RESEARCH ARTICLE OPEN ACCESS

Complement Inhibition for Acute Neuromyelitis Optica Spectrum Disorder Attacks

Insights From an International Case Series

Paulus S. Rommer,[1,2,*] Wei Jiang,[3,*] Jan P. Nolte,[1,2] Takahisa Mikami,[4] Jerome De Seze,[5] Pedro Sánchez,[6,7] Asaff Harel,[8,9] Samir Alkabie,[8] Kimihiko Kaneko,[10] Philippe A. Bilodeau,[4] Tatsuro Misu,[10] Laurent Kremer,[5] Kévin Bigaut,[5] Frank Leypoldt,[11] Orhan Aktas,[12] Marius Ringelstein,[12,13] Volker Siffrin,[6,7] Lin-Jie Zhang,[3] Hengri Cong,[14] Mallory Lowe,[15] Paula Barreras,[16] Haiwen Chen,[17] Amanda L. Piquet,[15] Elias S. Sotirchos,[17] Ryan Kammeyer,[15,18] Jadyn Zook,[15] Jeffrey L. Bennett,[19] Thomas Berger,[1,2] Kazuo Fujihara,[10,20] Michael Levy,[4] Fu-Dong Shi,[3,14,†] and Friedemann Paul[6,7,†]

Correspondence
Prof. Rommer
paulus.rommer@meduniwien.ac.at

Neurol Neuroimmunol Neuroinflamm 2026;13:e200548. doi:10.1212/NXI.0000000000200548

Abstract

Background and Objectives

Neuromyelitis optica spectrum disorder (NMOSD) is a severe autoimmune disease mainly driven by aquaporin-4 antibodies (AQP4-IgG). During an attack, AQP4-IgG activates the complement system, leading to astrocyte destruction, inflammation, neuronal damage, and thus devastating and often irreversible neurologic deficits. Terminal complement inhibitors such as eculizumab and ravulizumab effectively prevent relapses, yet their therapeutic potential in stopping ongoing complement-mediated injury during acute attacks remains insufficiently explored.

Methods

We conducted a multinational retrospective case series across NMOSD-specialized centers in 6 countries, analyzing 33 AQP4-IgG–positive patients (mean age: 48.1 years; 28 women) treated with component 5 (C5) inhibition during or shortly after acute relapse (mean 20.1 days from symptom onset; range 2–62). Eculizumab was used in 25 patients and ravulizumab in 8. Two additional patients were excluded because of delayed treatment initiation beyond 62 days.

Results

Lesion locations included myelitis (57.6%) and optic neuritis (30.3%). Expanded Disability Status Scale scores worsened from a pre-relapse median of 0 (interquartile range [IQR] 0–2) to a nadir of 6.5 (IQR 3.5–8), improving to 3.5 (IQR 3–6.5) at 1–3 months and 2.5 (IQR 2–6) at 6 months. All patients stabilized clinically; 20 continued C5 inhibition as attack-preventing therapy. Good, moderate, and poor/absent recovery were observed in 15, 11, and 7 patients, respectively. Earlier treatment was associated with better outcomes: treatment within 21 days yielded an odds ratio of 1.58 (95% CI 0.32–8.52) for good response. Plasma exchange was administered in 57.6% and was associated with higher overall response rates, but not with good response alone.

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Supplementary Material

*These author contributed equally to this work as co-first authors.

†These authors contributed equally to this work as co-senior authors.

[1]Department of Neurology, Medical University of Vienna, Austria; [2]Center for Clinical Neurosciences and Mental Health, Medical University of Vienna, Austria; [3]Department of Neurology, Tianjin Medical University General Hospital, China; [4]Department of Neurology, Massachusetts General Brigham and Harvard Medical School, Boston, United States; [5]Department of Neurology, Strasbourg University Hospital, France; [6]Experimental and Clinical Research Center, a Cooperation Between the Max Delbrück Center for Molecular Medicine in the Helmholtz Association and Charité Universitätsmedizin Berlin, Germany; [7]Neuroscience Clinical Research Center, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin Institute of Health, Germany; [8]Department of Neurology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Lenox Hill Hospital, New York, United States; [9]Northwell Comprehensive Multiple Sclerosis Center, Department of Neurology, Long Island Jewish Medical Center/ North Shore University Hospital/ Donald and Barbara Zucker School of Medicine at Hofstra, New York, United States; [10]Department of Neurology, Tohoku University Graduate School of Medicine, Sendai, Japan; [11]Neuroimmunology, Inst. of Clinical Chemistry and Department of Neurology, University Hospital Schleswig-Holstein and Kiel University, Germany; [12]Department of Neurology, Medical Faculty and University Hospital, Heinrich-Heine-Universität Düsseldorf, Germany; [13]Department of Neurology, Centre for Neurology and Neuropsychiatry, LVR-Klinikum, Heinrich Heine University Düsseldorf, Germany; [14]Department of Neurology, China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, China; [15]Department of Neurology, University of Colorado School of Medicine Anschutz Medical Campus, Aurora, United States; [16]Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, United States; [17]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, United States; [18]Department of Pediatrics, Section of Child Neurology, University of Colorado School of Medicine, Aurora, United States; [19]Departments of Neurology and Ophthalmology, Programs in Neuroscience and Immunology, University of Colorado School of Medicine, Denver, United States; and [20]Department of Multiple Sclerosis Therapeutics, Fukushima Medical University School of Medicine, and Multiple Sclerosis and Neuromyelitis Optica Center, Southern TOHOKU Research Institute for Neuroscience, Koriyama, Japan.

The Article Processing Charge was funded by the authors.

Glossary

AQP4-IgG = aquaporin-4 immunoglobulin G; **C5 inhibition** = pharmacologic blockade of complement component 5; **EDSS** = Expanded Disability Status Scale; **Gd-enhancement** = gadolinium contrast enhancement; **GFAP** = glial fibrillary acidic protein; **IQR** = interquartile range; **IVMP** = IV methylprednisolone; **MAC** = membrane attack complex; **NfL** = neurofilament light chain; **NMOSD** = neuromyelitis optica spectrum disorder; **OR** = odds ratio; **PLEX** = plasma exchange.

Discussion

These findings highlight the potential of complement inhibition as a treatment option for acute NMOSD attacks, particularly in patients with insufficient response to standard therapies. Given the absence of clinical worsening and the encouraging course observed in most of the patients, further investigation into the role of C5 inhibition in acute attack management is warranted.

Classification of Evidence

This retrospective case series provides Class IV evidence that the C5 complement inhibitors eculizumab or ravulizumab may improve disability in patients with NMOSD when given during or shortly after acute relapse.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease characterized by severe immune-mediated demyelination and neuroaxonal damage, classically involving the optic nerves, spinal cord, and area postrema.[1] Antibodies against aquaporin-4 (AQP4-IgG), a water channel protein expressed on astrocytes, are found in most of the patients.[2,3] These antibodies trigger a pathophysiologic cascade leading to complement activation, lesion formation involving astrocyte destruction, demyelination, and neuronal and astrocytic death,[4] resulting in severe neurologic deficits.[5] Over time, the cumulative impact of attacks causes the significant high morbidity and mortality in NMOSD,[6] which thus mandates an immediate and effective therapeutic intervention: for both the prevention of further attacks and the reduction of irreversible damage during the acute attack.

