N. Collongues
Department of Neurology, University Hospital of Strasbourg, Strasbourg, France

N. Collongues
Department of Pharmacology, Addictology, Toxicology, and Therapeutics, Strasbourg University, Strasbourg, France

M. Ringelstein
Department of Neurology, University Clinic and Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

M. Ringelstein
Department of Neurology, Center for Neurology and Neuropsychiatry, LVR-Klinikum, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

Á. Cobo-Calvo · G. Arrambide
Neurology-Neuroimmunology Department, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain

Y. Hacohen
Department of Neurology, Great Ormond Street Hospital for Children, London, UK

Y. Hacohen
Department of Neuroinflammation, UCL Institute of Neurology, University College London, London, UK

S. Mariotto
Neurology Unit, Department of Neurosciences, Biomedicine, and Movement Sciences, University of Verona, Verona, Italy

R. Marignier
Hospices Civils de Lyon, Service de Neurologie, Sclérose en Plaques, Pathologies de la Myéline et Neuro-Inflammation, Hôpital Neurologique Pierre Wertheimer, Bron Cedex, France

F. Paul
Neuroscience Clinical Research Center, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

N. Asgari (✉)
Department of Regional Health Research & Molecular Medicine, University of Southern Denmark, Campusvej 55, 5230 Odense, Denmark
e-mail: nasgari@health.sdu.dk

Results: From 6337 records, 3825 duplicates were removed; 2512 were screened, 2327 excluded, leaving eight trials. The prior treatment, relapse history, and definitions and adjudication of relapse varied across studies. Rituximab showed higher hazard ratio (HR) point estimates for time to first relapse compared with ravulizumab with or without immunosuppressive therapies (IST) (HR 5.00, 95% CI 0.25, 101.01) and eculizumab ± IST (HR 1.17, 95% CI 0.12, 10.89), but were lower compared with satralizumab ± IST (HR 0.29, 95% CI 0.04, 2.23). In patients not receiving IST, rituximab showed numerically higher HR compared with ravulizumab (HR 3.33, 95% CI 0.13, 83.16) and eculizumab (HR 1.59, 95% CI 0.05, 50.17), but lower point estimates compared with inebilizumab (HR 0.31, 95% CI 0.04, 2.31) and satralizumab (HR 0.27, 95% CI 0.03, 2.21).
Conclusion: This NMA showed hazard ratio point estimates favoring eculizumab and ravulizumab over rituximab. However, wide, overlapping confidence intervals and between-study heterogeneity indicate substantial uncertainty. Head-to-head trials or registry-based studies are needed to determine the most effective treatment for AQP4-IgG-positive NMOSD.

Keywords: Neuromyelitis optica spectrum disorder; Rituximab; Inebilizumab; Satralizumab; Ravulizumab; Tocilizumab; Eculizumab; Network meta-analysis; Randomized controlled trials

Key Summary Points

Neuromyelitis optica spectrum disorder (NMOSD) is a severe neuro-autoimmune disease in which relapse prevention is essential to reduce the risk of irreversible neurological disability.

Rituximab has been widely used off-label, and several monoclonal antibodies are now approved for relapse-prevention in patients with AQP4-IgG-positive NMOSD; however, their relative effectiveness compared with rituximab remains uncertain.

We conducted a network meta-analysis to compare time to first relapse between rituximab and newly approved monoclonal antibody therapies in patients who are AQP4-IgG-positive with NMOSD using data from clinical trials.

This network meta-analysis found higher hazard ratios for time to first relapse with rituximab compared with eculizumab and ravulizumab, and lower hazard ratios compared with satralizumab and inebilizumab; however, these differences were not statistically significant.

Wide confidence intervals and between-trial heterogeneity limit definitive conclusions, highlighting the need for head-to-head trials or real-world comparative studies.

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory autoimmune disease of the central nervous system (CNS), associated with autoantibodies targeting the astrocyte water channel aquaporin-4 (AQP4), which leads to immune-mediated damage [1]. AQP4-IgG-positive NMOSD is a distinct disorder from multiple sclerosis with unique pathophysiology, clinical characteristics [2–5] and treatment approaches [6]. AQP4-IgG-positive NMOSD follows a relapsing course where cumulative attacks frequently lead to severe neurological disability [7]. A main goal of immunotherapies investigated in clinical trials is to prevent future attacks and reduce the

risk of relapses and associated disability worsening [8].

Several new interventions have been introduced in recent years to manage AQP4-IgG-positive NMOSD [9]. Historically, rituximab and other immunosuppressive therapies such as azathioprine, mycophenolate mofetil, and methotrexate have been used off-label [10]. An open-label study compared the efficacy of rituximab to azathioprine and found rituximab to be more effective [11]. A randomized, double-blind, placebo-controlled trial was conducted in 2020 and reported no relapses among 19 patients who are AQP4-IgG-positive with NMOSD treated with rituximab, compared to seven relapses in the placebo group ($n = 19$) during the 72-week study period [12].

