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Eculizumab Use in Neuromyelitis Optica Spectrum Disorders

Routine Clinical Care Data From a European Cohort

Marius Ringelstein, MD,*† Susanna Asseyer, MD,* Gero Lindenblatt, MD, Katinka Fischer, MD, Refik Pul, MD, Jelena Skuljec, PhD, Lisa Revie, MD, Katrin Giglhuber, MD, Vivien Häußler, MD, Michael Karenfort, MD, Kerstin Hellwig, MD, Friedemann Paul, MD, Judith Bellmann-Strobl, MD, Carolin Otto, MD, Klemens Ruprecht, MD, Tjalf Ziemssen, MD, Alexander Emmer, MD, Veit Rothhammer, MD, Florian T. Nickel, MD, Klemens Angstwurm, MD, Ralf Linker, MD, Sarah A. Laurent, MD, Clemens Warnke, MD, Sven Jarius, MD, Mirjam Korporal-Kuhnke, MD, Brigitte Wildemann, MD, Stephanie Wolff, MD, Maria Seipelt, MD, Yavor Yalachkov, MD, Nele Retzlaff, MD, Uwe K. Zettl, MD, Paulus S. Rommer, MD, Markus C. Kowarik, MD, Jonathan Wickel, MD, Christian Geis, MD, Martin W. Hümmert, MD, Corinna Trebst, MD, Makbule Senel, MD, Ralf Gold, MD, Luisa Klotz, MD, Christoph Kleinschnitz, MD, Sven G. Meuth, MD, PhD, Orhan Aktas, MD,* Achim Berthele, MD,* and Ilya Ayzenberg, MD,*† for the German Neuromyelitis Optica Study Group (NEMOS)

Correspondence
Dr. Ringelstein
marius.ringelstein@med.uni-duesseldorf.de
or Dr. Ayzenberg
ilya.ayzenberg@ruhr-uni-bochum.de

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Abstract

Background and Objectives

Attack prevention is crucial in managing neuromyelitis optica spectrum disorders (NMOSDs). Eculizumab (ECU), an inhibitor of the terminal complement cascade, was highly effective in preventing attacks in a phase III trial of aquaporin-4 (AQP4)-IgG seropositive(+) NMOSDs. In this article, we evaluated effectiveness and safety of ECU in routine clinical care.

Methods

We retrospectively evaluated patients with AQP4-IgG+ NMOSD treated with ECU between December 2014 and April 2022 at 20 German and 1 Austrian university center(s) of the Neuromyelitis Optica Study Group (NEMOS) by chart review. Primary outcomes were effectiveness (assessed using annualized attack rate [AAR], MRI activity, and disability changes [Expanded Disability Status Scale {EDSS}]) and safety (including adverse events, mortality, and attacks after meningococcal vaccinations), analyzed by descriptive statistics.

Results

Fifty-two patients (87% female, age 55.0 ± 16.3 years) received ECU for 16.2 (interquartile range [IQR] 9.6 – 21.7) months. Forty-five patients (87%) received meningococcal vaccination before starting ECU, 9 with concomitant oral prednisone and 36 without. Seven of the latter (19%) experienced attacks shortly after vaccination (median: 9 days, IQR 6–10 days). No

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*These authors contributed equally to this work.

†These authors are the corresponding authors.

From the Department of Neurology (M.R., K.F., S.G.M., O.A.), Medical Faculty; Department of Neurology (M.R.), Center for Neurology and Neuropsychiatry, LVR-Klinikum, Heinrich-Heine-University Düsseldorf; Experimental and Clinical Research Center (S.A., F.P., J.B.-S.), a Cooperation Between the Max Delbrück Center for Molecular Medicine in the Helmholtz Association and Charité Universitätsmedizin; Charité - Universitätsmedizin Berlin (S.A., F.P., J.B.-S.), corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Experimental and Clinical Research Center; Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) (S.A., F.P., J.B.-S.), Berlin; Department of Neurology (G.L.), Johanna Etienne Hospital, Neuss; Center for Translational Neuro- and Behavioral Sciences (R.P., J.S., C.K.), University Medicine Essen, University of Duisburg-Essen; Department of Neurology (L.R., L.K.), University Hospital, Münster; Department of Neurology (K.G., A.B.), School of Medicine and Health, Technical University of Munich, Klinikum Rechts der Isar; Department of Neurology and Institute of Neuroimmunology and MS (INIMS) (V.H.), University Medical Center Hamburg-Eppendorf; Department of General Pediatrics (M.K.), Neonatology and Pediatric Cardiology, University Children's Hospital, Medical Faculty, Heinrich-Heine-University Düsseldorf; Department of Neurology (K.H., R.G., I.A.), St. Josef-Hospital, Ruhr University Bochum; Department of Neurology (C.O., K.R.), Charité-Universitätsmedizin Berlin, corporate member of Freie Universität and Humboldt-Universität zu Berlin; Center of Clinical Neuroscience (T.Z.), Department of Neurology, Dresden; Department of Neurology (A.E.)Halle; Department of Neurology (V.R., F.T.N.), Erlangen; Department of Neurology (K.A., R.L.), Regensburg; Department of Neurology (S.A.L., C.W.), University Hospital, Köln; Department of Neurology (S.J., M.K.-K., B.W.), Molecular Neuroimmunology Group, University of Heidelberg; Department of Neurology (S.W.), Gießen; Department of Neurology (M.Seipelt), Marburg; Department of Neurology (Y.Y.), Frankfurt; Department of Neurology (N.R., U.K.Z.), Rostock, Germany; Department of Neurology (P.S.R.), Medical University of Vienna, Austria; Department of Neurology (M.C.K.), University Hospital, Tübingen; Section of Translational Neuroimmunology (J.W., C.G.), Department of Neurology, Jena University Hospital; Department of Neurology (M.W.H., C.T.), Hannover Medical School; and Department of Neurology (M.Senel), University Hospital, Ulm, Germany.

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Coinvestigators are listed in the supplemental digital content available at Neurology.org/N.

Glossary

AAR = annualized attack rate; **BfR** = Bundesinstitut für Risikobewertung; **bMRI** = brain MRI; **DFG** = Deutsche Forschungsgemeinschaft; **EDSS** = Expanded Disability Status Scale; **G-BA** = Gemeinsamer Bundesausschuss; **gMG** = generalized myasthenia gravis; **IQR** = interquartile range; **IVMP** = intravenous methylprednisolone; **NEMOS** = Neuromyelitis Optica Study Group; **NMOSD** = neuromyelitis optica spectrum disorder; **OLE** = open-label extension; **OR** = odds ratios; **PNH** = paroxysmal nocturnal hemoglobinuria; **SAE** = serious adverse event; **scMRI** = spinal cord MRI.

postvaccinal attack occurred in the 9 patients vaccinated while on oral prednisone before starting ECU and in 25 (re-)vaccinated while on ECU. During ECU therapy, 88% of patients were attack-free. The median AAR decreased from 1.0 (range 0–4) in the 2 years preceding ECU to 0 (range 0–0.8; $p < 0.001$). The EDSS score from start to the last follow-up was stable (median 6.0), and the proportion of patients with new T2-enhancing or gadolinium-enhancing MRI lesions in the brain and spinal cord decreased. Seven patients (13%) experienced serious infections. Five patients (10%; median age 53.7 years) died on ECU treatment (1 from myocardial infarction, 1 from ileus with secondary sepsis, and 3 from systemic infection, including 1 meningococcal sepsis), 4 were older than 60 years and severely disabled at ECU treatment start (EDSS score ≥ 7). The overall discontinuation rate was 19%.