Attacks of NMOSD are medical emergencies, which require rapid and targeted therapeutic approaches to prevent tissue damage in the CNS.[7,8] Current expert recommendations for acute attacks include high-dose IV corticosteroids and, in refractory cases, plasma exchange (PLEX) or immunoadsorption.[9] Despite these therapies, response is often incomplete, leaving a subset of patients with significant disability after attacks.[8]

Recent insights into the pathophysiology of NMOSD have led to the regulatory approval of highly specific and effective therapies: eculizumab, ravulizumab, inebilizumab, and satralizumab.[10-14] While these therapies are approved for the *prevention* of attacks in AQP4-IgG+ patients, there is growing interest in their potential for treating acute attacks. In particular, complement inhibitors such as eculizumab and ravulizumab have a rapid onset of action, achieving complete complement blockade within approximately 60 minutes of administration.[15,16] Complement inhibitors prevent the cleavage of complement component 5 (C5) into its active parts C5a and C5b. C5a is an important anaphylatoxin that causes further recruitment of immune cells,[17] and C5b initiates the formation of the membrane attack complex (MAC). Thus, tissue damage is prevented and the inflammatory cascade is attenuated.[18]

This pharmacodynamic profile makes C5 inhibitors promising candidates for the mitigation of the acute damage caused by complement-mediated NMOSD attacks. However, evidence for this application is limited, and aside from a growing number of individual cases,[19-21] there are no published studies on its use in acute treatment.

This case series presents a collection of internationally identified patients with AQP4-IgG+ NMOSD who received C5 inhibitors for the treatment of acute NMOSD attacks. We gathered patients in whom complement inhibition was administered either after conventional escalation therapies had been exhausted or as a first-line treatment during acute attacks. We report on the potential efficacy, safety, and rapid therapeutic effects of C5 inhibition in acute NMOSD management. This case series provides a foundation for a prospective randomized trial on complement inhibition in the management of acute NMOSD attacks.

The primary research question was whether complement C5 inhibition is an effective treatment for acute AQP4-IgG–positive NMOSD relapses when administered during or shortly after attack onset, as measured by short-term disability outcomes.

Methods

This case series investigates the use of complement inhibitors for the treatment of acute relapses in 33 patients with AQP4-

IgG–positive NMOSD. The primary objective was to assess the clinical response to complement inhibitors (eculizumab or ravulizumab), measured by the Expanded Disability Status Scale (EDSS) and functional scores, as well as secondary parameters such as biomarkers (e.g., glial fibrillary acidic protein [GFAP],[22] if available). In addition, statistical analysis was performed to investigate parameters that may influence the response to treatment, including age, disease severity, prior treatments, disease duration, and the time to C5 inhibition.

Study Design

This was a retrospective, descriptive analysis of individual cases treated with C5 inhibition for acute worsening in a relapse. The inclusion criteria were as follows:

1. A confirmed diagnosis of NMOSD based on international consensus criteria[1];
2. Seropositivity for AQP4-IgG;
3. Presentation of an acute NMOSD attack characterized by new or worsening neurologic deficits;
4. C5 inhibition (with either eculizumab or ravulizumab) initiated as attack treatment, defined by persistent neurologic deficits without recovery to pre-relapse baseline EDSS score, no initiation of new maintenance therapy before or during C5 inhibition, and administration within 62 days of relapse onset.

The 2-month (≤62 days) cutoff was selected pragmatically, acknowledging that, in clinical practice, sequential therapies such as repeated corticosteroid courses and plasmapheresis frequently delayed C5 inhibition; this time frame ensured sufficient patient inclusion in the absence of an established standard in the literature.

Of the initially enrolled 35 patients, 2 were excluded because of the predefined cutoff, resulting in 33 patients included in the analysis.

Patient Selection

Patients were selected based on the occurrence of an acute attack in which standard first-line therapies, such as corticosteroids and/or PLEX, were either insufficient or deliberately omitted in favor of C5 inhibition because of its anticipated rapid onset of action. The cases represent diverse clinical scenarios, including patients with a long history of NMOSD receiving maintenance treatments, newly diagnosed patients treated during their first attack, and individuals with complex comorbidities. Because this was a retrospective case series, no internal control group of patients treated without complement inhibition was available for inclusion. While data on patients receiving corticosteroids and/or PLEX alone exist in the literature, heterogeneity in study designs, treatment protocols, and patient populations precluded direct comparisons. Therefore, this analysis remains exploratory and descriptive in nature.

Definition of Relapse

Relapse was defined according to the 2015 NMOSD diagnostic criteria[1] as new or worsening focal neurologic deficits lasting ≥24 hours in the absence of fever or infection. Attack onset was defined as the first neurologic symptom of functional relevance, confirmed clinically and, when available, radiologically.

Interventions

Complement inhibitors were administered after a thorough clinical evaluation and a determination of need for escalated therapy. Routine attack treatments prior to complement inhibition were documented; PLEX was not performed in most cases. The timing of complement inhibitor administration relative to symptom onset was systematically recorded, along with detailed dosage and administration protocols. Complement inhibition was administered using either eculizumab or ravulizumab, with detailed documentation of the number of infusions given. This included cases where treatment was used exclusively for attack management as well as those where it was followed by maintenance therapy with agents other than C5 inhibitors. For patients who had not yet completed the necessary meningococcal vaccinations, antibiotic prophylaxis was provided during treatment and for at least 2 weeks after the last vaccination.

Data Collection and Outcome Measures

Clinical data were gathered retrospectively from patient records by participating physicians using standardized tables and synopsis and included the following:

1. Baseline demographics and clinical characteristics,
2. Details of the acute attack, including severity (EDSS score) and magnetic resonance imaging (MRI) findings,
3. Treatment protocols, including adjunctive therapies,
4. Outcomes, measured by functional recovery (e.g., changes in EDSS score), resolution of MRI gadolinium (gd) enhancement, and time to clinical improvement,
5. In a subgroup of patients, blood samples during relapse and 4 weeks after treatment were analyzed for neurofilament light chain (NfL) and GFAP.

Biomarker Testing

The levels of NFL and GFAP in serum were measured using a single molecule array (SIMOA) HD-X analyzer in combination with the Simoa Neurology 2-Plex B Advantage PLUS Kit (GFAP, NF-light) from Quanterix (Catalog Number: 104670). Serum samples were procured on Day 0, prior to the commencement of eculizumab treatment, and on Day 28, subsequent to the initiation of eculizumab therapy. Immediately after collection, these samples were promptly flash-frozen and subsequently cryopreserved for further analysis.