More recently, monoclonal antibodies targeting CD19 (inebilizumab) or interleukin-6 receptor (IL-6R; satralizumab, tocilizumab) or inhibiting the terminal complement cascade (eculizumab, ravulizumab) were used as relapse preventive treatments in AQP4-IgG-positive NMOSD [13]. However, no direct comparison between rituximab and more recently developed antibodies has been performed. Evaluating rituximab against high-cost novel therapies could have important clinical and economic

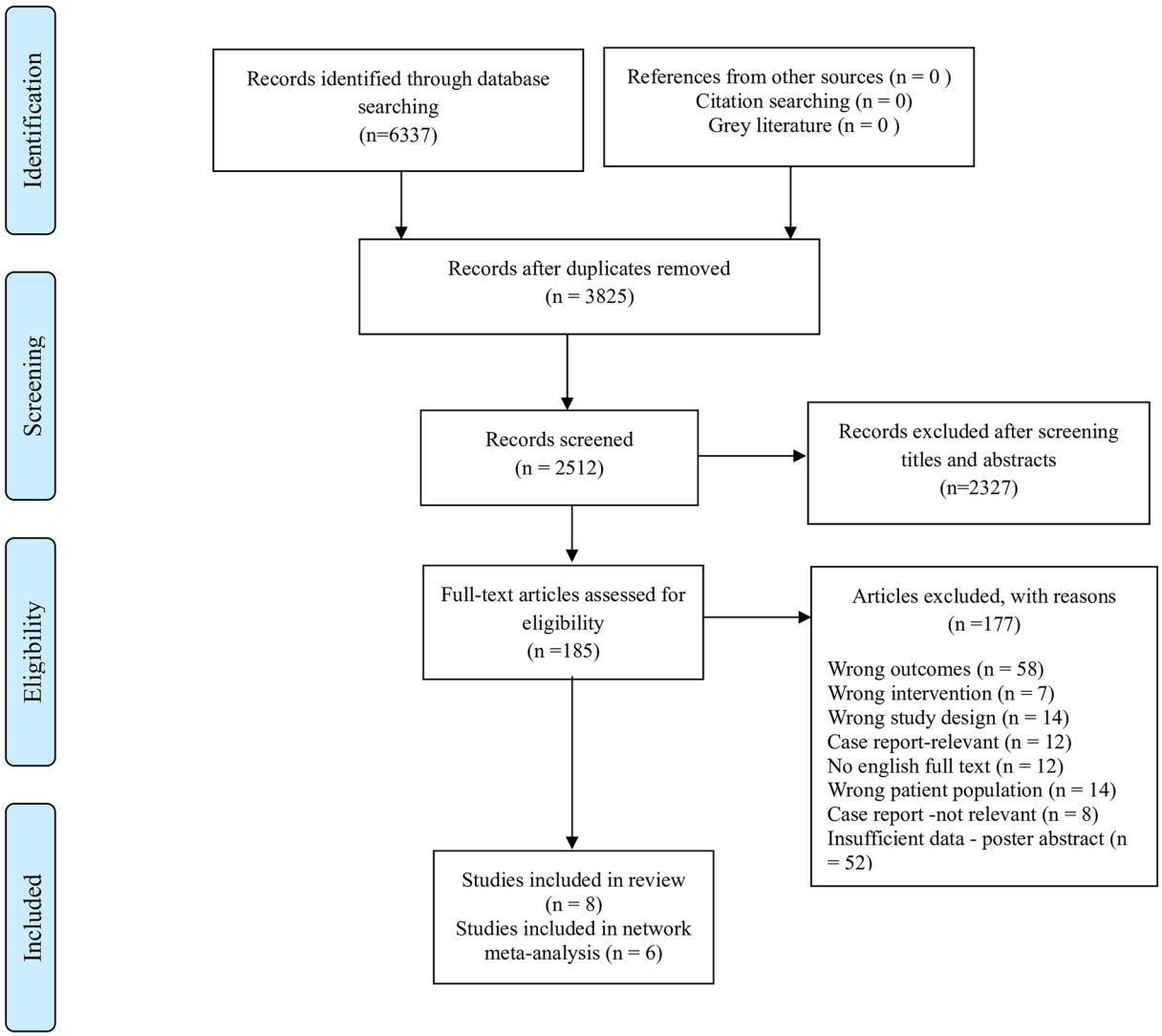

Fig. 1 Flowchart of the study

implications, potentially informing treatment decisions and optimizing healthcare resource utilization.

A frequentist network meta-analysis (NMA) allows for the simultaneous comparison and synthesis of multiple interventions within a network of clinical trials [14]. Four NMA studies have analyzed trials in NMOSD, but they all have limitations, e.g., not assessing rituximab [15, 16], lack of head-to-head comparisons of individual therapies or absence of data specific to patients who are AQP4-IgG-positive with NMOSD [17], and inclusion of non-trial data or no inclusion of newer agents such as ravulizumab [18]. Previous relapse frequency and severity and predefined acute relapse criteria, and uniform relapse adjudication are critical to direct comparison between different interventions [19]. Given the limitations of previous NMAs, the present review aims to compare the effect of rituximab on time to first relapse with other emerging interventions in patients who are AQP4-IgG-positive with NMOSD through a systematic review and NMA.

METHODS

Registration

This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20] and registered on the Open Science Framework (OSF) under the registration of the identifier UW5MQ. The PRISMA flow diagram of the study is presented in Fig. 1.

