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Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders
A Systematic Review and Meta-analysis

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IMPORTANCE Neuromyelitis optica spectrum disorders (NMOSDs) are autoimmune astrocytopathies characterized by predominant involvement of the optic nerves and spinal cord. In most patients, an IgG autoantibody binding to astrocytic aquaporin 4, the principal water channel of the central nervous system, is detected. Rituximab, a chimeric monoclonal antibody specific for the CD20 B-lymphocyte surface antigen, has been increasingly adopted as a first-line off-label treatment for patients with NMOSDs.

OBJECTIVE To perform a systematic review and a meta-analysis of the efficacy and safety of rituximab use in NMOSDs, considering the potential predictive factors related to patient response to rituximab in this disease.

EVIDENCE REVIEW English-language studies published between January 1, 2000, and July 31, 2015, were searched in the MEDLINE, Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov databases. Patient characteristics, outcome measures, treatment regimens, and recorded adverse effects were extracted.

FINDINGS Forty-six studies were included in the systematic review. Twenty-five studies that included 2 or more patients with NMOSDs treated with rituximab were included in the meta-analysis. Differences in the annualized relapse rate ratio and Expanded Disability Status Scale score before and after rituximab therapy were the main efficacy measures. Safety outcomes included the proportion of deaths, withdrawals because of toxic effects, and adverse effects.

RESULTS Among 46 studies involving 438 patients (381 female and 56 male [sex was not specified in 1 patient]; mean age at the outset of treatment, 32 years [age range, 2-77 years]), rituximab therapy resulted in a mean (SE) 0.79 (0.15) (95% CI, −1.08 to −0.49) reduction in the mean annualized relapse rate ratio and a mean (SE) 0.64 (0.27) (95% CI, −1.18 to −0.10) reduction in the mean Expanded Disability Status Scale score. A significant correlation was observed between disease duration and the Expanded Disability Status Scale score. Adverse effects were recorded in 114 of 438 (26%) patients treated with rituximab. Specifically, 45 patients (10.3%) experienced infusion-related adverse effects, 40 patients (9.1%) had an infection, 20 patients (4.6%) developed persistent leukopenia, 2 patients (0.5%) were diagnosed as having posterior reversible encephalopathy, and 7 patients (1.6%) died.

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis provides evidence that rituximab therapy reduces the frequency of NMOSD relapses and neurological disability in patients with NMOSDs. However, the safety profile suggests caution in prescribing rituximab as a first-line therapy.

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Neuromyelitis optica spectrum disorders (NMOSDs) are autoimmune astrocytopathies characterized by optic neuritis and transverse myelitis and, in most patients, by IgG autoantibodies binding to astrocytic aquaporin 4 (AQP4), the predominant water channel of the central nervous system.[1-4] It has been demonstrated that AQP4-IgG has pathogenic potential: the antibody binds to the extracellular domain of AQP4, activates complement that leads to complement-mediated destruction of astrocytes, induces internalization of the water channel, and mediates antibody-dependent cell cytotoxicity.[5,6] The detection of AQP4-IgG predicts relapses of myelitis and optic neuritis, with cumulative neurological disability, and justifies prompt initiation of immunosuppressive drugs.[7-10] Current treatment options are corticosteroids and immunosuppressive drugs, including (but not exclusively) azathioprine, mycophenolate mofetil, and methotrexate.[4] These therapies may be effective because they can prevent relapses in most patients. However, this outcome often requires prolonged and even lifelong immunosuppression. Moreover, some patients have refractory disease and continue to experience frequent relapses or require high dosages of corticosteroids or other immunosuppressive drugs, with deleterious adverse effects.

Rituximab is a mouse and human chimeric IgG1 monoclonal antibody that binds to CD20 B-lymphocyte surface antigen, which is involved in B-cell activation, differentiation, and growth. Studies have shown the efficacy of rituximab in treating autoimmune diseases,[11,12] and the drug has been increasingly administered to patients with refractory or severe NMOSDs.[13,14] To date, experience with the use of rituximab in NMOSDs is still based on single-cohort studies. Moreover, recent studies[15,16] have shown that rituximab treatment may increase NMOSD relapse frequency in some patients, especially soon after the outset of treatment. To our knowledge, data are lacking on the efficacy of rituximab in AQP4-IgG–seropositive and –seronegative patients with NMOSDs and the influence of disease duration and severity on clinical response. In the present study, we performed a systematic review and a meta-analysis to evaluate the efficacy and safety of rituximab use for the treatment of NMOSDs.

Key Points

Question Is rituximab an efficacious and safe therapy for patients with neuromyelitis optica spectrum disorders (NMOSDs)?

Findings In this systematic review and meta-analysis, rituximab therapy significantly reduced the annualized relapse rate ratio and neurological disability in patients with NMOSDs. Adverse effects were recorded in 26% of patients.

Meaning Rituximab therapy may reduce the frequency of NMOSD relapses and neurological disability of NMOSDs; however, the safety profile suggests caution in prescribing rituximab as a first-line therapy.