Statistical Analysis

Recovery was assessed descriptively, broadly following a previously reported approach.[8] To allow for more granularity, response to C5 inhibition was adapted and classified as good,

moderate, or poor/absent.[23,24] A good response was defined as full recovery from the attack or a partial but marked improvement, indicated by an EDSS decrease by ≥ 1 in the case of a nadir EDSS score of ≤3, or a decrease by ≥ 2 for a nadir EDSS score of >3. A moderate response was defined as improvement less than that stated above and poor/absent recovery as either no improvement or improvement not captured by the EDSS.

Continuous variables were summarized using mean and SD, except for EDSS score, which was reported as medians and interquartile ranges (25th–75th percentiles). Two-group comparisons were performed with the Welch *t* test or the Wilcoxon rank-sum test, while Welch analysis of variance or the Kruskal-Wallis test was used in case of 3 or more groups, as appropriate. The assumption of normality was assessed using quantile-quantile plots. Spearman rank correlation was applied to assess the association between time to initiation of C5 inhibition and EDSS score at 1–3 months. Categorical variables were presented as absolute frequencies and percentages and compared using the Fisher exact test. The conditional maximum likelihood estimate of the odds ratio (OR) was reported as an effect size, along with its exact 95% CI. To this end, good treatment response was compared with moderate or poor/absent response. Conditional probabilities of good treatment response, given selected clinical characteristics, were reported alongside the corresponding ORs. Sensitivity analyses were performed using cumulative logit models, with treatment response (poor/absent < moderate < good) as the dependent variable and individual clinical characteristics as independent variables. The proportional odds assumption was assessed using likelihood ratio tests, and partial cumulative logit models were applied where necessary. To further investigate the association between good treatment response and time to C5 inhibition or time between treatments, Firth logistic regression was used. In addition, the C5 inhibition subgroups (with or without concomitant PLEX) were compared with 30 patients from a previous study who had received both PLEX and IV methylprednisolone (IVMP).[25] Inverse probability of treatment weighting was derived from a logistic propensity score model including age, disease duration, and EDSS score at relapse. Differences in EDSS scores at last follow-up were assessed using weighted Wilcoxon rank-sum tests, with variance estimation accounting for center-level clustering. Covariate balance was evaluated using standardized mean differences. CIs and 2-sided *p* values were interpreted in an exploratory manner. Missing data were assumed to be missing at random. All statistical analyses were conducted in R version 4.4.0.[26]

Standard Protocol Approvals, Registrations, and Patient Consents

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Vienna, Austria (EK 1133/2022). Additional local institutional approvals or exemptions were obtained at participating centers in China, France, Germany, Japan, and the United States according to national regulations. Because complement inhibition is an approved therapy in all involved countries and this analysis was retrospective, specific written informed consent was waived or covered by institutional policies. For all published data containing potentially identifiable information, consent for publication was obtained where applicable. No animal experiments were performed, and the study was not registered as a clinical trial.

Data Availability

The data supporting the findings of this study are available from the corresponding author on reasonable request. Restrictions apply to the availability of some data because of privacy and ethical considerations.

Results

A total of 33 patients from centers across Austria, China, France, Germany, Japan, and the United States were included in this case series. Two cases have already been published but are also included in this multicenter analysis.[27] Owing to the initiation of C5 inhibition beyond the predefined two-month threshold, 2 patients were excluded from the prespecified analysis, resulting in a final analysis cohort of 33 patients. Three main reasons for initiating complement inhibition were identified: insufficient response to standard attack therapy (24 patients), contraindications or infeasibility of established acute therapies (4 patients), and fulminant or life-threatening relapses (5 patients).

The mean age of the final cohort was 48.1 years (SD 16.2), with a female predominance (85%). The mean disease duration was 3.3 years (SD 6.9), 42.4% of the patients were experiencing their first attack, and 58% of the cohort were not on immunomodulatory treatment at attack onset. The baseline median EDSS score prior to attack was 0 (IQR 0–2). Among those on treatment, 5 were receiving anti-CD20 therapy (39%), 2 were on anti-CD19 therapy (15%), 1 was treated with an IL-6 receptor inhibitor (8%), 2 were on mycophenolate mofetil (15%), and 3 were maintained on oral corticosteroids (23%). Baseline characteristics are given in Table 1.

During the acute attack, the first median EDSS score at presentation was 5.0 (IQR 3–6.5, range 0–8.5). At nadir, the median EDSS score increased to 6.5 (IQR 3.5–8, range 0–9). The median EDSS deterioration from the pre-relapse state to nadir was 4.0 (IQR 2.0–7.5, range 0–9). Myelitis was the predominant clinical manifestation, reported in over half of the patients (57.6%), followed by optic neuritis (30.3%). Ten patients (30.3%) presented with more than 1 symptom. MRI activity (new T2 lesions) was present in 97% (1 missing data), whereas postgadolinium enhancement on MRI was observed in 75.8% of the cases.

C5 inhibition was initiated in all patients around the time of EDSS nadir, with a mean of 20.1 days from symptom onset

Table 1 Baseline Characteristics

	N = 33
Female patients[a]	28 (84.8)
Age at relapse[b] **(y)**	48.1 (16.2)
Disease duration[b] **(y)**	3.3 (6.9)
First attack[a]	14 (42.4)
Prior maintenance treatment[a]	13 (39.4)
Baseline EDSS score prior to relapse[b]	0 (0–2)

Abbreviations: EDSS = Expanded Disability Status Scale.
[a] Number (percentage).
[b] Mean (SD).

(SD 12.5). The variability in the interval to C5 inhibition reflected differences in treatment strategies and, in some newly diagnosed patients, may be attributed to delays in obtaining AQP4-IgG serostatus results. All but 3 patients received IV corticosteroids (87.9% received 1 g of methylprednisolone daily, 3% 2 g daily as high-dose pulses), and more than half underwent PLEX or immunoadsorption (57.6%). The mean time between the last corticosteroids or PLEX/immunoadsorption and C5 inhibition was 5.8 days (SD 6.5).