Discussion

Eculizumab proved to be effective in preventing NMOSD attacks. An increased risk of attacks after meningococcal vaccination before ECU start and potentially fatal systemic infections during ECU—particularly in patients with comorbidities—must be considered. Further research is necessary to explore optimal timing for meningococcal vaccinations.

Classification of Evidence

This study provides Class IV evidence that eculizumab reduces annualized attack rates and new MRI lesions in AQP4-IgG+ patients with NMOSD.

Introduction

Neuromyelitis optica spectrum disorders (NMOSDs) are predominantly anti-aquaporin-4 (AQP4)-IgG-mediated inflammatory diseases of the CNS, characterized by relapsing attacks affecting the optic nerves, the spinal cord, and the brainstem/brain.[1-4] Attack prevention is crucial to avoid disability accumulation.[5] Various therapeutic strategies such as CD19-specific or CD20-specific monoclonal antibody-mediated B-cell depletion,[6,7] interleukin-6 (IL-6) receptor blockade,[8,9] and complement inhibition[10,11] were successful in phase II/III trials, particularly in AQP4-IgG+ patients with NMOSDs. This led to the approval of inebilizumab, rituximab (RTX, only in Japan), satralizumab, eculizumab (ECU), and ravulizumab (RAV) for AQP4-IgG+ NMOSD in many countries worldwide.[12] However, data on clinical experience with these agents outside of controlled trials are scarce.

In NMOSDs, AQP4-IgG binding to the astrocytic water channel activates the complement pathway, which induces astrocyte death[13] and perivascular complement deposition associated with prominent vascular fibrosis.[14] ECU, a humanized monoclonal antibody, binds to the terminal complement protein C5 and inhibits its cleavage into C5a and C5b. Because the risk of meningococcal infections has been estimated to be 2,000-fold higher in patients treated with ECU than in the untreated population,[15] meningococcal vaccination or antibiotic prophylaxis is mandatory for patients treated with complement inhibitors.

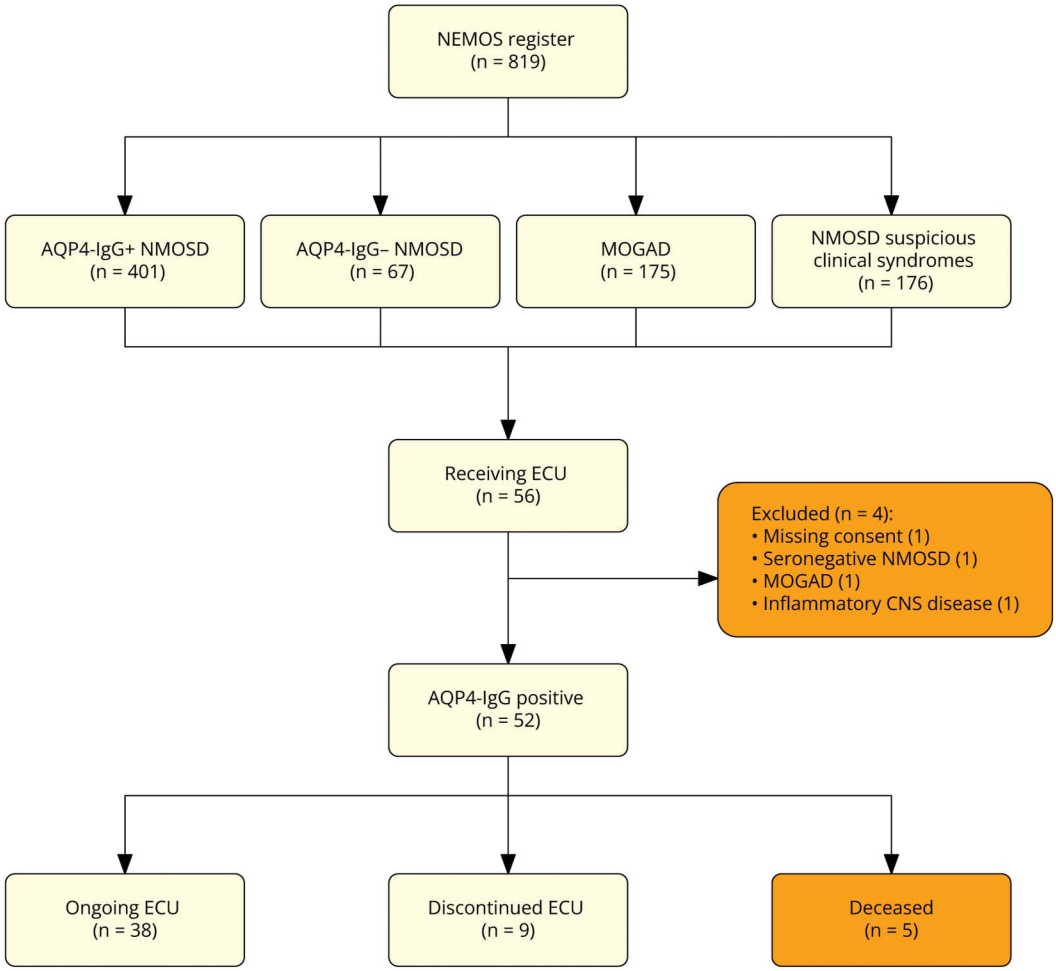
ECU has first been approved for treating paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS) in 2007 and 2011, respectively.[16] In neurologic disorders, ECU has been licensed for generalized myasthenia gravis (gMG)[17] and was first successfully investigated in NMOSDs in an open-label pilot trial with 14 patients in 2009/2010.[18] In the pivotal PREVENT trial on AQP4-IgG+ NMOSD, ECU (n = 96 patients) led to a 94.2% attack risk reduction compared with placebo (n = 47)[10] with sustained effects in the open-label extension (OLE) phase.[19] The rate of treatment-related serious adverse events (SAEs) was 8.0 in 100 patient-years, including severe infections in 18.2% of patients.[19,20] Of interest, serious infections occurred less frequently with ECU than with placebo, regardless of concomitant immunosuppressive medications or previous RTX use.[21] There was 1 reported death under ECU and azathioprine (AZA) in the PREVENT trial categorized as possibly related to ECU treatment,[10] and there were no fatalities during the OLE.[19]

This study evaluated the effectiveness and safety of ECU and meningococcal vaccinations in a large NMOSD cohort.

Methods

The study has been performed within the Neuromyelitis Optica Study Group (NEMOS).[22] On informed consent, NEMOS includes AQP4-IgG+ and seronegative patients with NMOSD, patients with NMOSD suspicious clinical

Figure 1 Flowchart Illustrating the Recruitment of 52 Eculizumab (ECU)-Treated AQP4-IgG Seropositive Patients With NMOSD for This Study From the Neuromyelitis Optica Study Group (NEMOS)



AQP4-IgG = aquaporin-4-immunoglobulin G; MOGAD = myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSDs = neuromyelitis optica spectrum disorders.

syndromes, and patients with myelin oligodendrocyte glycoprotein antibody-associated diseases in Germany, Austria, and Switzerland. Of this cohort, we included all ECU-treated AQP4-IgG+ patients with NMOSD from 21 neurologic departments in Germany (n = 20) and Austria (n = 1) from December 2014 until April 2022 in the analysis, irrespective of the disease or treatment duration (Figure 1).