Search Strategy

A comprehensive literature search was conducted using PubMed, Scopus, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials databases. We screened all studies published up to October 31, 2024. Additionally, we reviewed abstracts from the following scientific meetings held between 2021 and 2024: the American Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), the American Academy of Neurology (AAN) Annual Meeting, and the Congress of the European Academy of Neurology (EAN). Reference lists of included articles and trial website registries such as ClinicalTrials.gov were also screened. The literature search was updated by screening PubMed through November 1, 2025. The search strategy used to identify studies in PubMed is detailed in Supplementary Table 1.

Eligibility Criteria

The inclusion criteria were as follows: (P) Population: patients who are AQP4-IgG-positive with NMOSD; (I) Intervention: rituximab, eculizumab, inebilizumab, ravulizumab, satralizumab, and tocilizumab; (C) Comparator: placebo or any other intervention; (O) Outcomes: as described in the "Outcomes" section; and (S) Study type: randomized clinical trials (RCTs) and open-label trials. The following studies were excluded: (a) observational studies such as cohort, case–control, cross-sectional, case series, and case reports; (b) studies that did not compare a medication with placebo or another medication; (c) reviews, animal studies, hypothesis papers, in vitro studies, and books; (d) systematic reviews, meta-analyses, and network meta-analyses; (e) non-peer-reviewed articles; and (f) qualitative studies.

Outcomes

The primary outcome of the present study was time to relapse, consistent with NMOSD trials that have reported time to relapse as the primary endpoint [21]. Because the objective of this analysis was to compare all approved monoclonal antibody therapies with rituximab, secondary outcomes were defined as any outcomes assessed in the rituximab trials [11, 12] that were also reported in other included trials. The secondary outcomes in the rituximab trials were changes in EDSS score, annualized relapse rate (ARR), quantification of nerve and spinal cord impairment (QOSI), steroid reduction rate, AQP4 antibody titers, human

anti-chimeric antibody (HACA) and anti-JC virus (JCV) antibodies, and lymphocyte subsets (CD19 and CD20) [11, 12]. However, these endpoints were not uniformly assessed across trials, so we could not directly compare them between studies.

Study Screening and Selection

Covidence web-based platform was used to manage the literature search records. The investigators (MB, SS, SL, SJ, VP, CZ, and AL) independently screened the titles and abstracts of the studies. The full texts of the retrieved studies were then reviewed by the two independent investigators to identify those that met the eligibility criteria (MB, SS). Any disagreements regarding screening or study selection were resolved through consultation with a senior researcher (NA).

Data Extraction

Data extraction was independently performed by four investigators (MB, SS, AA, and AB). The extracted data included first author's name, name of the study, publication year, study type, interventions, use of immunosuppressive therapy (IST), number of patients, number of patients who are AQP4-IgG-positive with NMOSD, duration of follow-up, number of relapses, and time to first relapse. Any disagreements were resolved by the senior reviewer.

Quality Assessment

Four reviewers (AA, AB, AS, and BA) independently evaluated the quality of the included studies using the Joanna Briggs Institute (JBI) critical appraisal checklists [22]. The JBI tool for randomized controlled trials (RCTs) was used to assess RCTs, while the checklist for quasi-experimental studies (non-randomized experimental studies) was applied to open-label trials. Any discrepancies in the quality assessment were resolved by a third investigator.

NMA and Outcome

The analysis was conducted in two groups based on the use of concomitant immunosuppressive therapy (IST). Patients who received IST together with the monoclonal antibody were classified as the combination therapy group, while those who received the intervention without concomitant IST were classified as the monotherapy group. IST included azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine, and cyclophosphamide, which were permitted at the investigator's discretion. In the first analysis, we included all patients who are seropositive, representing combination ± monotherapy. In the second analysis, only patients who received monotherapy were included. We did not perform a separate analysis exclusively for combination therapy, as patients in the RIN-1 trial received monotherapy [12]. We excluded patients who are AQP4-IgG-negative with NMOSD from the NMA.

The only outcome consistently reported across all studies was time to first relapse, which served as the primary endpoint in all trials. In the RIN-1 trial, this outcome was presented as a group difference, whereas other studies reported it as a hazard ratio (HR). For consistency, the RIN-1 result was converted to an HR [23, 24], and the NMA results were reported as HRs. In the PREVENT study, the HR for the monotherapy group was not reported; therefore, we for this study estimated the HR based on the time to first relapse data. As a result of the small number of studies included in the network meta-analysis, formal statistical assessment of heterogeneity was not performed, as heterogeneity measures have limited power and may yield unreliable estimates in sparse networks. Nevertheless, a qualitative assessment of potential sources of heterogeneity was conducted and is reported in the Supplementary Material.