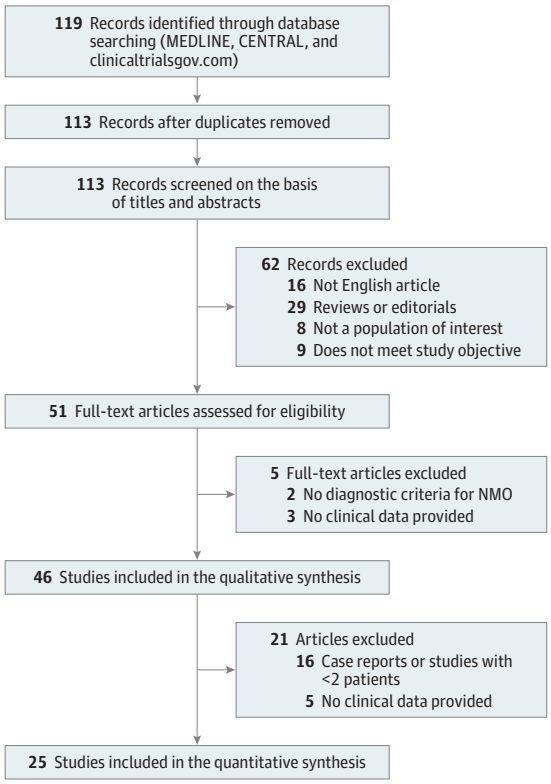
Methods

Study Selection

Two of us (V.D. and R.L.) independently searched the MEDLINE, Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov databases (published between January 1, 2000, and July 31, 2015) using the terms *neuromyelitis optica* and *rituximab* or *Devic disease* and *rituximab*. A flowchart of the search strategy is shown in **Figure 1**. The search was limited to English-language studies of humans. Because no randomized clinical trial was identified, only uncontrolled observational studies were included. The studies were read in their entirety to assess the appropriateness for their inclusion in the meta-analysis.

Case reports and studies that included fewer than 2 patients were excluded from the meta-analysis. Information extracted included study design, participant characteristics, treatment regimens, and outcome measures. For each study, the following patient characteristics were retrieved, when available: mean age, proportion of women, follow-up duration, mean disease duration, annualized relapse rate (ARR) ratio, Expanded Disability Status Scale (EDSS) score before and after rituximab therapy, AQP4-IgG serostatus, rituximab regimen, mean number of rituximab reinfusions, and adverse effects, as well as the proportion of patients who at the time of rituximab treatment received immunomodulatory drugs, corticosteroids plus another immunosuppressant, plasma exchange, or intravenous immunoglobulin (IVIG).

Figure 1. Study Selection Algorithm According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines



CENTRAL indicates Central Register of Controlled Trials; and NMO, neuromyelitis optica.

Table. Clinical and Demographic Characteristics of 438 Patients From 46 Studies Included in the Systematic Review

Studies, No.	Patients, No./ Sex, F:M[a]	Mean (Range)			Rituximab Regimen[a]	Rituximab Reinfusions per Patient, No., Mean	Therapy Before Rituximab Administration[b]	Therapy After Rituximab Administration	AQP4-IgG–Positive Serostatus[c]
		Age at Treatment Outset, y	Disease Duration at First Infusion of Rituximab, mo	Follow-up After Rituximab Therapy, mo					
46 Studies (16 reports)[13,14,16-61]	438/ 381:56	32 (2-77)	50 (1.5-276)	27.5 (3-272)	In 44.4% (139 of 313) of patients, 375 mg/m^2 weekly for 4 wk In 49.8% (156 of 313) of patients, 1 g every 2 wk for 2 times In 2.9% (9 of 313) of patients, 500 mg/m^2 weekly for 2 wk In 2.9% (9 of 313) of patients, other regimens	5 In those receiving 375 mg/m^2 weekly for 4 wk 3.6 In those receiving 1 g every 2 wk for 2 times 1.6 In those receiving 500 mg/m^2 weekly for 2 wk	Immunomodulatory drugs in 32.5% (124 of 382) of patients Immunosuppressive drugs in 37.4% (143 of 382) of patients Plasma exchange or intravenous immunoglobulin in 15.2% (58 of 382) patients None in 14.9% (57 of 382) of patients	Immunomodulatory drugs in none Immunosuppressive drugs in 6.8% (30 of 438) of patients Plasma exchange or intravenous immunoglobulin in 1.1% (5 of 438) of patients Tocilizumab in 3 patients in the study by Ayzenberg et al[37]	In 82.7% (320 of 387) of patients

Abbreviation: AQP4, aquaporin 4.

[a] Available for 313 patients.

[b] Available for 382 patients.

[c] Available for 387 patients.

Data were abstracted by one of us (V.D.) using a standardized data extraction form and were checked by another of us (R.L.). Any discrepant data were rereviewed, and disagreement was resolved by discussion and consensus.