Clinical and paraclinical data were obtained by the treating physicians and entered in the NEMOS database. All data were analyzed retrospectively by chart review. Patients were continuously treated at the contributing centers with regular assessments of clinical (attacks and Expanded Disability Status Scale [EDSS] score) and paraclinical (MRI, AQP4-IgG, and other laboratory tests) data. AQP4-IgG was investigated exclusively by cell-based assays.[23-25]

Our analyses focused on ECU safety and effectiveness, given as annualized attack rate (AAR), active or new/progressive lesions on MRI, and longitudinal disability changes (EDSS). An attack was defined as "a definitely new neurologic symptom" or "clear acute worsening of previous neurologic deficits" with objective clinical signs, lasting for ≥ 24 hours and attributable to an inflammatory CNS event. Last available MRIs of the brain and the cervicothoracic spinal cord, before and during ECU therapy, were classified as "nonactive" or "active" according to the absence/presence of new/enlarging T2-enhancing or contrast-enhancing T1 lesions, respectively. No standardized MRI protocols were used. MRI scans were evaluated by 2 radiologists (at least 1 neuroradiologist) during regular clinical workup. Safety aspects comprised infusion-related reactions, serious infections, exacerbation of autoimmune comorbidities, and fatalities. Considering previously reported exacerbation of autoimmune diseases after meningococcal vaccination,[26-29] we further focused our analysis on disease activity in patients vaccinated before and after starting ECU.

Statistical Analysis

The AAR before ECU treatment was calculated by dividing the total number of attacks within the past 2 years before

Table 1 Cohort Description and Previous Immunotherapies

	AQP4-IgG+, n = 52
Ethnicity, n (%)	
White	47 (90)
Latin American	1 (2)
African	1 (2)
Asian	2 (4)
Arabian	1 (2)
Sex, n: female/male (% female)	45/7 (87)
NMOSD based on 2015 criteria: yes/no (% yes)	52/0 (100)
Age at disease manifestation in y: mean (SD)	48.3 (17.0)
ECU-treated pediatric patients (% yes)	1/52 (2%)
Disease duration before ECU in y: median (IQR)	4.1 (0.7–7.3)
All attacks before ECU, n: median (IQR)	3.0 (2.0–5.0)
Attacks during past 2 y before ECU, n: median (IQR)	2.0 (1.0–3.0)
Attacks under last immunotherapy, n: median (IQR)	1.0 (0.0–2.0)
AAR in the 2 y before ECU, median (IQR)	1.0 (0.5–1.5)
Age at ECU start in y: mean (SD)	55.0 (16.3)
BMI at ECU start, median (IQR)	26.0 (23.6–28.6)
EDSS score at the last follow-up before ECU, median (IQR)	6.0 (3.0–7.4)
ECU treatment duration in y: median (IQR)	1.3 (0.8–1.8)
All immunotherapies before ECU, n (%)	
Azathioprine	13 (25)
Belimumab	1 (2)
Cyclophosphamide	4 (8)
Fingolimod	2 (4)
Glatiramer acetate	3 (6)
Hydroxychloroquine	1 (2)
IVIG	9 (17)
IVMP quarterly	1 (2)
Long-term PLEX	3 (6)
Methotrexate	4 (8)
Mitoxantrone	1 (2)
Mycophenolate mofetil	4 (8)
Natalizumab	2 (4)
Rituximab[a]	31 (60)
Steroids	6 (12)
Tocilizumab	5 (10)
Intrathecal triamcinolone	1 (2)

Abbreviations: AAR = annualized attack rate; AQP4-IgG = aquaporin-4-immunoglobulin G; BMI = body mass index; ECU = eculizumab; EDSS = Expanded Disability Status Scale; IQR = interquartile range; IVIGs = IV immunoglobulins; IVMP = IV methylprednisolone; NMOSDs = neuromyelitis optica spectrum disorders; PLEX = plasma exchange.
[a] Eleven of 52 patients received rituximab in the past 6 mo before ECU start, so initial additional effects of the ongoing B-cell depletion are possible in this subgroup.

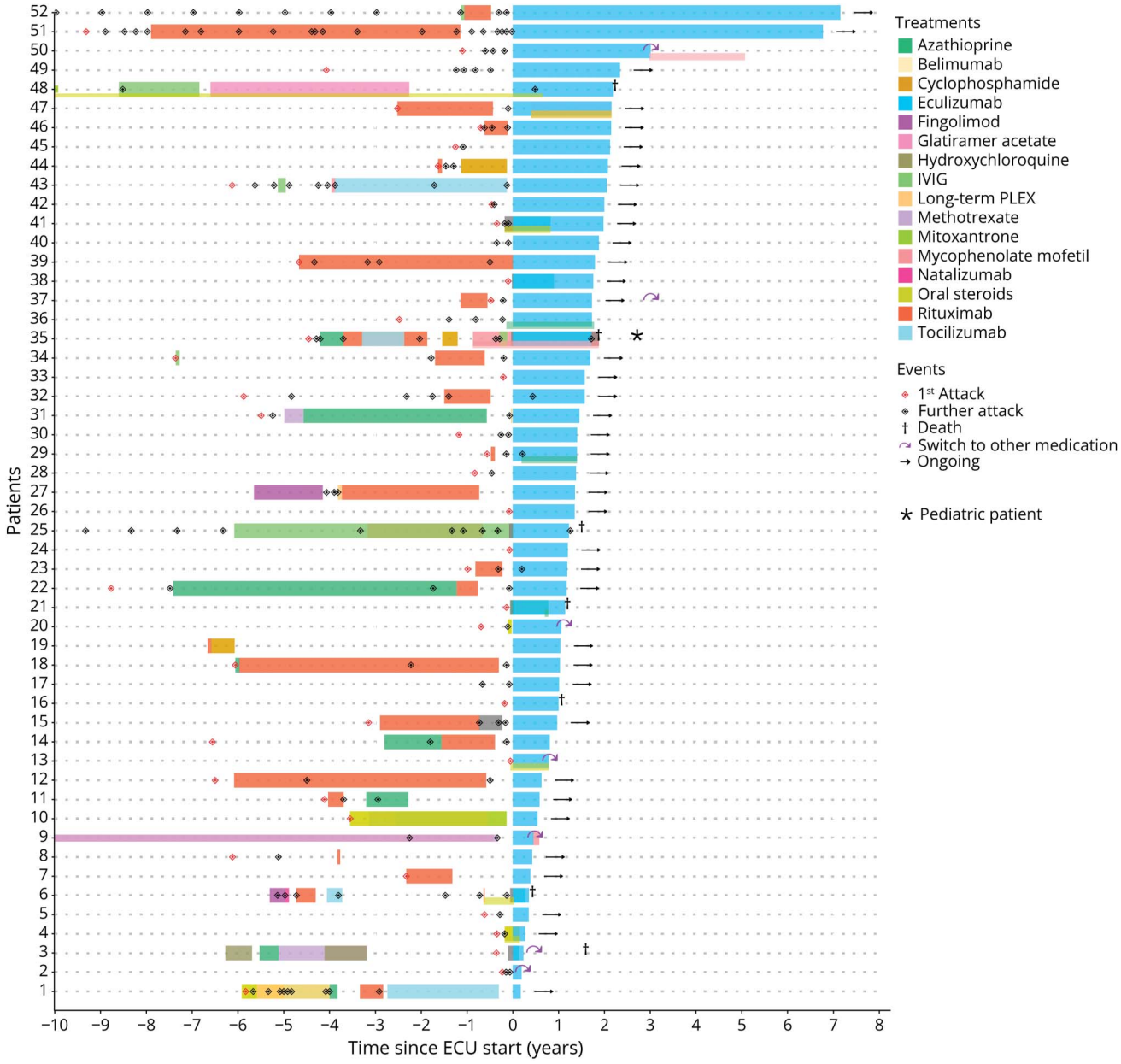
the initial ECU administration by 2. In patients with a disease duration of <2 years before ECU treatment, we also categorically divided the total number of attacks by 2 because there were no attacks before the disease onset. Owing to the individual lengths of ECU treatment, the AAR during ECU therapy denotes the number of attacks in proportion to the exact treatment duration. Attacks occurring within 21 days after vaccination were defined as *postvaccinal* attacks.