A network meta-analysis was conducted using the netmeta package in R version 4.5.1 (The R Foundation for Statistical Computing, Vienna, Austria) to synthesize both direct and indirect evidence across interventions. Pooled HRs and 95% confidence intervals (CIs) for time to

Table 1 Characteristics of the included studies

Study acronym	Year of publication	Type of trial	Tested drug	Comparator	Sample size	AQP4-NMOSD	Age criteria	EDSS criteria	Baseline relapse criteria	Race or region	Quality assessment
RIN-1 [12]	2020	Phase 3 RCT	Rituximab	Placebo	38	38	16–80	≤ 7.0	No criteria	Japanese: 38	13/13
Nikoo et al. study [11]	2017	Phase 3 open-label	Rituximab	Azathioprine	86	42	18–50	≤ 7.0	No criteria	Iranian: 86	7/13
PREVENT [27]	2019	Phase 3 RCT	Eculizumab	Placebo	143	143	≥ 18	≤ 7.0	≥ 2 in previous 12 months or ≥ 3 in 24 months	Asian: 52 Black/White American: 17 White: 70 Other/unknown: 4	13/13
CHAMPION [30]	2023	Phase 3 open-label	Ravulizumab	Placebo	105	105	≥ 18	≤ 7.0	≥ 1 in previous 12 months	Asian: 36 Black/White American: 14 White: 53 Other/unknown: 2	7/13

Table 1 continued

Study acronym	Year of publication	Type of trial	Tested drug	Comparator	Sample size	AQP4-NMOSD	Age criteria	EDSS criteria	Baseline relapse criteria	Race or region	Quality assessment
N-MOmentum [28]	2019	Phase 2/3 RCT	Inebilizumab	Placebo	230	213	≥ 18	≤ 7.5	≥ 1 in previous 12 months	Asian: 47 American Indian/ Alaskan native: 19 Black or African American: 20 White: 120 Other/ unknown: 24	13/13
SAkuraStar [25]	2019	Phase 3 RCT	Satralizumab	Placebo	95	64	18–74	≤ 6.5	≥ 1 in previous 12 months	Asian (non-Japanese): 14 American Indian/ Alaskan native: 2 Black or African American: 16 White: 59 Other/ unknown: 4	13/13

Table 1 continued

Study acronym	Year of publication	Type of trial	Tested drug	Comparator	Sample size	AQP4-NMOSD	Age criteria	EDSS criteria	Baseline relapse criteria	Race or region	Quality assessment
SAkuraSky [26]	2020	Phase 3 RCT	Satralizumab	Placebo	83	55	12–74	≤ 6.5	≥ 2 in previous 12 months	Asia: 34 Europe/other: 49	13/13
TANGO [29]	2020	Phase 2 open-label	Tocilizumab	Azathioprine	118	103	≥ 18	≤ 7.5	≥ 2 in previous 12 months or ≥ 3 in 24 months	Chinese: 118	12/13

EDSS Expanded Disability Status Scale, *ARR* annualized relapse rate, *RCT* randomized clinical trials, *AQP4* aquaporin

relapse were estimated using a random-effects model. The structure of the evidence network was visualized with a network plot. To rank treatments, *P*-scores were calculated, representing the certainty that a given treatment is superior to competing alternatives (range 0–1), with higher scores indicating better ranking. Two independent NMA experts performed the data analysis (AAS, SM).

Ethical Approval

This study is a systematic review and network meta-analysis of previously published data. As no primary data collection from human participants was conducted, ethical approval was not required.

RESULTS

Eligibility

Figure 1 shows the flowchart of the study. A total of 6337 studies were identified through the database searches. After removal of 3825 duplicates, 2512 records remained for title and abstract screening. Following the exclusion of 2327 records, 185 full-text articles were assessed for eligibility. Ultimately, eight unique trials were included in the study. An updated search identified an additional 215 records, none of which met the eligibility criteria.

Study Characteristics

The eight included studies reported data on six different therapies (Table 1). The quality assessment and information on the eligibility criteria, relapse definitions, and treatment protocols of the included studies are summarized in the Supplementary Material, Tables S2–6. In brief, variation in the inclusion criteria, acute relapse protocol definitions, and relapse adjudication was observed. Varying information appeared on prior treatment and previous relapse frequency and

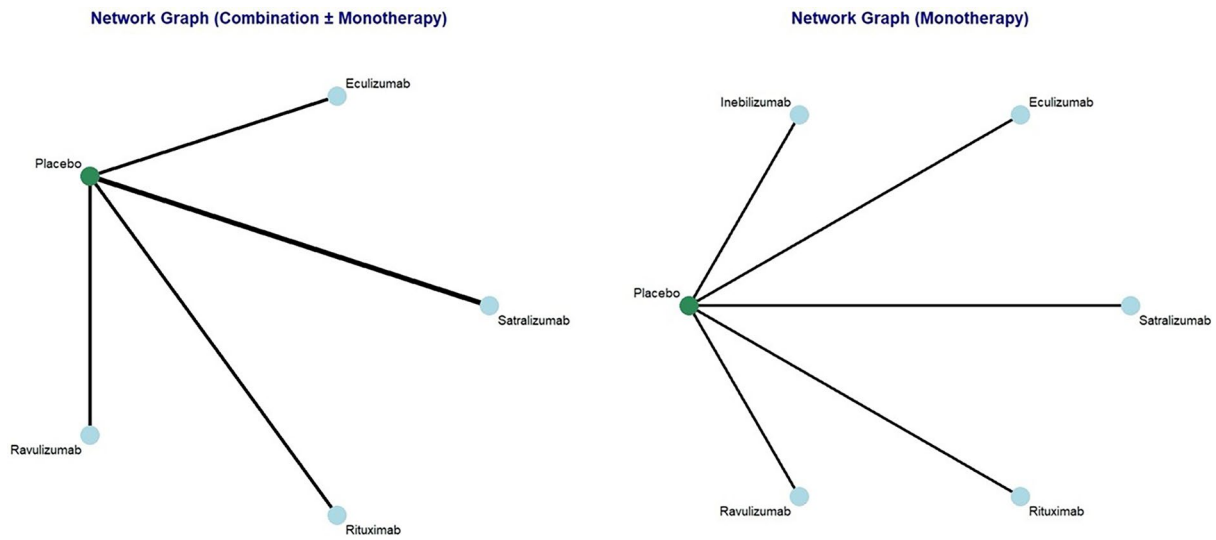

Fig. 2 Network plot comparing different therapies in combination therapy ± monotherapy and monotherapy for the time to first relapse outcome. The thickness of each line corresponds to the number of studies, and each node represents a medication

severity in the study population (Supplementary Material, Tables S3–6).