Efficacy and Safety Measures

In this systematic review and meta-analysis, 2 primary efficacy outcome measures were assessed, namely, differences in the ARR ratio and the mean EDSS score before and after rituximab therapy. Safety outcomes included the proportion of deaths, withdrawals because of toxic effects, and adverse effects.

Statistical Analysis

The efficacy outcome measures were pooled using the method of inverse variance, with random effects on the logit-transformed proportions. The combined estimates are reported with 95% CIs. The I^2 test was used to assess the presence of between-study heterogeneity. Representative forest plots showing the ratios of the individual studies and the combined effect were generated to provide an overview of the results.

A meta-regression with random effects was performed to assess the influence of covariables on the ARR ratio and EDSS score. These included the mean disease duration, AQP4-IgG serostatus (frequency of AQP4-IgG–seropositive patients in each study), mean number of rituximab reinfusions, proportion of patients receiving immunomodulatory drugs (glatiramer acetate or interferon beta), immunosuppressive drugs, plasma exchange or IVIG, and the different rituximab regimens (375 mg/m^2 weekly for 4 weeks or 1 g weekly for 2 weeks). The meta-analysis was performed using a software program (Comprehensive Meta-Analysis; Biostat).

Results

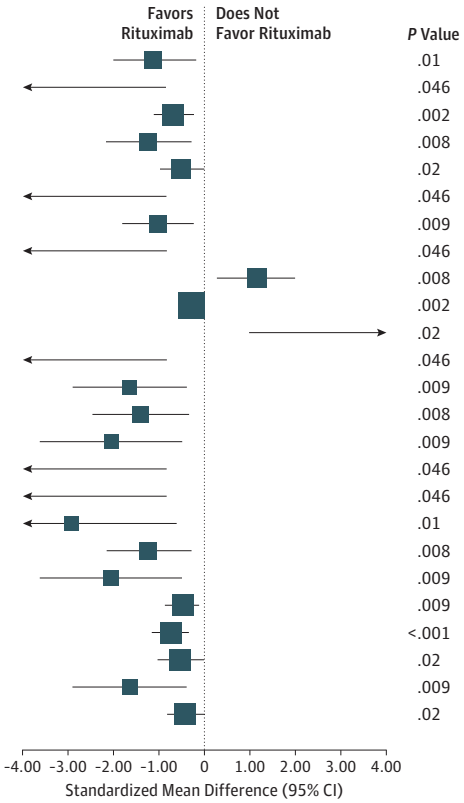
Study Characteristics

Forty-six studies were identified and included in the systematic review.[13,14,16-61] The data from the 3 studies by Kim et al[30,44,58] were pooled because the authors described the same patient population at different time points. Single-case reports and articles without sufficient clinical data were excluded from the quantitative synthesis. Twenty-five studies[13,16,17,19,22,29,31,33,34,36-38,42,43,46-48,53-55,57-61] were included in the meta-analysis.

The combined data sets of all studies included a total of 438 patients (381 female and 56 male, with sex not specified in 1 patient) treated with rituximab. The main characteristics of the patients included are summarized in the **Table**. The mean age of all patients at the outset of treatment was 32 years (age range, 2-77 years). The AQP4-IgG serostatus was reported for 387 patients, of whom 320 (82.7%) were AQP4-IgG seropositive. The mean disease duration at first infusion of rituximab was 50 months (range, 1.5-276 months), and the mean follow-up after rituximab therapy was 27.5 months (range, 3-272 months). In 57 patients (13%), rituximab was used as a first-line therapy, while 124 patients (28.3%) were treated with immunomodulatory drugs before rituximab, 143 patients (32.6%)

Figure 2. Forest Plot Showing the Annualized Relapse Rate Ratio of Patients With Neuromyelitis Optica Spectrum Disorders After Rituximab Therapy

Source	Standardized Mean Difference (95% CI)	P Value
Cree et al,[17] 2005	-1.123 (-2.007 to -0.238)	.01
Capobianco et al,[19] 2007	-45.012 (-89.145 to -0.879)	.046
Jacob et al,[13] 2008	-0.693 (-1.130 to -0.257)	.002
Jarius et al,[22] 2008	-1.237 (-2.158 to -0.317)	.008
Bedi et al,[29] 2011	-0.523 (-0.959 to -0.087)	.02
Mahmood et al,[31] 2011	-45.012 (-89.145 to -0.879)	.046
Pellkofer et al,[33] 2011	-1.028 (-1.794 to -0.262)	.009
Tosello et al,[36] 2012	-45.012 (-89.145 to -0.879)	.046
Lindsey et al,[34] 2012	1.118 (0.286 to 1.951)	.008
Kim et al,[58] 2015	-0.317 (-0.518 to -0.117)	.002
Ayzenberg et al,[37] 2013	5.730 (1.008 to 10.453)	.02
Bourre et al,[38] 2013	-45.012 (-89.145 to -0.879)	.046
Gredler et al,[42] 2013	-1.646 (-2.874 to -0.418)	.009
Ip et al,[43] 2013	-1.401 (-2.444 to -0.358)	.008
Yang et al,[46] 2013	-2.059 (-3.607 to -0.511)	.009
Alsharoqui et al,[47] 2014	-45.012 (-89.145 to -0.879)	.046
Musafir et al,[55] 2014	-45.012 (-89.145 to -0.879)	.046
Weinfurtner et al,[57] 2015	-2.920 (-5.169 to -0.672)	.01
Beres et al,[48] 2014	-1.237 (-2.158 to -0.317)	.008
Longoni et al,[53] 2014	-2.059 (-3.607 to -0.511)	.009
Mealy et al,[54] 2014	-0.503 (-0.883 to -0.123)	.009
Zéphir et al,[61] 2015	-0.745 (-1.137 to -0.354)	<.001
Radaellli et al,[59] 2016	-0.552 (-1.011 to -0.093)	.02
Perumal et al,[16] 2015	-1.646 (-2.874 to -0.418)	.009
Torres et al,[60] 2015	-0.434 (-0.796 to -0.071)	.02