The cohort was described using absolute and relative frequencies, along with the mean or median and appropriate measures of variability such as SD, interquartile range (IQR), the interval between the lower and upper quartile, range, and minimum (min) and maximum (max). In most cases, values were not normally distributed; hence, nonparametrical tests were used. To test for significant differences between medians of 2 unpaired groups, for example, vaccinated vs unvaccinated patients, the Wilcoxon test for independent samples was applied. In the case of paired data, such as AAR before ECU start and AAR under ECU therapy, the Wilcoxon signed-rank test was used. In normally distributed data, *t* tests or Welch tests were applied. To assess the correlation between categorical variables, Fisher exact tests were used in cases where cell numbers were less than 5 while χ^2 tests were used otherwise. The results were presented in terms of odds ratios (ORs) along with their corresponding 95% confidence intervals. Otherwise, statistical test results are presented as p values with alpha = 0.05 as the predetermined significance level. Version 4.0.5 of the R Statistics package was used for statistical analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval to conduct this study was obtained from the institutional review board of the Heinrich-Heine University Düsseldorf (#3419) and from each participating center by their local institutional review boards according to ICH/GCP. All patients provided written informed consent for data collection.

Figure 2 Disease Courses of All 52 AQP4-IgG Seropositive Patients With NMOSD Before and During Eculizumab (ECU) Treatment, Highlighting Previous Immunotherapies, Add-on Treatments During ECU, and Every Attack, Indicated by Red and Black Diamonds



Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Cohort Description

We included data of 52 patients (87% female, 90% White) with AQP4-IgG+ NMOSD in this study (Table 1) fulfilling the international consensus criteria for NMOSD.[4] Fifty patients were adults, and 2 patients were younger than 18 years at disease manifestation (6.2 and 17.3 years), 1 still younger than 18 years at ECU start. Thirteen patients had autoimmune comorbidities, including systemic lupus erythematosus (SLE; n = 4), Hashimoto thyroiditis (n = 4), Sjögren syndrome (n = 2), myasthenia gravis (n = 2), type 1 diabetes mellitus (n = 2), Grave disease, sarcoidosis, membranous glomerulonephritis, systemic scleroderma, rheumatoid arthritis, vitiligo, hyperthyroidism, immune thrombopenia, and antiphospholipid syndrome (1 each).

Disease Course Before Eculizumab Treatment

The median disease duration before ECU start was 4.1 (IQR 0.7–7.3) years. At disease manifestation, the mean age was 48.3 years (SD ± 17.0); at ECU start, the mean age was 55.0 years (SD ± 16.3). Before ECU start, patients had experienced

a median of 3.0 attacks (range 1–21). Considering the past 2 years before ECU start, 2.0 attacks (median; min 0, max 8 attacks) were recorded (Table 1, Figure 2). The median AAR (IQR) was 1.3 (0.5–3.1) for the overall disease duration and 1.0 (0.5–1.5) during the 2 years before ECU treatment, respectively. The median EDSS score at ECU start was 6.0 (IQR 3.0–7.3), with 26 patients (50%) having an EDSS score ≥ 6.0 (range 6.0–9.5). Baseline brain MRI (bMRI) and spinal cord MRI (scMRI) scans were available in 47 and 41 of the 52 patients, respectively. The last available bMRI was performed at 2.2 (IQR 0.8–5.2) months and scMRI at 1.8 (IQR 0.9–6.0) months before treatment initiation. New, enlarging, or active lesions were found in 18 of 47 bMRI scans (39%) and 24 of 41 scMRI scans (59%) before treatment initiation.

Immunotherapies Before Eculizumab Treatment

Most patients (39/52, 75%) had received at least 1 immunotherapy before ECU (1 [n = 17], 2 [n = 10], 3 or more immunotherapies [n = 12]; Table 1). The most frequent treatment before ECU was RTX, given to 31 patients (60%; administered with 1.000 mg every 6 months in 20 of 31 patients). Within the past 24, 12, and 6 months before ECU initiation, 26 (50%), 21 (40%), and 11 (21%) of the 52 patients were treated with RTX, respectively. The second and third most frequent immunotherapies were AZA (25%) and IV immunoglobulins (IVIGs; 17%). 13 patients (25%) were treatment-naive before ECU start (Figure 2).

Initiation of Eculizumab Therapy

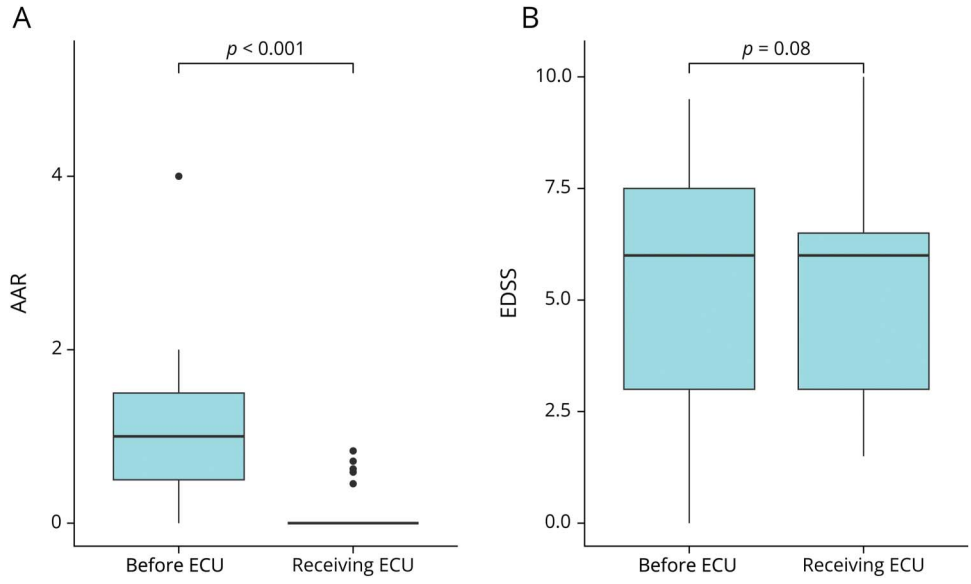
ECU was initiated in most patients (34/52; 65%) because of recent (<3 months) attack activity (33/34) or an asymptomatic enlarging lesion on MRI (1/34). 10 of these 34 patients were treatment-naive, and 24 were switched from another immunotherapy (13 from RTX, 4 from AZA, 2 from IVIG, 3 from oral prednisolone, 1 from tocilizumab, and 1 from methotrexate and hydroxychloroquine). In the remaining 18 patients, ECU was started because of attacks further back (≥3 months) under the last therapy (n = 10), as a first therapy (n = 3), and because of side effects of previous immunotherapy (n = 1), refusal to reimburse RTX costs by the insurance company (n = 1), wish for pregnancy (n = 1), or unknown reasons (n = 2).