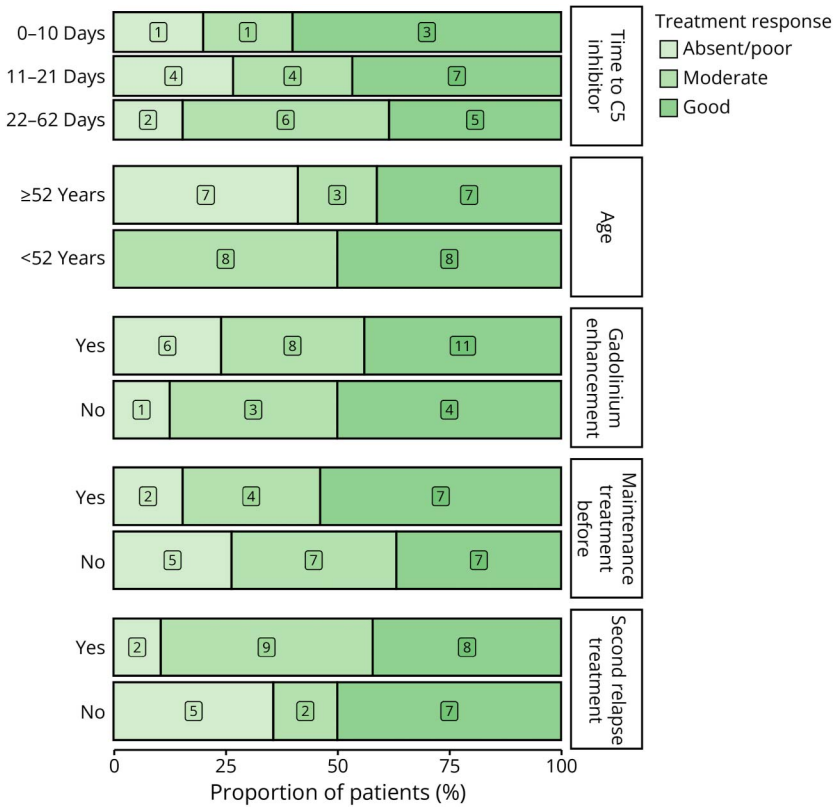
In our final cohort of 33 patients, 25 received eculizumab and 8 received ravulizumab. The number of cycles of C5 inhibition varied: 1 patient (3%) received a single infusion, 3 patients (9%) received 2 infusions, 7 patients (21%) received 4 infusions, and 1 patient each (3%) received 5 and 6 infusions over a median period of 6 weeks (IQR 2–6 weeks). In 20 patients (61%), C5 inhibitors were initiated during the acute attack and subsequently continued as maintenance therapy. Five patients showed full recovery, 27 showed partial recovery, and 1 showed no recovery. Further analysis revealed that 15 patients showed a good response, 11 had a moderate response, and 7 had a poor/absent response. The median EDSS score improved from 6.5 (IQR 3.5–8) at nadir to 3.5 (IQR 3–6.5) at short-term follow-up (1–3 months) and further to 2.5 (IQR 2–6) at follow-up after 6 months (n = 17, 51.5%).

There was a significant variation in mean age across response categories, with younger age associated with better treatment outcomes (good response: 43.4 years [SD 16.3], moderate: 46.8 years [SD 16.8], poor/absent: 60.3 years [SD 8.8], p = 0.013). A trend toward a more favorable treatment response was observed with earlier initiation of C5 inhibition, despite heterogeneous outcomes (eFigure 1). When comparing good with moderate/poor treatment response, a good response was observed in 60% of patients who received the C5 inhibitors within 10 days after symptom onset compared with 42.9% of those treated later (OR: 1.96, 95% CI 0.19–26.94). The mean time to initiation of C5 inhibition after symptom onset was 20.1 days. Using this value as a threshold for exploratory analysis, treatment within 21 days was associated with an OR of 1.58 (95% CI 0.32–8.52) for good response. A longer delay in initiating C5 inhibition was associated with higher EDSS scores at 1–3 months (r = 0.27). This association between time to treatment and follow-up EDSS scores was more pronounced in patients with a favorable treatment response (r = 0.43). Logistic regression indicated that, among patients who received C5 inhibition either as first-line treatment or immediately after IVMP, each additional week of delay in C5 inhibition was associated with lower odds of a good treatment response (OR = 0.68, 95% CI 0.19–2.06). In the subgroup that received prior treatment (IVMP and/or PLEX), a 1-week longer delay from the last treatment to C5 inhibition demonstrated a similar trend (OR = 0.57, 95% CI 0.17–1.29). Notably, patients receiving plasmapheresis had a longer time to C5 therapy initiation, with a mean of 25.3 days (SD 13.4) in comparison with 12.9 days (SD 6.3) in the group without a second relapse treatment (p = 0.001). They were also younger, presented more often with myelitis as a leading symptom, and showed a higher EDSS score in comparison (Figure 1 and eTable 1). 42% of patients who received plasmapheresis as a second-line treatment had a good response as opposed to 50% patients who did not receive the treatment (OR: 0.73, 95% CI 0.15–3.61). In the sensitivity analysis, plasmapheresis as a second-line treatment was associated with a reduced likelihood of a good response alone, but an increased likelihood of any response (good or moderate vs poor/absent; OR: 4.72; 95% CI 0.76–29.38). Trajectories of all patients are shown in eFigure 2.

Meanwhile, maintenance treatment with immunosuppressive drugs prior to the current relapse was associated with a beneficial treatment response (54%), compared with 37% without prior treatment (OR: 1.96, 95% CI 0.38–10.59). By comparison, Gd enhancement on MRI was linked to poorer outcomes, with 44% showing good responses in comparison with 50% without Gd enhancement (OR: 0.79, 95% CI 0.11–5.31). In first-onset attacks, a good response was observed in 35.7% of cases, compared with 52.6% in patients with established disease (OR: 0.51; 95% CI 0.10–2.52). Myelitis as a leading symptom decreased the chance of a good treatment response (OR: 0.73, 95% CI 0.15–3.6), with 42% achieving good treatment responses in contrast to 50% in patients with other leading symptoms. Conversely, 50% of the patients with optic neuritis as a leading symptom showed a beneficial outcome compared with 43.5% with other symptoms (OR: 1.29, 95% 0.23–7.42). Patients with more than 1 symptom had a lower likelihood of a good treatment response, with an OR of 0.73 (95% CI 0.12–4.12), whereas 40% with multiple symptoms had a beneficial outcome vs 48% with 1 leading symptom.

After the attack, 20 patients continued C5 inhibition (60% eculizumab, 40% ravulizumab), whereas 13 were switched to alternative maintenance therapies. Among these, 8 patients (61.5%) received B cell–depleting therapy (4 anti-CD19 therapy and 4 anti-CD20 therapy), 3 received IL-6R inhibitors

Figure 1 Treatment Response by Clinical and Therapeutic Factors



Proportions of patients with good, moderate, or poor/absent treatment responses, stratified by time to C5 inhibition, presence of gadolinium enhancement, use of maintenance therapy prior to relapse, and administration of a second-line relapse treatment (i.e., PLEX or immunoadsorption). PLEX = plasma exchange.

(23.1%), and 2 were treated with corticosteroids (15.4%). Patients who remained on C5 inhibition were younger on average (44.2 years (SD 18.9) vs 54.2 years (SD 8.3), p = 0.045) and had a shorter disease duration (mean 2.71 years (SD 5.4) vs mean 4.25 years (SD 9), p = 0.81). At 6 months, patients (n = 17) receiving C5 inhibitors as a maintenance therapy (70.6%) had a better median functional recovery (median EDSS score 2.25 (IQR 2–3) vs 6.0 (IQR 3–6.5), p = 0.253). Sensitivity analyses revealed differences in the estimated odds ratios across models, although none reached statistical significance (eTable 2).

When comparing C5 inhibition with PLEX with the control group treated with PLEX and IVMP from a previous study,[28] the weighted median EDSS score at last follow-up was comparable between groups (3 [IQR 2–6.5] vs 3 [IQR 2–4], p = 0.133). A similar pattern was observed when comparing C5 inhibition without PLEX with the PLEX/IVMP group (3 [IQR 2–3.5] vs 3 [IQR 2–3], p = 0.484). Weighting achieved acceptable balance despite heterogeneity between the 2 studies (eFigure 3). In the control group, the EDSS score at last follow-up was uniformly assessed at 6 months. Among patients who received C5 inhibition with PLEX, 73.7% underwent 6-month assessments, whereas of those without PLEX, only 21.4% were assessed at 6 months. The remaining patients were evaluated at 1–3 months, during which outcomes tended to improve with longer follow-up, limiting direct comparability between groups (Figure 2).