Standardized mean differences of the annualized relapse rate ratio before and after rituximab therapy are shown with 95% CIs.

were receiving immunosuppressive drugs at the time of first infusion of rituximab, and 58 patients (13.2%) had plasma exchange or IVIG before rituximab therapy. The rituximab regimen was available for 313 patients and varied among studies: 139 patients (44.4%) received 375 mg/m^2 weekly for 4 weeks, 156 patients (49.8%) were treated with 1 g every 2 weeks for 2 times, and 9 patients (2.9%) received 500 mg weekly for 2 weeks, while different therapeutic regimens were used in another 9 patients (2.9%).

Efficacy on the ARR Ratio

A forest plot of the standardized mean difference in the ARR ratio before and after rituximab therapy is shown in **Figure 2**. The mean (SE) reduction in the mean ARR ratio after rituximab therapy was 0.79 (0.15) (95% CI, −1.09 to −0.50).

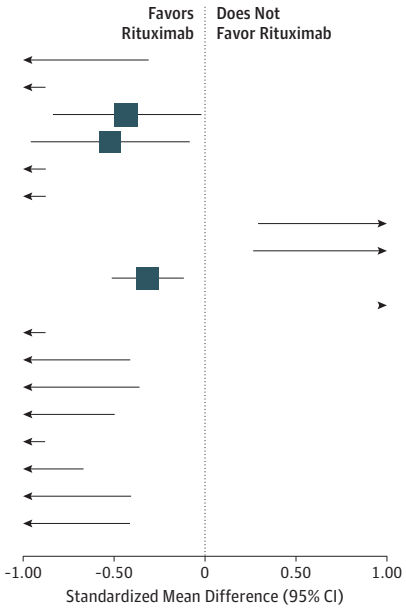
Moderate heterogeneity was detected (I^2 = 53%). To investigate the reasons for such heterogeneity and to evaluate the effect of the different covariates on the ARR ratio reduction, a meta-regression was performed. No significant correlation was detected between the outcome (ARR ratio change) and the following variables: mean number of rituximab reinfusions (P = .96; 95% CI, −0.40 to 0.42), immunomodulatory drugs before rituximab (P = .23; 95% CI, −0.40 to 0.42), IVIG (P = .42; 95% CI, −9.08 to 3.80), plasma exchange (P = .69; 95% CI, −4.96 to 7.52), different rituximab regimens (375 mg/m^2 weekly for 4 weeks [P = .30; 95% CI, −3.87 to 1.20] and 1 g every 2 weeks for 2 times [P = .68; 95% CI, −4.97 to 7.52]), disease duration (P = .71; 95% CI, −0.01 to 0.02), and AQP4-IgG serostatus (P = .40; 95% CI, −7.97 to 3.15).

Efficacy on the EDSS Score

The EDSS score was reported in 18 studies[13,16,17,19,29,31,33,34,36-38,42-44,46,47,57,60] included in the meta-analysis (**Figure 3**). Rituximab treatment resulted in a mean (SE) reduction in the mean EDSS score by 0.64 (0.27) (95% CI, −1.18 to −0.10). Substantial between-study heterogeneity was detected by the I^2 test (I^2 = 62%). To explore the reasons for this heterogeneity, a meta-regression was performed. A significant correlation was observed between disease duration and the EDSS score (P = .04; 95% CI, −0.02 to 0.10). No significant correlation was detected between the standardized mean difference of the EDSS score and the following variables: mean number of rituximab reinfusions (P = .67; 95% CI, −1.24 to 1.90), therapy with immunomodulatory drugs before rituximab (P = .59; 95% CI, −5.60 to 21.60), IVIG (P = .73; 95% CI, −18.50 to 12.59), plasma exchange (P = .76; 95% CI, −13.40 to 19.40), different rituximab regimens (375 mg/m^2 weekly for 4 weeks [P = .64; 95% CI, −7.48 to 4.07] and 1 g every 2 weeks for 2 times [P = .56; 95% CI, −8.10 to 4.07]), and AQP4-IgG serostatus (P = .27; 95% CI, −29.90 to 16.03).