Attack Rate, MRI, and Disability Changes During Eculizumab Therapy

39 patients (75%) were treated with ECU monotherapy, and 13 (25%) received add-on oral prednisolone (n = 7), AZA (n = 3), mycophenolate mofetil (MMF; n = 2), or MMF and prednisolone (n = 1), partly administered in the context of other autoimmune comorbidities (n = 3). The median observation period on ECU treatment was 16.2 (IQR 9.6–21.7, range 2.0–85.8) months; 43 patients were treated for at least 6 months and 36 patients for at least 12 months.

A total of 6 attacks in 6 of 52 patients (12%) occurred during ECU therapy after a median of 5.6 (IQR 3.3–12.9) months (mean 8.7, SD 7.6) during a median observation period of 18.1 (IQR 15.5–20.4) months on ECU. These attacks included optic neuritis (n = 2), myelitis (n = 2), and brainstem encephalitis (n = 2). 4 of the 6 relapsing patients were receiving the standard ECU maintenance dose (1,200 mg every 2 weeks), 1 adult received 900 mg, and the pediatric patient

Figure 3 Significant Decrease of the Annualized Attack Rate (AAR) Between the 2 Years Before Eculizumab (ECU) Initiation and During ECU Treatment ($p < 0.001$; A) Clinical Stabilization Measured By a Constant Median Expanded Disability Status Scale (EDSS; Longitudinal Data Available in 45 Patients) Score Between ECU Start (6.0) and the Last Follow-Up During ECU Treatment (6.0; $p = 0.08$; B)



received 600 mg biweekly. None of the 6 relapses occurred within the first 30 days of starting ECU (median 165 days, range 72–626), rather ruling out a possible therapeutic lag. 2 of 39 patients (5%) relapsed during ECU monotherapy and 4 of 13 patients (31%) under ECU with add-on therapy. 2 of the 6 attacks were treated with IV methylprednisolone (IVMP) only, 2 required IVMP plus apheresis therapy, 1 required oral prednisolone, and 1 patient did not receive attack therapy.

The median AAR in the total cohort decreased from 1.0 (IQR 0.5–1.0) in the 2 years before ECU start to 0 (IQR 0) under ECU ($p < 0.001$; Figure 3A). 88% of the patients were attack-free during ECU therapy. Similarly, the median (IQR) AAR in the subgroup of patients treated with ECU for at least 12 months (n = 36, only 35 longitudinal AAR value pairs available) decreased from 1 (0.5–1.5) in the 2 years before ECU start to 0 (0) under ECU ($p < 0.01$). The median (IQR) AAR of patients who received RTX within 6 months of starting ECU (n = 11; 8 with ECU monotherapy) vs those who did not was similar, with an AAR of 1 (0.5–1.0) vs 1 (0.5–1.5) ($p = 1$) within 2 years before start of ECU and 0 (0 – 0.3) vs 0 (0) ($p = 0.06$) under ECU, respectively.

Longitudinally, the median EDSS scores between ECU start and the last follow-up during ECU treatment were stable (6.0; $p = 0.08$) (Figure 3B). They remained unchanged in 22 of 45 (49%), improved in 15 of 45 (33%), and deteriorated in 8 of 45 (18%) patients (in 4 of these 8 patients in the context of an attack). Longitudinal EDSS data were not available in 7 patients, and 1 of them experienced an attack during ECU therapy. Seven of 8 patients with EDSS score deterioration received ECU with add-on immunotherapy, corresponding to an EDSS score progression in 7 of 13 patients (54%) in the "add-on-"treated group. In other 4 of these 13 patients, the EDSS score improved, and in 2 of 13, it remained unchanged.

Follow-up bMRI scans and scMRI scans during ECU treatment were available in 27 and 28 patients, respectively, and were obtained 10.0 months (median, IQR 7.2–21.2) and 11.6 months (median, IQR 6.3 – 20.5) after ECU start. The proportion of patients with new or enlarging T2-enhancing or contrast-enhancing T1 MRI lesions decreased significantly compared with the last MRI before ECU start (44% vs 7%; $p < 0.05$ for bMRI and 64% vs 16%; $p < 0.001$ for scMRI; Figure 4A+B).

Meningococcal Vaccination and Attack Activity

Forty-five patients (87%) received at least 1 vaccination against *Neisseria meningitidis* before ECU start. Thirty-six (80%) of these patients received both vaccines against serogroups ACW135Y and serogroup B, 4 (9%) only against serogroup B, 4 (9%) only against serogroups ACW135Y, and 1 (2%) only against serogroup C. Twenty-five patients (48%) were first vaccinated (n = 5) or re-vaccinated (n = 20) against meningococcal infection during ECU treatment. 2 patients (4%) did not receive any vaccination against *Neisseria meningitidis* (eTable 1). In 21 patients, antibiotics were administered because of an incomplete or missing immunization against meningococcal disease.

In total, 7 attacks occurred in temporal association with meningococcal vaccination (median: 9 days thereafter, IQR: 6–10; Table 2). Notably, all 7 attacks manifested in patients vaccinated before the initiation of ECU therapy. Five attacks occurred after simultaneous vaccination against serogroups ACW135Y and serogroup B while 1 attack each was noted after vaccination against serogroup B and serogroups ACW135Y. None of these patients received concomitant oral prednisone during the vaccination. All 7 attacks were confirmed by MRI and required apheresis therapy.

By contrast, none of the 9 patients who received meningococcal vaccination before ECU therapy and concurrently took oral prednisone (in varying doses) suffered subsequent

Figure 4 Significant Decrease of New or Contrast-Enhancing Lesions in 27 Patients With Available Longitudinal Brain MRI Scans ($p = 0.006$; A) and 25 Patients With Longitudinal Spinal Cord MRI Scans ($p < 0.001$; B) Before and During Eculizumab (ECU) Treatment