In a subgroup of patients, NfL and GFAP levels were measured; however, owing to the small sample size, no significant associations were observed (eFigure 4).

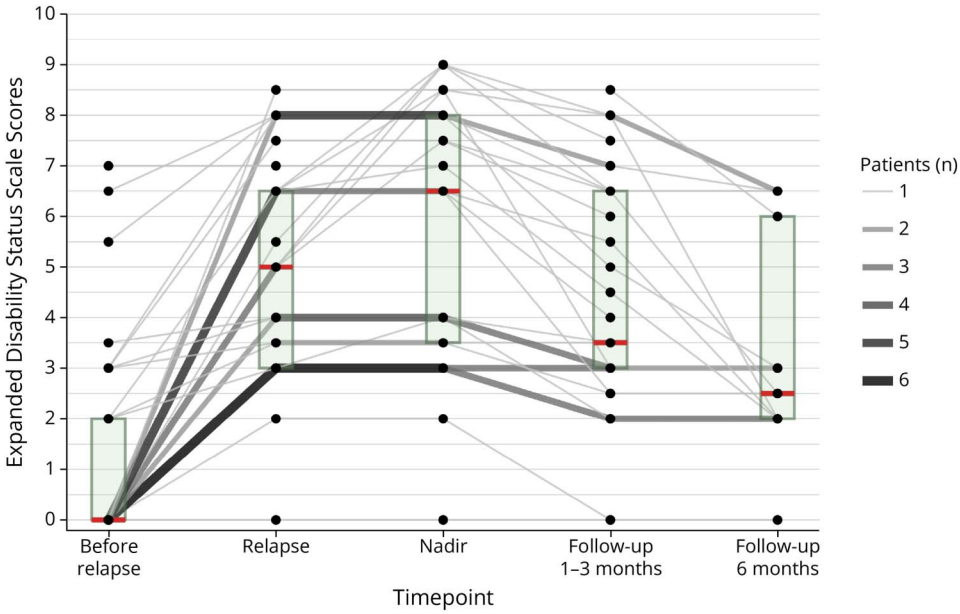
Regarding vaccination status, only 8 patients (24.2%) had received meningococcal vaccination prior to their first C5-inhibitor infusion. The remaining 25 patients required antibiotic prophylaxis before vaccination was completed.

Complement inhibition was overall well tolerated across the 33 patients. No infusion-related reactions occurred, and no meningococcal infections were observed; all patients had received vaccination and antibiotic prophylaxis according to local protocols.

Infections were uncommon. One case of community-acquired pneumonia occurred during ravulizumab therapy in a 46-year-old man who had recently received rituximab, high-dose corticosteroids, immunoadsorption, and PLEX; the infection resolved with standard antibiotic treatment. Another patient with a preexisting history of recurrent urinary tract infections experienced further episodes under complement inhibition; given her long-standing rituximab exposure and low-dose steroid use, these events were considered unrelated. No opportunistic infections were documented.

Hematologic adverse events were rare. A single case of reversible thrombocytopenia occurred after 4 doses of

Figure 2 EDSS Trajectories Over 5 Time Points in All Patients



EDSS scores are shown at 5 time points: prior to relapse, during relapse, at the nadir before initiation of C5 inhibition, 1–3 months after relapse, and 6 months after relapse, in all 33 patients. Box plots illustrate the interquartile range at each time point, with the median indicated in red. The thickness and grayscale intensity of connecting lines reflect the number of patients with overlapping trajectories. In 25 patients, the nadir EDSS score matched the first postrelapse measurement, resulting in horizontal lines between these 2 time points. EDSS = Expanded Disability Status Scale.

eculizumab in a 52-year-old woman. Platelets declined from 159 × 10^9/L to 85 × 10^9/L and normalized within 2 weeks after discontinuation. This patient was only on concomitant low-dose prednisone and had not received rituximab, mycophenolate, or azathioprine, making a causal relationship with eculizumab more likely.

One patient died of rapidly progressive breast cancer during follow-up; this event was judged unrelated to complement inhibition, and the patient had also received high-dose corticosteroids and PLEX prior to treatment.

No treatment discontinuations occurred due to adverse events. Overall, complement inhibition was safe in the acute relapse setting, with only isolated and mostly mild adverse events. Observed infections and cytopenias occurred in the context of prior or concomitant immunotherapies such as rituximab, corticosteroids, and PLEX, and no meningococcal or opportunistic infections were recorded.

Classification of Evidence

This retrospective case series provides Class IV evidence that the C5 complement inhibitors eculizumab or ravulizumab may improve disability in patients with NMOSD when given during or shortly after acute relapse.

Discussion

This international case series presents one of the largest cohorts to date of patients with AQP4-IgG–positive NMOSD treated with complement inhibitors during acute attacks. It includes both newly diagnosed and pretreated individuals with relapses ranging from severe spinal cord involvement to bilateral optic neuritis and brainstem syndromes, across all age groups. Complement inhibition was initiated either early or after insufficient response to corticosteroids and PLEX. Clinical stabilization or improvement was achieved in most cases, supporting the potential role of C5 inhibition beyond relapse prevention.

Patients using eculizumab or ravulizumab, although currently licensed only as maintenance therapies, showed potential clinical benefits in the acute setting, with 46% showing a good clinical response and an additional 33.3% achieving moderate improvement. These outcomes appear more favorable than those reported by NEMOS,[28] which found that approximately 1 in 6 patients with myelitis and 1 in 3 patients with optic neuritis achieved good response. In our cohort, the median EDSS score increased from 0 (IQR 0–2) before relapse to 6.5 (IQR 3.5–8) at nadir, followed by an improvement to 3.5 (IQR 3–6.5) at 1–3 months and 2.5 (IQR 2–6) at 6 months.

Our data also show that good outcomes were less likely in patients with delayed initiation of C5 therapy after attack onset; thus, time to treatment with C5 inhibitors may be a factor influencing the outcome. In exploratory logistic regression, each additional week of delay in initiating C5 inhibition was associated with lower odds of a good treatment response, further supporting the importance of early complement blockade. These findings support the use of C5 inhibition as an effective rescue strategy, including in cases where conventional therapies such as corticosteroids and/or PLEX had been ineffective or omitted.

The clinical effect of complement inhibition reflects its immediate blockade of C5 cleavage, simultaneously preventing MAC formation and C5a-mediated inflammation. This

rapidly halts astrocyte injury and immune cell recruitment. Notably, complement inhibition becomes effective within 60 minutes,[15] offering a faster and more targeted onset than PLEX. By contrast, PLEX reduces serum complement factors by up to 40%, but levels typically return to baseline within 24 hours,[29,30] allowing ongoing complement activation until pathogenic antibodies are sufficiently removed. In addition, rapid inhibition of complement activity may provide a milieu more suitable to CNS repair.[31] In this cohort, the timely initiation of C5 inhibitors—particularly within 21 days of symptom onset—was associated with better outcomes, underscoring the importance of early intervention.