Figure 3. Forest Plot Showing the Expanded Disability Status Scale Score of Patients With Neuromyelitis Optica Spectrum Disorders After Rituximab Therapy

Source	Standardized Mean Difference (95% CI)	P Value
Cree et al,[17] 2005	-1.237 (-2.158 to -0.317)	.008
Capobianco et al,[19] 2007	-45.012 (-89.145 to -0.879)	.046
Jacob et al,[13] 2008	-0.434 (-0.844 to -0.024)	.04
Bedi et al,[29] 2011	-0.523 (-0.959 to -0.087)	.02
Mahmood et al,[31] 2011	-45.012 (-89.145 to -0.879)	.046
Tosello et al,[36] 2012	-45.012 (-89.145 to -0.879)	.046
Lindsey et al,[34] 2012	1.118 (0.286 to 1.951)	.008
Pellkofer et al,[33] 2011	1.028 (0.262 to 1.794)	.009
Kim et al,[58] 2015	-0.317 (-0.518 to -0.117)	.002
Ayzenberg et al,[37] 2013	5.730 (1.008 to 10.453)	.02
Bourre et al,[38] 2013	-45.012 (-89.145 to -0.879)	.046
Gredler et al,[42] 2013	-1.646 (-2.874 to -0.418)	.009
Ip et al,[43] 2013	-1.401 (-2.444 to -0.358)	.008
Yang et al,[46] 2013	-2.059 (-3.607 to -0.511)	.009
Alsharoqui et al,[47] 2014	-45.012 (-89.145 to -0.879)	.046
Weinfurtner et al,[57] 2015	-2.920 (-5.169 to -0.672)	.01
Torres et al,[60] 2015	-22.501 (-44.594 to -0.407)	.046
Perumal et al,[16] 2015	-1.646 (-2.874 to -0.418)	.009



Standardized mean differences of the Expanded Disability Status Scale score before and after rituximab therapy are shown with 95% CIs.

Safety

Adverse effects were recorded in 114 of 438 (26%) patients treated with rituximab. Specifically, 45 patients (10.3%) experienced infusion-related adverse effects, 40 patients (9.1%) had an infection, 20 patients (4.6%) developed persistent leukopenia, 2 patients (0.5%) were diagnosed as having posterior reversible encephalopathy, and 7 patients (1.6%) died. None of the patients developed progressive multifocal leukoencephalopathy.

Discussion

In patients with NMOSDs, disability is attack related because each disease relapse causes an accumulation of disability.[62] Within 5 years of the disease onset, half of the individuals diagnosed as having neuromyelitis optica require the use of a wheelchair or become functionally blind.[4] For this reason, the main goal of NMOSD therapy is to prevent disease relapses. This systematic review and meta-analysis provides sufficient data to support the efficacy of rituximab therapy in reducing relapse rates and disability in patients with NMOSDs.

Rituximab was originally approved for the treatment of B-cell lymphoma in adults, but it has been increasingly used in autoimmune diseases in which B cells are considered to have a prominent role, such as in systemic lupus erythematosus, rheumatoid arthritis, immune thrombocytopenic purpura, and myasthenia gravis.[11,12] In NMOSDs, the pathogenic role of AQP4-IgG, as demonstrated in in vitro and in vivo studies,[4,5] justifies therapies targeting antibody-producing B cells. Rituximab primarily acts by depleting plasma cell precursors because the expression of CD20—the rituximab target antigen—is restricted to the late pre-B-cell stage, and it is maintained until the B lymphocytes differentiate into antibody-producing plasma cells, when the expression is usually downregulated. On average, B-cell depletion after rituximab therapy lasts for 12 months in the peripheral blood before the generation of a new B-lymphocyte population. It has been demonstrated that rituximab therapy does not alter the frequencies of autoreactive and polyreactive B cells; therefore, it does not reset the defective early B-cell tolerance checkpoints.[63] This finding may explain the occurrence of NMOSD relapses after rituximab therapy in some patients and may justify rituximab reinfusions during follow-up to avoid the reexpansion of autoreactive B cells and reduce the risk of NMOSD relapses. The meta-regression analysis performed in this study showed that the number of rituximab reinfusions does not affect the ARR ratios and EDSS scores in patients with NMOSDs. However, how to monitor the biological effects of rituximab therapy to decide when treatment should be repeated is a matter of debate. Kim et al[44] proposed a bimonthly assessment of CD19/CD27-positive memory B-cell frequency, which needs validation in further studies. Rituximab has been increasingly used as a first-line therapy in NMOSDs.