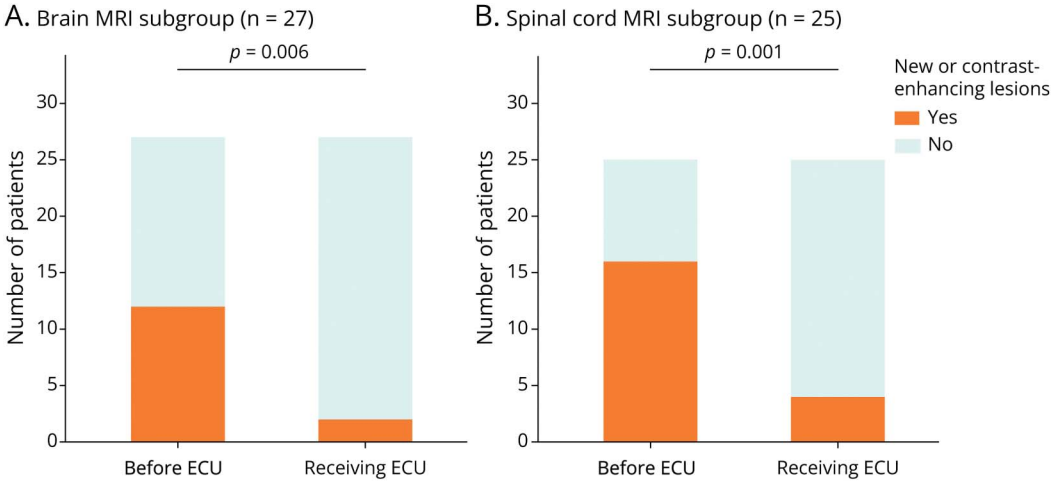


Table 2 Detailed Information of 7 Patients Who Experienced Postvaccinal Attacks

Patient no.	1	2	3	4	5	6	7
N. meningitidis vaccination before ECU start	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Serogroups vaccinated against	B, ACW135Y	B, ACW135Y	B, ACW135Y	B, ACW135Y	B	ACW135Y	B, ACW135Y
First vaccination against N. meningitidis	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time between vaccination and attack	10 d	8 d	18 d	11 d	2 d	5 d	9 d
Type of attack	Thoracal myelitis	Cervical longitudinal myelitis	Optic neuritis + longitudinal myelitis at multiple levels	Brainstem syndrome	Cervical myelitis	Thoracal myelitis	Cervicothoracal longitudinal myelitis
MRI-confirmed attack	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome of attack treatment	Partial remission under PLEX + alternating steroids	Full remission under PLEX	Partial remission under PLEX + RTX initiation	Partial remission under PLEX	Partial remission under steroids + PLEX	Partial remission under PLEX	Partial remission under PLEX
Immunotherapy before ECU							
Medication, protocol	none	RTX, biannually, 1000 mg	IVIG, monthly, 1–2g/kg body weight for 2–5 d	RTX, initiation with 1000 mg	none	RTX, biannually, 1000 mg	TCZ, monthly, 8 mg/kg body weight
Time between last infusion and vaccination	NA	139 d	242 d	231 d	NA	292 d	17 d
Time between last acute treatment (IV steroids and/or PLEX) and vaccination	59 d (PLEX and IV steroids)	60 d (PLEX)	200 d (IV steroids)	16 d (PLEX)	16 d (PLEX)	84 d (PLEX)	8 d (PLEX)
AAR in the past 2 y before vaccination	0.5	1	2	1	1	2	0.5
Add-on therapy	none	none	none	MMF, 1,000 mg/d	none	none	none
Further vaccinations							
Serogroups vaccinated against	B	B	B	B	B, ACW135Y	B	none

Abbreviations: AAR = annualized attack rate; ECU = eculizumab; EDSS = Expanded Disability Status Scale; MMF = mycophenolate mofetil; NA = not applicable; N. meningitidis = Neisseria meningitidis; PLEX = plasma exchange; RTX = rituximab; TCZ = tocilizumab.

attacks. Of these patients, 8 were simultaneously vaccinated against serogroups ACW135Y and serogroup B while 1 patient was only vaccinated against serogroup B.

In addition, no temporarily associated relapses were observed in 25 patients vaccinated or boostered against meningococcal disease during ECU therapy. Overall, 7 of 36 patients (19.4%) who had been vaccinated before ECU start without concomitant prednisone therapy experienced attacks.

The risk of postvaccinal attacks was not associated with the presence of additional comorbid autoimmune diseases (OR 1.16, CI95% [0.18,10.53]).

There was no difference in the overall number of vaccinations administered within 4 weeks of the initial meningococcal vaccination between patients who experienced postvaccinal attacks and those who did not (in both groups: median: 2, range: 1–3 and 1–4 vaccinations, respectively). There was no difference in median AAR in the previous 2 years before vaccination (median: 1, range: 0.5–2 in the group with postvaccinal relapses vs median: 0.5, range: 0–2 in the relapse-free group, $p = 0.19$). The comparison of patients without concomitant prednisolone use during the vaccination showed similar results (median AAR 1, range: 0–2 vs 1, range 0.5–2, respectively). The proportion of patients with recent attacks in the preceding 3 months before vaccination was also similar among those with and without postvaccinal attacks (57% vs 48%, $p = 0.70$).

Thirteen patients were further vaccinated against pneumococcal disease (8 before ECU and 5 during ECU

Table 3 Demographic and Clinical Aspects of 5 Fatalities During Eculizumab Treatment

Patient no.	1	2	3	4	5
Sex	Female	Male	Female	Female	Female
AQP4-IgG serostatus	Pos	Pos	Pos	Pos	Pos
MOG-IgG serostatus	Neg	Neg	Neg	Neg	Neg
NMOSD based on 2015 criteria	Yes	Yes	Yes	Yes	Yes
Disease duration before ECU (y)	> 15	0 – 1	0 – 1	1 – 5	> 20
AAR in the 2 y before ECU	1.5	0.5	0.5	1.5	0.5
Relapses under last immunotherapy	Yes	NA	NA	Yes	No
EDSS score at ECU start	8.5	8.0	8.5	0.0	7.0
ECU treatment duration (mo)	4.8	12.0	13.2	20.4	26.4
Age at death (decade)	6th	8th	7th	2nd	8th
Time between last ECU infusion and death (d)	30	24	21	57	12
Immunotherapies before ECU	FIN, NTZ, RTX, TCZ	Steroid	AZA	AZA, CYC, IVIG, MMF, RTX, TCZ	AZA, GLAT, IVIG, MIT, RTX
Autoimmune comorbidities before ECU	None	None	None	SLE	None
Comedication at the time of death	Steroid	None	AZA	MMF	Steroid
Cause of death	Candida sepsis, pneumonia	Sepsis after mechanical and paralytic ileus	Urosepsis with Klebsiella pneumoniae, secondary aneurysmatic SAH	Meningococcal sepsis (serogroup B, sequence type 35 complex), fulminant NMOSD attack	Myocardial infarction
Vaccination against serogroups ACW135Y before ECU	No	Yes	No	Yes[a]	Yes
Vaccination against serogroup B before ECU	No	Yes	No	Yes[a]	Yes
Vaccination against serogroup C before ECU	No	No	Yes	No	No

Abbreviations: AAR = annualized attack rate; AQP4-IgG = aquaporin-4-immunoglobulin G; AZA = azathioprine; CYC = cyclophosphamide; DM = diabetes mellitus; ECU = eculizumab; EDSS = Expanded Disability Status Scale; FIN = fingolimod; GLAT = glatiramer acetate; IVIGs = IV immunoglobulins; MIT = mitoxantrone; MMF = mycophenolate mofetil; MOG-IgG = myelin-oligodendrocyte-glycoprotein immunoglobulin G; NA = not applicable; NAT = natalizumab; neg = negative; NMOSDs = neuromyelitis optica spectrum disorders; pos = positive; RTX = rituximab; SAH = subarachnoid hemorrhage; SLE = systemic lupus erythematosus; TCZ = tocilizumab.
[a] Patient 4 received MMF and IVIG at the time of vaccination

therapy). Only 1 patient experienced an attack 3 weeks after pneumococcal vaccination, performed during ECU therapy.