Functional recovery appeared more pronounced in younger patients and those receiving background immunotherapy, suggesting a potential interaction between individual factors and treatment response. Patients with myelitis as the leading clinical manifestation also tended to have poorer outcomes, suggesting that spinal cord involvement may be linked to more severe disease or slower recovery. In addition, patients who received PLEX tended to initiate C5 inhibition at a later time point and showed a more heterogeneous treatment response. Although the number of cases was too small for statistical significance, the proportion of patients with a complete response appeared lower in this subgroup. This observation may reflect delayed initiation of complement inhibition after PLEX or, alternatively, a more severe disease course in patients requiring escalation to PLEX (eFigure 5). In support of this interpretation, patients receiving PLEX had significantly higher EDSS scores at relapse and nadir and more frequently presented with myelitis and multiple symptoms (eTable 1). Because C5 inhibition was frequently initiated after a delay following PLEX in this subgroup, the specific contribution of complement blockade to the clinical response is difficult to disentangle from the preceding effects of PLEX. A synergistic effect of both therapies cannot be excluded.

Of interest, patients experiencing their first clinical attack were less likely to benefit, potentially because of diagnostic delays or lack of preexisting immunosuppression.

Despite the low sample size, the observed trend toward lower baseline or stable NfL levels in responders compared with nonresponders raises the hypothesis that serum NfL might serve as an early marker of therapeutic outcome in acute NMOSD attacks. By contrast, although GFAP has been proposed as a biomarker for disease prognosis and monitoring,[22] its levels were more variable and showed no consistent association with clinical outcome. Despite some contradictory patterns, several important insights can be drawn. First, the kinetics of GFAP elevation after a relapse remains poorly understood, and longer follow-up intervals may be necessary to detect meaningful changes.[32,33] Second, the small sample size of 6 patients limits the generalizability of these findings and precludes definitive conclusions.

The safety profile of complement inhibition in this cohort was favorable, with no treatment-related adverse events reported. Antibiotic prophylaxis was successfully implemented in patients who had not yet completed meningococcal vaccination, highlighting the feasibility of safe administration in urgent clinical contexts. While the high cost of C5 inhibitors remains a barrier to widespread use, this must be considered in the context of the substantial long-term economic burden associated with NMOSD relapses, which are a major contributor to cumulative disability, health care utilization, and loss of productivity.[34,35] One patient died during the observation period; however, the case appeared not to be related to complement inhibition. The patient died of breast cancer.

It is important to note that complement inhibition may also offer practical advantages over PLEX, particularly in settings with limited infrastructure or access to specialized procedures. Unlike PLEX, C5 inhibitors can be administered in a broader range of clinical environments and allow for seamless transitions from acute management to maintenance treatment, as illustrated in several of our cases. Tailoring postrelapse strategies based on individual disease course and comorbidities remains essential. The fact that 20 patients remained on C5 inhibition supports the utility of C5 inhibition as a tolerable treatment.

Nonetheless, several limitations have to be acknowledged. A major limitation of this study is its retrospective, uncontrolled design, which precludes definitive conclusions regarding the efficacy of complement inhibition in acute NMOSD attacks. While comparison with a recently published cohort[25] provides useful context, differences in patient selection, treatment protocols, and follow-up intervals limit the interpretability of these data. Potential confounders, including the reasons for choosing C5 inhibition over other escalation therapies, also cannot be fully accounted for. Nevertheless, after reanalyzing the raw data from the referenced study,[25] we found no substantial differences between C5 inhibition with or without PLEX and the control group treated with PLEX and IVMP. It is important to note that, because data were collected retrospectively, subtle adverse events may have been underreported. These limitations highlight the need for prospective, controlled studies to confirm these exploratory findings and to better define the role of complement inhibition in acute attack management.

In summary, this case series provides exploratory evidence that complement inhibition with eculizumab or ravulizumab may represent a promising therapeutic approach for acute NMOSD attacks. This is underlined by the heterogeneity of our enrolled patients, which further emphasizes the need for a controlled trial. By targeting a central pathophysiologic mechanism, C5 inhibition has the potential to limit disease progression and support short-term recovery. While the outcomes observed in this cohort appear favorable compared with historical data on corticosteroids and PLEX,[8,25,28] these comparisons must be interpreted with caution because of differences in study design, patient populations, and treatment protocols. Prospective, controlled studies are, therefore,

needed to define the role of complement inhibition in the acute management of NMOSD, including optimal timing, patient selection, and long-term effects.

Acknowledgment

The authors thank Dr. De-Cai Tian from Tiantan Hospital, Beijing, China, who kindly shared the raw data. With his permission, the authors reanalyzed and compared these data in the context of this article.

Author Contributions

P.S. Rommer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. W. Jiang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J.P. Nolte: analysis or interpretation of data. T. Mikami: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. De Seze: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P. Sánchez: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Harel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Alkabie: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K. Kaneko: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P.A. Bilodeau: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T. Misu: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Kremer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K. Bigaut: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Leypoldt: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. O. Aktas: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Ringelstein: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. V. Siffrin: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L.-J. Zhang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H. Cong: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Lowe: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P. Barreras: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. H. Chen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A.L. Piquet: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E.S. Sotirchos: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. R. Kammeyer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Zook: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J.L. Bennett: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T. Berger: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. K. Fujihara: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Levy: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F.-D. Shi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. F. Paul: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

The authors report no targeted funding.

Disclosure

P.S. Rommer has received personal fees for consultancy or lectures/education from A-med, Alexion/AstraZeneca, Almirall, Amicus, Biogen, Horizon/Amgen, Merck, Novartis, Roche, Sandoz, Sanofi, and Teva. He received research support from Amicus, Biogen, Merck, and Roche and has research collaborations with Indapta. His research was funded by the Austrian Science Fund (FWF). W. Jiang declares no conflicts of interest. J.P. Nolte has participated in meetings sponsored by Biogen and Novartis. T. Mikami's institution has received research grant support from Alexion in the past 12 months. J. De Seze has received honoraria for board membership and conference participation from Alexion/AstraZeneca. P. Sánchez received speaking honoraria from Roche and Novartis. A. Harel has received honoraria related to consultative services, advisory board participation, or lectures from Teva, Biogen, Alexion, Horizon/Amgen, Bristol Myers Squibb, TG Therapeutics, and Banner Life Sciences. S. Alkabie declares no conflicts of interest. K. Kaneko received speaker honoraria from Novartis, Chugai, and Biogen Japan and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. P.A. Bilodeau receives funding from the Department of Defense, the Canadian Institutes of Health Research (Banting Award), and the Ann Theodore Foundation