A significant correlation was observed herein between disease duration of patients with NMOSDs and the EDSS score after rituximab therapy, suggesting that early treatment may reduce disability. However, treatment adverse effects were observed in 26% (114 of 438) of patients. These adverse effects were minor in most cases, and 9.1% (40 of 438) of patients had an infection. While receiving rituximab treatment, 7 patients died. However, patient death may reflect the natural history of NMOSDs because the disease has been associated with a mortality rate of up to 12%.[64] These data suggest that, until the results of controlled trials become

available, the risk-benefit ratio of rituximab treatment should be carefully assessed in individual patients with NMOSDs.

A limitation of this systematic review and meta-analysis is the inclusion of observational studies with high heterogeneity. However, when we performed a meta-regression, only disease duration showed a significant correlation with the efficacy measures, suggesting that the observed heterogeneity may be mainly due to the variability of sample sizes (ie, the number of patients enrolled) in the studies included in the meta-analysis.

Conclusions

In summary, this systematic review and meta-analysis provides evidence that rituximab therapy reduces the frequency of disease relapses and neurological disability in patients with NMOSDs. It also suggests caution in prescribing rituximab as a first-line therapy until randomized trials determine the safety of the drug in this patient population.

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Study concept and design: Damato, Iorio.
Acquisition, analysis, or interpretation of data: Damato, Iorio.
Drafting of the manuscript: Iorio.
Critical revision of the manuscript for important intellectual content: Evoli.
Obtained funding: Evoli.
Administrative, technical, or material support: Evoli.
Study supervision: Iorio.

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REFERENCES

1. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet*. 2004;364(9451):2106-2112.

2. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med*. 2005;202(4):473-477.

3. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol*. 2007;6(9):805-815.

4. Iorio R, Pittock SJ. Neuromyelitis optica and the evolving spectrum of autoimmune aquaporin-4 channelopathies. *Clin Exp Neuroimmunol*. 2014;5(2):175-187. doi:10.1111/cen3.12103

5. Hinson SR, Romero MF, Popescu BF, et al. Molecular outcomes of neuromyelitis optica (NMO)–IgG binding to aquaporin-4 in astrocytes. *Proc Natl Acad Sci U S A*. 2012;109(4):1245-1250.

6. Iorio R, Fryer JP, Hinson SR, et al. Astrocytic autoantibody of neuromyelitis optica (NMO-IgG) binds to aquaporin-4 extracellular loops, monomers, tetramers and high order arrays. *J Autoimmun*. 2013;40:21-27.

7. Weinshenker BG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. *Ann Neurol*. 2006;59(3):566-569.

8. Matiello M, Lennon VA, Jacob A, et al. NMO-IgG predicts the outcome of recurrent optic neuritis. *Neurology*. 2008;70(23):2197-2200.

9. Iorio R, Damato V, Mirabella M, et al. Distinctive clinical and neuroimaging characteristics of longitudinally extensive transverse myelitis associated with aquaporin-4 autoantibodies. *J Neurol*. 2013;260(9):2396-2402.

10. Iorio R. Treatment-resistant depression and aquaporin-4 autoantibodies: is there a link? *Biol Psychiatry*. 2015;78(1):e1-e2. doi:10.1016/j.biopsych.2014.09.011

11. Rastetter W, Molina A, White CA. Rituximab: expanding role in therapy for lymphomas and autoimmune diseases. *Annu Rev Med*. 2004;55:477-503.

12. Iorio R, Damato V, Alboini PE, Evoli A. Efficacy and safety of rituximab for myasthenia gravis: a systematic review and meta-analysis. *J Neurol*. 2015;262(5):1115-1119.

13. Jacob A, Weinshenker BG, Violich I, et al. Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. *Arch Neurol*. 2008;65(11):1443-1448.

14. Greenberg BM, Graves D, Remington G, et al. Rituximab dosing and monitoring strategies in neuromyelitis optica patients: creating strategies for therapeutic success. *Mult Scler*. 2012;18(7):1022-1026.

15. Dai Y, Lu T, Wang Y, et al. Rapid exacerbation of neuromyelitis optica after rituximab treatment. *J Clin Neurosci*. 2016;26:168-170.

16. Perumal JS, Kister I, Howard J, Herbert J. Disease exacerbation after rituximab induction in neuromyelitis optica. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(1):e61. doi:10.1212/NXI.0000000000000061

17. Cree BA, Lamb S, Morgan K, Chen A, Waubant E, Genain C. An open label study of the effects of rituximab in neuromyelitis optica. *Neurology*. 2005;64(7):1270-1272.

18. Beyer AM, Wandinger KP, Siebert E, Zschenderlein R, Klehmet J. Neuromyelitis optica in a patient with an early onset demyelinating episode: clinical and autoantibody findings. *Clin Neurol Neurosurg*. 2007;109(10):926-930.

19. Capobianco M, Malucchi S, di Sapio A, et al. Variable responses to rituximab treatment in neuromyelitis optica (Devic's disease). *Neurol Sci*. 2007;28(4):209-211.

20. Birnbaum J, Kerr D. Optic neuritis and recurrent myelitis in a woman with systemic lupus erythematosus. *Nat Clin Pract Rheumatol*. 2008;4(7):381-386.