Two studies, RIN-1 [12] and the study by Nikoo et al. [11], provided efficacy data on rituximab, ARR being the primary outcome in the Nikoo et al. study. The SAkuraSky [25] and SAkuraStar [26] assessed satralizumab versus placebo. Other trials evaluated relapse-preventive therapies: PREVENT [27] for eculizumab, N-MOmentum [28] for inebilizumab, TANGO [29] for tocilizumab,

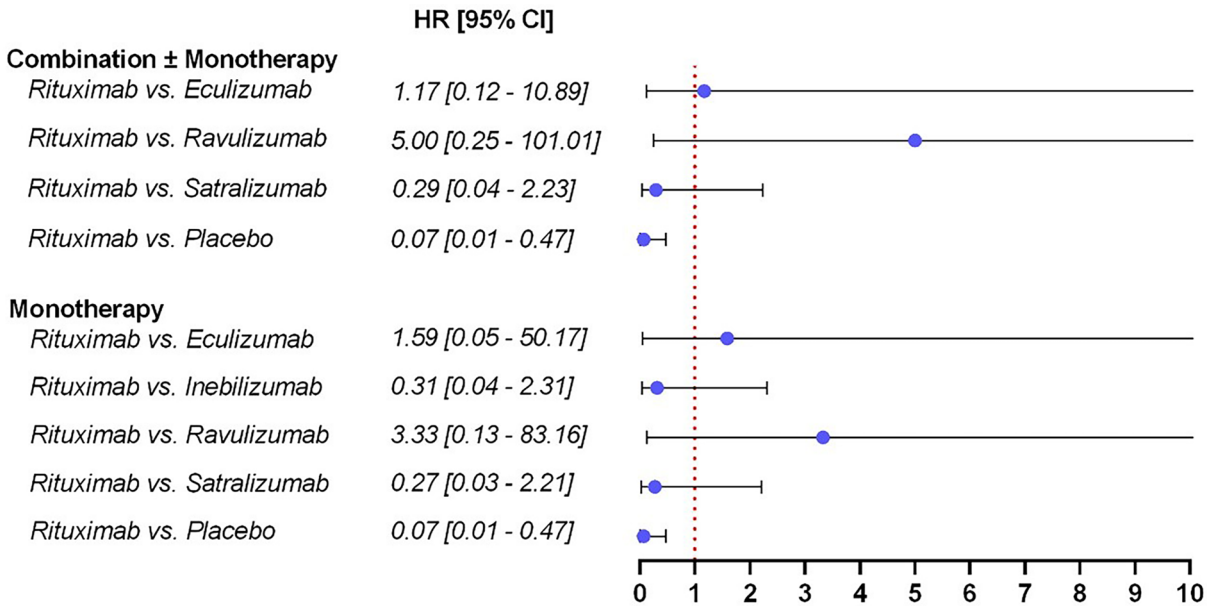

Fig. 3 Network forest plot comparing combination therapy ± monotherapy for time to first relapse. All pairwise comparisons are statistically non-significant with extremely wide confidence intervals. These results should not be used to draw conclusions about the comparative superiority of any therapy. *HR* hazard ratio, *CI* confidence interval

and CHAMPION-NMOSD [30] for ravulizumab. In both the TANGO and Nikoo et al. studies, the comparator was azathioprine [11, 29]. In the RIN-1, PREVENT, and CHAMPION-NMOSD trials, all enrolled participants were AQP4-IgG-positive patients with NMOSD. Patients in RIN-1, SAkuraStar, and N-MOmentum did not receive concomitant IST [12, 26, 28]. In the TANGO trial, patients receiving tocilizumab were permitted to continue concomitant immunosuppressive therapy for up to 12 weeks after enrollment [29]. In the RIN-1 trial, patients received tapered doses of prednisolone, with concomitant treatment maintained at 2–5 mg/day [12]. In the N-MOmentum trial, patients were given prednisone 20 mg/day (or equivalent) from days 1 to 14, followed by tapering through day 21 [28]. All therapies showed improved primary outcomes compared to placebo. No relapse was observed during trials with patients treated with rituximab and in those who received ravulizumab and eculizumab as monotherapy [12, 27, 30].