Breakthrough Sarcoidosis Initiative (ATF-BSI). His institution receives funding from Alexion Pharmaceuticals. T. Misu received speaker honoraria from Tanabe Mitsubishi, Novartis, Alexion, Viela Bio, Teijin, Chugai, Sanofi, GE Health Care Japan, CSL Behring, and Biogen Japan and research support from Cosmic Corporation and Medical Biological Laboratories. T. Misu also received a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. L. Kremer declares no conflicts of interest. K. Bigaut has received lecturing fees and travel grants from Biogen, Lilly, Merck, Novartis, Roche, Sanofi, and UCB. F. Leypoldt is supported by E-Rare Joint Transnational research support (ERA-Net, LE3064/2-1), Stiftung Pathobiochemie of the German Society for Laboratory Medicine, and HORIZON MSCA 2022 Doctoral Network 101119457–IgG4-TREAT and discloses speaker honoraria from Grifols, Teva, Biogen, Bayer, Roche, Novartis, and Fresenius; travel funding from Merck, Grifols, and Bayer; and service on advisory boards for Roche and Argenx within the past 3 years. O. Aktas received research funding from the German Research Association (DFG/GRK 2578) and German Ministry for Education and Research (BMBF/G-BA NUTSEN), as well as speaker honoraria from Alexion, Horizon/Amgen, Mitsubishi Tanake, Roche, and Sanofi, none related to this study. He is the Academic Editor for PLOS ONE and a board member of the German Neuromyelitis Optica Study Group (NEMOS). M. Ringelstein received speaker honoraria from Novartis, Bayer Vital GmbH, Roche, Alexion, Horizon/Amgen, and Ipsen and travel reimbursement from Bayer Schering, Biogen Idec, Merz, Genzyme, Teva, Roche, Alexion, Horizon/Amgen, and Merck, none related to this study. V. Siffrin has received research grants from Novartis, Roche, and Alexion. L.-J. Zhang, H. Cong, and MaLo declare no conflicts of interest. P. Barreras received funding from the AAN and Foundation for Sarcoidosis Research for neurosarcoidosis research not related to this study. H. Chen is an investigator in clinical trials sponsored by Roche/Genentech and UCB. A.L. Piquet reports research grants from the University of Colorado, Rocky Mountain MS Center, and the Foundation for Sarcoidosis; consulting fees from Kyverna, Genentech/Roche, UCB, Amgen, and Alexion; and honorarium from MedLink and publication royalties from Springer as co-editor of a medical textbook. E.S. Sotirchos has received fees for consulting/scientific advisory board participation from Alexion, Amgen, TG Therapeutics, and Roche/Genentech; has received speaker honoraria from Alexion and Roche/Genentech; is the site principal investigator for studies funded by Alexion, Roche/Genentech, UCB, and Ad Scientiam; and is the principal investigator for an investigator-initiated study funded by Astoria Biologica. R. Kammeyer has performed consultative services for Sanofi-Genzyme and Roche. He has received research support from the Colorado Child Health Research Institute. J. Zook declares no conflicts of interest. J.L. Bennett has performed consultative services for Amgen, Genentech, TG Therapeutics, Reistone Bio, Roche, Antigenomycs, Chugai, Mitsubishi Tanabe, Beigene, Novartis, CorEvitas, Immpact Bio, and ImCyse. He has served on Scientific Advisory or Data Safety Monitoring boards for Clene Nanomedicine and Roche. He has served on a Speakers Bureau for Alexion; has received research support from the NIH, National MS Society, and Alexion; and has received intellectual property interests from a patent on Aquaporumab. T. Berger has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from Amgen, Allergan, Bayer, Biogen, Bionorica, BMS, Genesis, GSK, GW/Jazz Pharma, Horizon, Janssen-Cilag, MedDay, Merck, Neuraxpharm, Novartis, Octapharma, Roche, Sandoz, Sanofi, Teva, and UCB. His institution has received financial support in the past 12 months through unrestricted research grants from Biogen, Bayer, BMS, Merck, Novartis, Roche, Sanofi, and Teva and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Bayer, Biogen, Merck, Novartis, Octapharma, Roche, Sanofi-Genzyme, and Teva. K. Fujihara received fees for consulting, speaking, and serving on steering committees of AbbVie, Alexion, Asahi Kasei Medical, Biogen, Chugai/Roche, Eisai, Japan Tobacco, MedImmune/Viela Bio, Merck, Merck Biopharma, Mitsubishi-Tanabe, Novartis, Takeda, Teijin, and UCB and a Grant-in-Aid for Scientific Research from the Ministry of Health, Welfare and Labor of Japan. M. Levy has received personal compensation for advising the following companies: Alexion, Horizon, Genentech/Roche, UCB, Sanofi, and Mitsubishi. Through the Massachusetts General Hospital, he received grants from Alexion/AstraZeneca Rare Disease, Horizon/Amgen, Genentech/Roche, UCB, and Sanofi for research projects. F.-D. Shi received honoraria and travel support (lectures, advisory boards, consultations) from Alexion/AstraZeneca, Novartis, Hansoh Pharmaceutical, Sinomab, Lundbeck and European Charcot Foundation, Chinese Neurological Association. He received research grants from Zai Lab, AstraZeneca, Novartis, Biogen. F-D. Shi was a co-founder of New Terrain from August, 2018 to December, 2019; Akriva from November, 2023 to September, 2025. F. Paul has received honoraria and research support from Alexion, Amgen, Bayer, Biogen, Chugai, MerckSerono, Novartis, Genzyme, Horizon/MedImmune, Shire, Teva, and UCB and serves on scientific advisory boards for Alexion, Roche, UCB and Novartis. He has received funding from Deutsche Forschungsgemeinschaft (DFG Exc 257), Bundesministerium für Bildung und Forschung (Competence Network Multiple Sclerosis), Guthy Jackson Charitable Foundation, EU Framework Program 7, and National Multiple Sclerosis Society of the USA. Go to Neurology.org/NN for full disclosures.

Publication History

Received by *Neurology® Neuroimmunology & Neuroinflammation* July 24, 2025. Accepted in final form December 5, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Romana Höftberger, MD.

References

1. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189. doi:10.1212/WNL.0000000000001729
2. 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. doi:10.1016/S0140-6736(04)17551-X