21. Cassinotto C, Joux J, Chausson N, Smadja D, Cabre P. Failure of rituximab in relapsing neuromyelitis optica: case report with two-year prospective follow-up [in French]. *Rev Neurol (Paris)*. 2008;164(4):394-397.

22. Jarius S, Aboul-Enein F, Waters P, et al. Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. *Brain*. 2008;131(pt 11):3072-3080.

23. Mangat P, Ravindran J, Cleland L, Limaye V. A case of longitudinally extensive transverse myelitis (LETM): neuromyelitis optica. *Clin Rheumatol*. 2008;27(suppl 2):S67-S69.

24. Mok CC, To CH, Mak A, Poon WL. Immunoablative cyclophosphamide for refractory lupus-related neuromyelitis optica. *J Rheumatol*. 2008;35(1):172-174.

25. Nasir S, Kerr DA, Birnbaum J. Nineteen episodes of recurrent myelitis in a woman with neuromyelitis optica and systemic lupus erythematosus. *Arch Neurol*. 2009;66(9):1160-1163.

26. Pellkofer HL, Suessmair C, Schulze A, Hohlfeld R, Kuempfel T. Course of neuromyelitis optica during inadvertent pregnancy in a patient treated with rituximab. *Mult Scler*. 2009;15(8):1006-1008.

27. Garcia-Martin E, Pinilla I, Pueyo V, Gil L, Martinez-Morales J, Fernandez J. Bilateral internuclear ophthalmoplegia in a patient with Devic's neuromyelitis optica. *Case Rep Neurol*. 2010;2(3):139-144.

28. Sánchez-Carteyron A, Alarcia R, Ara JR, Martín J. Posterior reversible encephalopathy syndrome after rituximab infusion in neuromyelitis optica. *Neurology*. 2010;74(18):1471-1473.

29. Bedi GS, Brown AD, Delgado SR, Usmani N, Lam BL, Sheremata WA. Impact of rituximab on relapse rate and disability in neuromyelitis optica. *Mult Scler*. 2011;17(10):1225-1230.

30. Kim SH, Kim W, Li XF, Jung IJ, Kim HJ. Repeated treatment with rituximab based on the assessment of peripheral circulating memory B cells in patients with relapsing neuromyelitis optica over 2 years. *Arch Neurol*. 2011;68(11):1412-1420.

31. Mahmood NA, Silver K, Onel K, Ko M, Javed A. Efficacy and safety of rituximab in pediatric neuromyelitis optica. *J Child Neurol*. 2011;26(2):244-247.

32. Nakashima I, Takahashi T, Cree BA, et al. Transient increases in anti–aquaporin-4 antibody titers following rituximab treatment in neuromyelitis optica, in association with elevated serum BAFF levels. *J Clin Neurosci*. 2011;18(7):997-998.

33. Pellkofer HL, Krumbholz M, Berthele A, et al. Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. *Neurology*. 2011;76(15):1310-1315.

34. Lindsey JW, Meulmester KM, Brod SA, Nelson F, Wolinsky JS. Variable results after rituximab in neuromyelitis optica. *J Neurol Sci*. 2012;317(1-2):103-105.

35. Patel V, Griffith NC, Blackwood E, Dias M, Cordato DJ. Spectrum disorder of neuromyelitis optica in a patient presenting with intractable vomiting and hiccups, transverse myelitis and acute encephalopathy. *J Clin Neurosci*. 2012;19(11):1576-1578.

36. Tosello B, Halbert C, Mancini J, Chabrol B, Boucraut J, Milh M. Neuromyelitis optica in children: two case reports [in French]. *Arch Pediatr*. 2012;19(8):827-831.

37. Ayzenberg I, Kleiter I, Schröder A, et al. Interleukin 6 receptor blockade in patients with neuromyelitis optica nonresponsive to anti-CD20 therapy. *JAMA Neurol*. 2013;70(3):394-397.

38. Bourre B, Lefaucheur R, Girault C. Treatment of NMO relapse in the elderly: rituximab when plasma exchange fails? *Acta Neurol Belg*. 2013;113(3):335-336.

39. Danés I, Agustí A, Vallano A, et al. Available evidence and outcome of off-label use of rituximab in clinical practice. *Eur J Clin Pharmacol*. 2013;69(9):1689-1699.

40. Dembinski K, Gieron-Korthals M, Martinez CR, Rodriguez L. Neuromyelitis optica in child: diagnostic and therapeutic challenges. *Case Rep Pediatr*. 2013;2013:124929.

41. Feyissa AM, Singh P, Smith RG. Neuromyelitis optica in patients with coexisting human immunodeficiency virus infections. *Mult Scler*. 2013;19(10):1363-1366.

42. Gredler V, Mader S, Schanda K, et al. Clinical and immunological follow-up of B-cell depleting therapy in CNS demyelinating diseases. *J Neurol Sci*. 2013;328(1-2):77-82.