Infusion-Related Reactions, SAEs, and Mortality

Infusion-related reactions were reported in 5 patients and comprised mild exanthema on the infusion arm, port occlusion and paravasation, nausea and vomiting, fever and shivering, and allergic reaction with generalized pruritus and periocular edema (leading to treatment discontinuation). The 2 latter patients with fever and allergic reaction received antiallergic medication before consecutive infusions.

Seven patients (13%) experienced serious infections requiring hospitalization (2 on ECU monotherapy and 5 with add-on immunotherapy with oral steroids, AZA, and MMF). Two were diagnosed with pneumonia (1 with sepsis); 2 with urosepsis (1 with fatal secondary subarachnoid hemorrhage); 1 with Candida sepsis (fatal course); 1 with meningococcal infection (fatal course); and 1 with multiple infections including erysipelas, pyelonephritis, and thoracic varicella zoster

infection. The patient with meningococcal sepsis (serogroup B) had completed the recommended meningococcal vaccination against serogroups ACW135Y and serogroup B under oral corticosteroid therapy 20 months before. This patient also suffered from SLE and, therefore, received add-on treatment with MMF for several months at the time of vaccination (Table 3). Two other patients had recurrent fever episodes of unknown origin; however, no infection has been reported. Two patients experienced exacerbation of SLE (during ECU monotherapy in one case and during ECU therapy with concomitant 5 mg prednisolone in another), leading to ECU discontinuation in both patients.

In total, 5 of 52 patients (10%), including 1 child (median age 54 years; range 13–73), died after 1.2 (median; IQR: 1.1–1.9) years on ECU treatment. One person died of myocardial infarction, 1 of ileus with secondary sepsis, and 3 in the context of systemic infections, including 1 of meningococcal sepsis (Table 3). Four of these 5 patients had severe disease courses (EDSS score ≥ 7) while the pediatric patient had no neurologic deficits at ECU start. Four of 5 patients died within 4 weeks of the last ECU infusion and the pediatric patient 57 days after the last infusion due to meningococcal sepsis.

Of the remaining 47 patients, 9 (19%) discontinued ECU treatment after a median treatment duration of 0.8 years (IQR: 0.4–1.2). Reasons for treatment discontinuation were recurrent UTIs with urosepsis (n = 1), disease activity (n = 1; disease progression on MRI (myelitis) associated with SLE exacerbation), infusion-related burden and exacerbation of previous autoimmune comorbidities (n = 1, SLE and autoimmune thrombopenia), infusion-related burden (n = 1), infusion-related allergic reaction (n = 1), refusal of meningococcal vaccination (n = 1), and (unknown) personal reasons (n = 3).

Two of 9 discontinuing patients died 4 and 16 months after ECU cessation: 1 patient had planned to prolong ECU treatment interval for personal reasons, experienced an NMOSD attack, and died several weeks thereafter (no further information available). The other person with infusion-related allergic reactions during ECU treatment was switched to RTX and then, again owing to infusion-related intolerance, to AZA and died severely disabled.

This study provides Class IV evidence that eculizumab reduces annualized attack rates and new MRI lesions in AQP4-IgG+ patients with NMOSD.

Discussion

In this study, we retrospectively analyzed routine clinical care data of a European cohort of AQP4-IgG+ patients with NMOSD treated with eculizumab. Despite a high baseline attack activity and disability (median EDSS score 6.0), the median AAR decreased substantially and 88% of patients remained attack-free during ECU treatment. These results are similar to previous findings in the pilot study on ECU in AQP4-IgG+ NMOSD (n = 14; 86% of patients remained attack-free; ARR decreased from 3.0 to 0),[18] in the PREVENT trial (n = 96; 97% attack-free; ARR decreased from 1.9 to 0),[10] and for RAV in the CHAMPION-NMOSD study (n = 58; 100% attack-free; ARR decreased from 1.9 to 0).[11] Notably, add-on immunosuppressants showed no advantage regarding the AAR compared with ECU monotherapy in our cohort, although our sample size was too small to draw conclusions. An investigation in a larger sample size would be necessary to detect a protective or potentially detrimental influence of add-on immunotherapy on disease activity. The heterogeneity of comorbidities and related add-on therapies precluded such statistical analyses in this study.

The decrease in brain and spinal cord MRI activity corroborates the clinical effectiveness of ECU. These findings are novel because MRI data have not yet been systematically analyzed in previous ECU and RAV trials. Nevertheless, asymptomatic MRI activity is not always a marker of disease activity in NMOSD.[30] Similar to the PREVENT[10] and CHAMPION-NMOSD studies,[11] EDSS scores remained stable on ECU despite a substantially higher baseline disability in our cohort (median EDSS score of 6.0 vs 4.0 and 3.25, respectively). Our routine clinical care data thus confirm the high therapeutic effectiveness of ECU in AQP4-IgG+ NMOSD.

Concerning safety, previous controlled trials and registries have revealed infusion-related reactions, headaches, nasopharyngitis, upper respiratory tract infection and UTI, back pain and diarrhea, nausea, and arthralgia as the most common adverse events of ECU in patients with NMOSD.[20] Severe infections, including bacterial and fungal sepsis (fatal in some cases), have also been reported in patients treated with ECU.[31] In our cohort, 7 patients (13%) experienced serious infections, including 1 case of meningococcal sepsis despite previous vaccination and 4 cases of non-meningococcal sepsis. A high level of preexisting disability and immobility and higher age and concomitant immunosuppressive therapy were potential risk factors of serious infections under treatment with ECU in our cohort in line with a recent consensus article[32]; however, (subsequently fatal) sepsis also occurred in a pediatric patient in the absence of neurologic disability.

Probably, the most relevant and novel safety finding of our study was the observation of disease attacks temporally associated with meningococcal vaccinations, performed before ECU initiation. Notably, a high number of attacks within the 2-week time window between the meningococcal vaccination and ECU start (or shortly thereafter) had already been reported in 4 of 14 patients (29%) in the ECU pilot study.[18] Concomitant oral prednisone during vaccination before ECU start and vaccination after ECU initiation were not associated with postvaccinal attacks in this cohort.

Moreover, the relapse rate in the past 2 years and previous attacks in the 3 months before vaccination were also not associated with a higher risk of postvaccinal attacks, suggesting that attack clustering is unlikely to be a causative factor. Despite the limited number of patients vaccinated against pneumococcal infection, only 1 attack has been observed during ECU treatment, indirectly indicating that postvaccinal attacks seem to be more frequently associated with meningococcal vaccines, given before ECU start and without concomitant steroid therapy.