Time to Relapse: Combination Therapy ± Monotherapy Network

The network diagram of the therapy comparisons for time to first relapse is shown in Fig. 2. Five studies, namely RIN-1, PREVENT, CHAMPION-NMOSD, SAkuraSky, and SAkuraStar, were included in this analysis. The monotherapy results for satralizumab from SAkuraStar were pooled with those from SAkuraSky, which reported satralizumab used in combination therapy. The TANGO and Nikoo et al. studies were excluded, as their comparator was azathioprine and time to first relapse was not reported in the Nikoo et al. study. The network forest plot showed that rituximab was associated with higher point estimates for the hazard of first relapse compared with ravulizumab ± IST (HR 5.00, 95% CI 0.25–101.01) and eculizumab ± IST (HR 1.17, 95% CI 0.12–10.89) (Fig. 3). In comparisons with satralizumab ± IST, the point estimate favored rituximab (HR 0.29, 95% CI 0.04–2.23). All comparisons were characterized by wide confidence intervals crossing the line of no effect, indicating substantial uncertainty in the relative treatment effects.

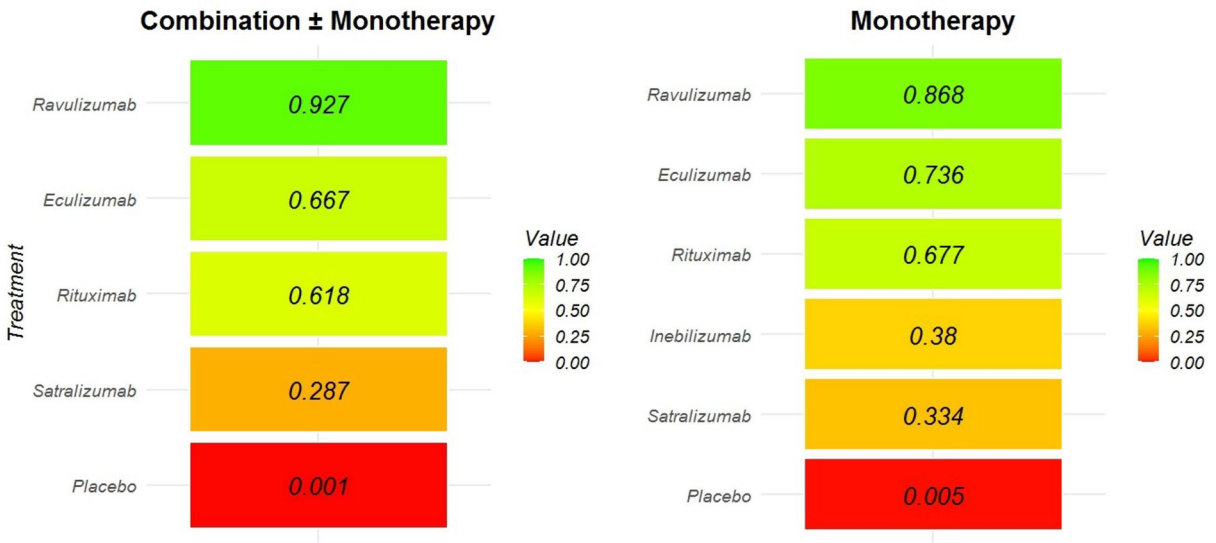

Fig. 4 Potential ranking probabilities of time to first relapse for each therapy, illustrating the likelihood of each being the optimal treatment. *P*-scores and treatment rankings are presented for descriptive purposes only and are highly uncertain. They should not be interpreted as evidence of treatment superiority or used to guide clinical decision-making

The ranking of different therapies shows that, in order, ravulizumab ± IST ($P = 0.927$), eculizumab ± IST ($P = 0.667$), rituximab ($P = 0.618$), and satralizumab ± IST ($P = 0.287$) have the highest likelihood of improving time to first relapse (Fig. 4).

Time to First Relapse: Monotherapy Network

Six studies, namely RIN-1, PREVENT, N-MOmentum, CHAMPION-NMOSD, SAkuraSky, and SAkuraStar, were included to compare time to first relapse in monotherapy group (Fig. 2). Rituximab monotherapy showed numerically higher hazard ratios for time to first relapse compared with ravulizumab (HR 3.33, 95% CI 0.13–83.16) and eculizumab (HR 1.59, 95% CI 0.05–50.17), whereas the point estimates favored rituximab over inebilizumab (HR 0.31, 95% CI 0.04–2.31) and satralizumab (HR 0.27, 95% CI 0.03–2.21) (Fig. 3). All comparisons were characterized by wide confidence intervals that included the null value (HR = 1.0), indicating substantial uncertainty in the relative treatment effects. The highest probability of being the most effective monotherapy therapy in preventing a first relapse was observed with ravulizumab ($P = 0.868$), followed by eculizumab ($P = 0.736$), rituximab ($P = 0.677$), inebilizumab ($P = 0.38$), and satralizumab ($P = 0.334$) (Fig. 4).

DISCUSSION

Off-label treatments such as rituximab have been widely used for several years, as no US Food and Drug Administration (FDA)-, European Medicines Agency (EMA)-, or Health Canada-approved therapies for NMOSD existed. In recent years, however, several new and more costly monoclonal antibody therapies have been investigated in RCTs and approved by the FDA and EMA [21]. This raises important questions about their relative effects on attack rates or time to first relapse, particularly in the absence of direct head-to-head trials. Because NMOSD is a rare condition and conducting large clinical trials is expensive, network meta-analysis provides a valuable tool for comparing available therapies. In this analysis, we compared the efficacy of newly approved therapies with rituximab, using time to first relapse as the outcome measure. Our findings suggest that hazard ratio point estimates numerically favored eculizumab and ravulizumab over rituximab for time to first relapse. However, caution is warranted when interpreting these results, as the comparison has wide confidence intervals, there are differences across trials such as relapse definitions and pre-enrollment disease characteristics, and the use of time to first relapse does not necessarily provide a complete measure of treatment efficacy. Despite numerical trends favoring newer monoclonal antibodies, rituximab is likely to remain a cornerstone of NMOSD treatment globally owing to its substantially lower cost and wider accessibility, particularly in resource-limited settings.