3. Papadopoulos MC, Verkman AS. Aquaporin 4 and neuromyelitis optica. *Lancet Neurol.* 2012;11(6):535-544. doi:10.1016/S1474-4422(12)70133-3
4. Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. *J Neuroinflammation.* 2021;18(1):208. doi:10.1186/s12974-021-02249-1
5. Berthele A, Levy M, Wingerchuk DM, et al. A single relapse induces worsening of disability and health-related quality of life in patients with neuromyelitis optica spectrum disorder. *Front Neurol.* 2023;14:1099376. doi:10.3389/fneur.2023.1099376
6. Duchow A, Bellmann-Strobl J, Friede T, et al. Time to disability milestones and annualized relapse rates in NMOSD and MOGAD. *Ann Neurol.* 2024;95(4):720-732. doi:10.1002/ana.26858
7. Abboud H, Petrak A, Mealy M, Sasidharan S, Siddique L, Levy M. Treatment of acute relapses in neuromyelitis optica: steroids alone versus steroids plus plasma exchange. *Mult Scler.* 2016;22(2):185-192. doi:10.1177/1352458515581438
8. Kleiter I, Gahlen A, Borisow N, et al. Neuromyelitis optica: evaluation of 871 attacks and 1,153 treatment courses. *Ann Neurol.* 2016;79(2):206-216. doi:10.1002/ana.24554
9. Kümpfel T, Giglhuber K, Aktas O, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD)–revised recommendations of the neuromyelitis optica study group (NEMOS). Part II: attack therapy and long-term management. *J Neurol.* 2024;271(1):141-176. doi:10.1007/s00415-023-11910-z
10. Pittock SJ, Berthele A, Fujihara K, et al. Eculizumab in Aquaporin-4–Positive neuromyelitis optica spectrum disorder. *New Engl J Med.* 2019;381(7):614-625. doi:10.1056/NEJMoa1900866
11. Pittock SJ, Barnett M, Bennett JL, et al. Ravulizumab in Aquaporin-4-Positive neuromyelitis optica spectrum disorder. *Ann Neurol.* 2023;93(6):1053-1068. doi:10.1002/ana.26626
12. Cree BAC, Bennett JL, Kim HJ, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. *Lancet.* 2019;394(10206):1352-1363. doi:10.1016/S0140-6736(19)31817-3
13. Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol.* 2020;19(5):402-412. doi:10.1016/S1474-4422(20)30078-8
14. Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med.* 2019;381(22):2114-2124. doi:10.1056/NEJMoa1901747
15. Monteleone JPR, Gao X, Kleijn HJ, Bellanti F, Pelto R. Eculizumab pharmacokinetics and pharmacodynamics in patients with generalized myasthenia gravis. *Front Neurol.* 2021;12:696385. doi:10.3389/fneur.2021.696385
16. Ortiz S, Pittock SJ, Berthele A, et al. Immediate and sustained terminal complement inhibition with ravulizumab in patients with anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder. *Front Neurol.* 2024;15:1332890. doi:10.3389/fneur.2024.1332890
17. Piatek P, Domowicz M, Lewkowicz N, et al. C5a-Preactivated neutrophils are critical for autoimmune-induced astrocyte dysregulation in neuromyelitis optica spectrum disorder. *Front Immunol.* 2018;9:1694. doi:10.3389/fimmu.2018.01694
18. Hinson SR, Pittock SJ, Lucchinetti CF, et al. Pathogenic potential of IgG binding to water channel extracellular domain in neuromyelitis optica. *Neurology.* 2007;69(24):2221-2231. doi:10.1212/01.WNL.0000289761.64862.ce
19. Watanabe M, Masaki K, Tanaka E, Matsushita T, Isobe N. The efficacy of eculizumab in the acute phase of neuromyelitis optica spectrum disorder: a case series study. *Cureus.* 2024;16(11):e73205. doi:10.7759/cureus.73205
20. Enriquez M, Rosenthal S, McLendon LA, Bennett JL, Piquet AL, Kammeyer R. Efficacy of eculizumab in acute refractory pediatric neuromyelitis optica: a case report. *Neuroimmunology Rep.* 2024;5:100213. doi:10.1016/j.nerep.2024.100213
21. Soni RH, Garcia M, Oak E, et al. Acute eculizumab treatment in a pediatric patient with AQP4-IgG+ NMOSD. *Mult Scler.* 2025;31(5):612-614. doi:10.1177/13524585241283650
22. Schindler P, Aktas O, Ringelstein M, et al. Glial fibrillary acidic protein as a biomarker in neuromyelitis optica spectrum disorder: a current review. *Expert Rev Clin Immunol.* 2023;19(1):71-91. doi:10.1080/1744666X.2023.2148657
23. Demuth S, Guillaume M, Bourre B, et al. Treatment regimens for neuromyelitis optica spectrum disorder attacks: a retrospective cohort study. *J Neuroinflammation.* 2022;19(1):62. doi:10.1186/s12974-022-02420-2
24. Carnero Contentti E, Lopez PA, Pettinicchi JP, et al. Treatment strategies and responses for attacks of neuromyelitis optica spectrum disorder: a real-world retrospective cohort study. *J Neurol Sci.* 2024;462:123099. doi:10.1016/j.jns.2024.123099
25. Xu Y, Wang H, Song T, et al. Efficacy and safety of apheresis therapy in AQP4 antibody-positive NMOSD attack: a propensity score-matched cohort study. *CNS Neurosci Ther.* 2024;30(5):e14780. doi:10.1111/cns.14780
26. R Core Team. *R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing*; 2025. Accessed March 31, 2025. r-project.org/
27. Kaneko K, Namioka Y, Ohyama A, et al. Two cases of anti-aquaporin 4 antibody-positive neuromyelitis optica treated with eculizumab early after relapse. *Neurol Therap (In Japanese).* 2022;39(4):731-735. doi:10.15082/jsnt.39.4_731
28. Jarius S, Ruprecht K, Wildemann B, et al. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. *J Neuroinflammation.* 2012;9:14. doi:10.1186/1742-2094-9-14
29. Wood L, Jacobs P. The effect of serial therapeutic plasmapheresis on platelet count, coagulation factors, plasma immunoglobulin, and complement levels. *J Clin Apher.* 1986;3(2):124-128. doi:10.1002/jca.2920030209
30. Volkin RL, Starz TW, Winkelstein A, et al. Changes in coagulation factors, complement, immunoglobulins, and immune complex concentrations with plasma exchange. *Transfusion.* 1982;22(1):54-58. doi:10.1046/j.1537-2995.1982.22182154218.x
31. Given KS, Acker EG, Macklin WB, Carlin D, Owens GP, Bennett JL. Complement inhibition rapidly blocks lesion extension and facilitates remyelination in neuromyelitis optica. *Acta Neuropathol Commun.* 2025;13(1):129. doi:10.1186/s40478-025-02019-7
32. Aktas O, Smith MA, Rees WA, et al. Serum glial fibrillary acidic protein: a neuromyelitis optica spectrum disorder biomarker. *Ann Neurol.* 2021;89(5):895-910. doi:10.1002/ana.26067
33. Kim SH, Gomes ABAGR, Schindler P, et al. Blood-based biomarkers for identifying disease activity in AQP4-IgG-Positive neuromyelitis optica spectrum disorder. *JAMA Neurol.* 2025;82(2):168-175. doi:10.1001/jamaneurol.2024.4400
34. Gil-Rojas Y, Amaya-Granados D, Quiñones J, Robles A, Samacá-Samacá D, Hernández F. Measuring the economic burden of neuromyelitis optica spectrum disorder in Colombia. *Mult Scler Relat Disord.* 2024;82:105376. doi:10.1016/j.msard.2023.105376
35. Royston M, Kielhorn A, Weycker D, et al. Neuromyelitis optica spectrum disorder: clinical burden and cost of relapses and disease-related care in US clinical practice. *Neurol Ther.* 2021;10(2):767-783. doi:10.1007/s40120-021-00253-4