43. Ip VH, Lau AY, Au LW, et al. Rituximab reduces attacks in Chinese patients with neuromyelitis optica spectrum disorders. *J Neurol Sci*. 2013;324(1-2):38-39.

44. Kim SH, Huh SY, Lee SJ, Joung A, Kim HJ. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. *JAMA Neurol*. 2013;70(9):1110-1117.

45. Ringelstein M, Harmel J, Distelmaier F, et al. Neuromyelitis optica and pregnancy during therapeutic B cell depletion: infant exposure to anti-AQP4 antibody and prevention of rebound relapses with low-dose rituximab postpartum. *Mult Scler*. 2013;19(11):1544-1547.

46. Yang CS, Yang L, Li T, et al. Responsiveness to reduced dosage of rituximab in Chinese patients with neuromyelitis optica. *Neurology*. 2013;81(8):710-713.

47. Alsharoqi I. Remarkable response of seropositive neuromyelitis optica to rituximab therapy: first report from kingdom of Bahrain. *Mult Scler Relat Disord*. 2014;3(6):761. doi:10.1016/j.msard.2014.09.206

48. Beres SJ, Graves J, Waubant E. Rituximab use in pediatric central demyelinating disease. *Pediatr Neurol*. 2014;51(1):114-118.

49. Berger JR, Neltner J, Smith C, Cambi F. Posterior reversible encephalopathy syndrome masquerading as progressive multifocal leukoencephalopathy in rituximab treated neuromyelitis optica. *Mult Scler Relat Disord*. 2014;3(6):728-731.

50. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology*. 2014;83(2):142-150.

51. Graves J, Vinayagasundaram U, Mowry EM, et al. Effects of rituximab on lymphocytes in multiple sclerosis and neuromyelitis optica. *Mult Scler Relat Disord*. 2014;3(2):244-252.

52. He D, Yu Y, Yan W, Dai Q, Xu Z, Chu L. Individualized rituximab treatment for relapsing neuromyelitis optica: a pediatric case report. *Pediatr Neurol*. 2014;51(2):255-258.

53. Longoni G, Banwell B, Filippi M, Yeh EA. Rituximab as a first-line preventive treatment in pediatric NMOSDs: preliminary results in 5 children. *Neurol Neuroimmunol Neuroinflamm*. 2014;1(4):e46. doi:10.1212/NXI.0000000000000046

54. Mealy MA, Wingerchuk DM, Palace J, Greenberg BM, Levy M. Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: multicenter study of treatment efficacy. *JAMA Neurol*. 2014;71(3):324-330.

55. Musafir SK, Shalkhly K, Zayed A, Walli F. Neuromyelitis optica: case reports from Oman. *Mult Scler Relat Disord*. 2014;3(6):741-742. doi:10.1016/j.msard.2014.09.159

56. Plate A, Havla J, Kümpfel T. Late-onset neutropenia during long-term rituximab therapy in neuromyelitis optica. *Mult Scler Relat Disord*. 2014;3(2):269-272.

57. Weinfurtner K, Graves J, Ness J, Krupp L, Milazzo M, Waubant E. Prolonged remission in neuromyelitis optica following cessation of rituximab treatment. *J Child Neurol*. 2015;30(10):1366-1370.

58. Kim SH, Jeong IH, Hyun JW, et al. Treatment outcomes with rituximab in 100 patients with neuromyelitis optica: influence of *FCGR3A* polymorphisms on the therapeutic response to rituximab. *JAMA Neurol*. 2015;72(9):989-995.

59. Radaelli M, Moiola L, Sangalli F, et al. Neuromyelitis optica spectrum disorders: long-term safety and efficacy of rituximab in Caucasian patients. *Mult Scler*. 2016;22(4):511-519.

60. Torres J, Pruitt A, Balcer L, Galetta S, Markowitz C, Dahodwala N. Analysis of the treatment of neuromyelitis optica. *J Neurol Sci*. 2015;351(1-2):31-35.

61. Zéphir H, Bernard-Valnet R, Lebrun C, et al. Rituximab as first-line therapy in neuromyelitis optica: efficiency and tolerability. *J Neurol*. 2015;262(10):2329-2335.

62. Jiao Y, Fryer JP, Lennon VA, et al. Updated estimate of AQP4-IgG serostatus and disability outcome in neuromyelitis optica. *Neurology*. 2013;81(14):1197-1204.

63. Chamberlain N, Massad C, Oe T, Cantaert T, Herold KC, Meffre E. Rituximab does not reset defective early B cell tolerance checkpoints. *J Clin Invest*. 2016;126(1):282-287.

64. Bichuetti DB, Oliveira EM, Souza NA, Tintoré M, Gabbai AA. Patients with neuromyelitis optica have a more severe disease than patients with relapsing-remitting multiple sclerosis, including higher risk of dying of a demyelinating disease. *Arq Neuropsiquiatr*. 2013;71(5):275-279.