In both the combination and monotherapy analyses, we observed higher hazard ratios for time to first relapse with rituximab compared to ravulizumab and eculizumab; however, the confidence intervals were extremely wide and there was an absence of significant p values. This likely reflects the small sample size of the RIN-1 trial, with only 38 participants, compared with 143 patients in PREVENT and 105 in CHAMPION, as well as the absence of relapses in the original rituximab and ravulizumab trials [12, 30] which limits the precision of the hazard ratio estimates. We found lower hazard ratios for time to first relapse with rituximab compared to satralizumab or inebilizumab; however, these differences were not statistically significant. Importantly, baseline characteristics differ across the trials. The RIN-1 study [12] included a small group of patients with NMOSD exclusively from Japan, a population generally associated with better clinical outcomes [31, 32]. In RIN-1 [12], there was no requirement for prior relapses before enrollment, whereas the PREVENT study [27] required patients to have experienced at least two or three relapses in the 12 and 24 months prior to enrollment, respectively. In the SAkuraStar [26], CHAMPION-NMOSD [30], and N-MOmentum studies [28], eligibility required

at least one relapse in the previous 12 months, while in SAkuraSky [25], at least two relapses were required. The ARR during the 24 months prior to enrollment in patients treated with eculizumab [27] and ravulizumab [30] was 1.9, but 1.4–1.5 in those receiving rituximab [12] and staralizumab [25]. This suggests that the complement inhibitor trials enrolled patients with higher baseline disease activity than the RIN-1 trial, particularly regarding relapse history and baseline ARR, which should be considered when interpreting comparative efficacy estimates.

Another important difference across trials was the definition and adjudication of relapses, which warrants cautious interpretation of our results. In the RIN-1 trial [12], relapses were assessed by the principal investigator at each center, whereas other trials relied on independent or blinded adjudication committees [25–28, 30]. For consistency, our analysis used the time to first adjudicated relapse. In contrast, the RIN-1 [12] and N-MOmentum [28] trials incorporated imaging data to confirm relapses in some cases, whereas the other trials relied primarily on clinical symptoms and objective signs [2]. Thus, the variation in protocol definitions and adjudication of relapse was a potential major confounding issue as a direct comparison may be misleading in the current study. Furthermore, heterogeneity in the inclusion criteria including information on prior treatment, relapse frequency and severity, ethnicity of study population, and the use of corticosteroid therapy during treatment initiation may have an impact on the response.

We focused on time to first relapse as the primary outcome, consistent with the design of the trials. However, this endpoint has important clinical limitations. It captures only the occurrence of a first relapse and does not reflect long-term disease control, relapse frequency over time, relapse severity, or cumulative neurological disability. ARR and disability outcomes such as EDSS would provide a more comprehensive picture of treatment efficacy. While previous NMAs have reported ARR [16, 18], we did not include this outcome because of the lack of precise data for patients who are seropositive in some trials [25, 26, 28] and to avoid relying on indirect estimates. The exclusion of these outcomes represents an additional limitation, as therapies that perform similarly on time to first relapse may differ meaningfully in their effects on relapse severity and long-term disability accumulation. Additionally, none of the secondary outcomes in the RIN-1 trial was assessed uniformly across trials, so we could not directly compare them between studies.

NMA is useful in rare conditions such as NMOSD, where conducting large head-to-head clinical trials is challenging. NMA allows identification of the most effective treatments among multiple options and helps guide clinical decision-making when direct comparative evidence is unavailable [33, 34]. However, the validity of NMA depends on the assumptions of transitivity and consistency across study designs and participant characteristics [34]. In the present analysis, this assumption is substantially challenged by several between-trial differences, including variation in baseline disease activity, ethnicity, prior therapies, concomitant immunosuppressant use, relapse definitions, and adjudication processes. Therefore, the validity of indirect comparisons in this NMA is severely limited. Moreover, all pairwise comparisons were statistically non-significant and associated with extremely wide confidence intervals. Thus, treatment rankings based on *P*-scores are highly uncertain and should not guide clinical decision-making. These results are best understood as hypothesis-generating, highlighting the need for future head-to-head trials and harmonized outcome definitions.

Our study has several limitations. A significant limitation is the small sample size in the eligible rituximab trial, with only 19 patients receiving rituximab [12]. As mentioned earlier, differences in baseline characteristics and inclusion criteria across trials represent another limitation. These include variations in cohort racial composition and whether treatments were used as first-line therapy or as add-on treatment. The CHAMPION-NMOSD study [30] was open-label, whereas the other trials were blinded and placebo-controlled, reflecting

robust clinical trial methodology [12, 25–28]. For CHAMPION, a placebo group from the PREVENT study was used, as the inclusion criteria were the same. There was only one trial for each treatment, except for satralizumab, which was studied in two trials [25, 26]. No direct comparisons were available across the included trials in the NMA. Follow-up duration also differed across studies. For example, in the RIN-1 trial [12], time to first relapse was assessed over 72 weeks; the PREVENT trial [27] was terminated after 23 relapses occurred; and CHAMPION-NMOSD [30] concluded after all patients in the ravulizumab group had either completed a minimum of 50 weeks of treatment or discontinued earlier. However, hazard ratios were reported in these studies, which account for follow-up time and mitigate this bias. Some trials reported zero relapse events in one treatment arm, which introduces instability and inflated uncertainty in hazard ratio estimation within the network meta-analysis. To address this, a continuity correction (adding 0.5 to all cells) was applied. However, this approach may introduce bias and should be interpreted with caution. We did not include the extension phases of the above trials because these lacked a placebo arm, which precluded meaningful comparisons of outcomes. The absence of safety comparisons is an additional limitation. Meaningful safety comparisons would require observational and real-world data, which were beyond the scope of this NMA.

CONCLUSIONS

This network meta-analysis found hazard ratio point estimates favoring eculizumab and ravulizumab over rituximab. All comparative estimates were associated with wide and overlapping confidence intervals, reflecting statistically non-significant differences and uncertainty in relative treatment effects. Head-to-head randomized trials would represent the optimal approach to directly compare these therapies; however, given the substantial costs involved and the limited commercial incentive to compare newer therapies against an affordable and widely accessible treatment such as rituximab, real-world and registry-based studies represent the most feasible alternative. Harmonizing relapse definitions and outcome measures across studies would further improve comparability and strengthen the evidence for clinical decision-making.

ACKNOWLEDGEMENTS

We thank Professor Tim Friede and Professor Brian G. Weinshenker for scientific discussion and expert assistance.

Author Contributions. Mahdi Barzegar and Nasrin Asgari conceived and designed the study. Mahdi Barzegar prepared the first draft of the manuscript. Mahdi Barzegar and Nasrin Asgari revised the manuscript and supervised the overall conduct of the study. Data extraction was performed by Mahdi Barzegar, Sara Samadzadeh, Sini Laakso, Shima Jahani, Viktoria Papp, Clarissa Zappe, and Antonia Lefter. Quality assessment was independently conducted by Achim Berthele and Ayse Altintas (Group 1) and by Aksel Siva and Barbara Willekens (Group 2). Disagreements regarding screening, eligibility assessment, and study selection were resolved by Nasrin Asgari. Network meta-analysis and statistical analyses were independently performed by Alireza Afshari-Safavi and Sören Möller. Mahdi Barzegar, Sara Samadzadeh, Bertrand Audoin, Achim Berthele, Ayse Altintas, Barbara Willekens, Sini Laakso, Shima Jahani, Viktoria Papp, Clarissa Zappe, Antonia Lefter, Aksel Siva, Alireza Afshari-Safavi, Sören Möller, Beatrijs Wokke, Rosa Cortese, Zsolt Illes, Saif Huda, Rommer Paulus, Silvia Messina, Nicolas Collongues, Marius Ringelstein, Álvaro Cobo-Calvo, Yael Hacohen, Georgina Arrambide, Jacqueline Palace, Sara Mariotto, Romain Marignier, Ruth Geraldes, Friedemann Paul, and Nasrin Asgari contributed to manuscript review and editing, critically revised the manuscript for important intellectual content, and approved the final version for publication. Mahdi Barzegar and Nasrin Asgari had full access to the data and take responsibility for the integrity of the work as a whole.

Funding. No funding or sponsorship was received for the publication of this article.

Declarations

Conflict of Interest. Sini Laakso has received lecture fees from Alexion, Argenx, Janssen, Lundbeck, Merck, Novartis, Sanofi, and Teva; congress and travel expenses from Merck, Novartis, and UCB Pharma; and advisory fees from Argenx, Johnson & Johnson, Novartis, Sanofi, and UCB Pharma. Barbara Willekens has received lecture fees from Alexion, Argenx, Janssen, Lundbeck, Merck, Novartis, Sanofi, and Teva; congress and travel support from Merck, Novartis, and UCB Pharma; and advisory fees from Argenx, Johnson & Johnson, Novartis, Sanofi, and UCB Pharma. Silvia Messina has received speaker honoraria from UCB, Amgen, Novartis, TSF, Dynamics, Biogen, Roche, Sanofi, and Alexion, and has received research grants from the Italian Ministry of Health, Lundbeck, Euroimmun, TSF, GJF, and FISM. Mahdi Barzegar is an Advisory Board member of *Neurology and Therapy*. Sara Samadzadeh, Bertrand Audoin, Achim Berthele, Ayse Altintas, Shima Jahani, Viktoria Papp, Clarissa Zappe, Antonia Lefter, Aksel Siva, Alireza Afshari-Safavi, Sören Möller, Beatrijs Wokke, Rosa Cortese, Zsolt Illes, Saif Huda, Rommer Paulus, Nicolas Collongues, Marius Ringelstein, Álvaro Cobo-Calvo, Yael Hacohen, Georgina Arrambide, Jacqueline Palace, Sara Mariotto, Romain Marignier, Ruth Geraldes, Friedemann Paul, and Nasrin Asgari have nothing to disclose.

Ethical Approval. This study is a systematic review and network meta-analysis of previously published data. As no primary data collection from human participants was conducted, ethical approval was not required.

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