Considering the retrospective nature of this study and the limited number of patients analyzed, data from larger and, ideally, prospective cohorts are needed to clarify whether meningococcal vaccinations might put patients at risk of NMOSD attacks. Mechanisms that specifically underlie an increased attack activity in NMOSD after meningococcal vaccination are unknown. However, the activation of autoimmune and autoinflammatory diseases after vaccination is a well-known phenomenon, especially in women and in patients with more than 1 autoimmune disease.[26] Single cases and case series of SLE,[27] bullous pemphigoid,[28] and Guillain-Barré syndrome[29] after different meningococcal vaccinations were previously reported. By contrast, no disease exacerbation has been observed in a systematic study of juvenile idiopathic arthritis.[33]

The European eculizumab product information warns of potential disease deterioration due to complement activation after meningococcal vaccinations, and Canadian recommendations report on possible complement activation specifically in the context of vaccination against meningococcal serogroup B.[34] However, because vaccination against serogroups ACW135Y and serogroup B is mandatory in patients subjected to anticomplement therapy in most countries worldwide, these warnings are of little clinical value. Alternatively, starting complement inhibitors on prophylactic antibiotics and vaccinating later might be a safer approach, enabling both prompt initiation of ECU treatment and safe vaccinations.

Sufficient meningococcal vaccine response remains another highly relevant safety aspect in therapeutic complement inhibition. Despite full vaccination against serogroups ACW135Y and serogroup B before the first ECU infusion, the pediatric patient from our cohort experienced fulminant meningococcal sepsis 1.7 years later, leading to ECU discontinuation, followed by a fatal NMOSD attack (case 4, Table 3). A possible supporting reason in this individual case was the MMF-treated SLE comorbidity. Indeed, infections with encapsulated bacteria during complement blockade have been reported in different indications despite previous vaccination.[35] In NMOSD, this includes 1 patient from the ECU pilot study who developed meningococcal sepsis 2 months after her initial ECU infusion,[18] 1 patient from the PREVENT-OLE study with a Neisseria gonorrhoeae infection,[19] and 2 patients in the CHAMPION-NMOSD trial suffering from meningococcal infections after 21 and 483 days of RAV treatment, respectively.[11] By contrast, neither the PREVENT study nor a 2-year postmarketing surveillance from Japan observed meningococcal infections.[10,36] The substantially higher overall incidence of meningococcal infections in Europe and the United States seems to be the most plausible explanation for these differences.[37] Further studies on vaccination responses and predictors of meningococcal infection despite vaccination in patients treated with complement inhibitors seem highly warranted.

Five patients (10%) from our cohort died during ECU treatment. This finding contrasts with previous observations on complement inhibitors in NMOSD because there were no fatalities in the pilot study (during ECU treatment), PREVENT-OLE study, CHAMPION-NMOSD trial,[11,18,19] and a recent Japanese, manufacturer-funded postmarketing surveillance.[36] Only 1 patient (0.96%) from the PREVENT study died of infectious pleural empyema under ECU and AZA treatment, classified as probably related to the trial medication.[10] One large Japanese study on the safety profile of ECU in 1,055 patients with PNH, aHUS, or gMG reported 40 patients (3.8%) who died because of SAEs, 34 of them due to serious infections, including 2 cases with meningococcal sepsis.[31] More recently, 1 additional patient with NMOSD with concomitant SLE was reported, who developed type B insulin resistance and severe Klebsiella pneumoniae pneumonia during ECU treatment and died of sepsis-related multiorgan failure 18 months after ECU initiation.[38]

In our cohort, 4 of 5 patients who died during/shortly after ECU treatment were aged older than 50 years and severely disabled at ECU treatment start (EDSS score ≥ 7). In sum, we suppose that severe disability, immobility, and higher age at disease onset contributed to an increased risk of infections and mortality in our cohort. Thus, overall disability, age, autoimmune comorbidities, and previous or concomitant immunosuppression should be carefully considered when making decisions to start ECU.

Our study is limited by its retrospective nature and the heterogeneity in data collection from 21 participating centers (contributing 1–7 patients per center; eTable 2) with, in consequence, partly incomplete data sets in some cases and by the limited number of patients in some subgroup analyses. The homogeneous ethnicity (90% White) and the relatively brief observation period on ECU (median 16.2 months) limit the generalizability to other populations and restrict the ability to draw definitive conclusions regarding its long-term safety and effectiveness. Our study may thus underestimate the risks associated with the use of ECU. The strength of our study is that it is one of the largest ECU NMOSD cohorts reported so far, including older patients and those with severe disability in a clinical routine setting rather than in the more strictly controlled setting of a phase III study. Given the safety signals

observed in this study, prospective, nonmanufacturer-funded registries are urgently needed.

Eculizumab therapy was associated with reduced attack rate and stable EDSS scores in our cohort, confirming clinical trial data. However, in this study, ECU treatment goes along with a higher risk of serious and potentially fatal complications than reported in the clinical trials, including meningococcal and other systemic infections. Further factors, including potential immune deficiency after multiple pretreatments, higher age, disability, and concomitant diseases, should be included in individual infection risk assessment.

The observation of an increased risk of attacks temporarily associated with meningococcal vaccination before ECU initiation in patients not co-treated with oral steroids is a critical finding with possible implications for treatment initiation and patient management. Later vaccination after ECU initiation seems to be safer regarding postvaccinal attacks. However, the number of patients included was too small to draw definite conclusions. Moreover, further studies are needed to evaluate the protective role of concomitant steroids during vaccination before ECU or RAV treatment and the effect of prednisone and/or other immunotherapies on the efficacy of meningococcal vaccination and on potential immune markers (e.g., serum bactericidal antibody test) that may predict the degree of protection against meningitis/meningococcal sepsis.

In summary, this study provides important insights into the effectiveness and safety of eculizumab in NMOSD and highlights the importance of carefully evaluating the risk-benefit profile in older patients with severe disability.

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Appendix 1 Authors

Name	Location	Contribution
Marius Ringelstein, MD	Department of Neurology, Medical Faculty; Department of Neurology, Center for Neurology and Neuropsychiatry, LVR-Klinikum, Heinrich-Heine-University Düsseldorf, Germany	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
Susanna Asseyer, MD	Experimental and Clinical Research Center, a cooperation between the Max Delbrück Center for Molecular Medicine in the Helmholtz Association and Charité Universitätsmedizin Berlin; Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Experimental and Clinical Research Center; Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany	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
Gero Lindenblatt, MD	Department of Neurology, Johanna Etienne Hospital, Neuss, Germany	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; additional contributions (in addition to 1 or more of the above criteria)
Katinka Fischer, MD	Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data; additional contributions (in addition to 1 or more of the above criteria)
Refik Pul, MD	Center for Translational Neuro- and Behavioral Sciences, University Medicine Essen, University of Duisburg-Essen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jelena Skuljec, PhD	Center for Translational Neuro- and Behavioral Sciences, University Medicine Essen, University of Duisburg-Essen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Lisa Revie, MD	Department of Neurology, University Hospital, Münster, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Katrin Giglhuber, MD	Department of Neurology, School of Medicine and Health, Technical University of Munich, Klinikum rechts der Isar, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Vivien Häußler, MD	Department of Neurology and Institute of Neuroimmunology and MS (INIMS), University Medical Center Hamburg-Eppendorf, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Michael Karenfort, MD	Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Kerstin Hellwig, MD	Department of Neurology, St. Josef-Hospital, Ruhr University Bochum, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Friedemann Paul, MD	Experimental and Clinical Research Center, a cooperation between the Max Delbrück Center for Molecular Medicine in the Helmholtz Association and Charité Universitätsmedizin Berlin; Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Experimental and Clinical Research Center, Lindenberger Weg 80; Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC), Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Judith Bellmann-Strobl, MD	Department of Neurology, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität and Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Carolin Otto, MD	Department of Neurology, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität and Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Klemens Ruprecht, MD	Department of Neurology, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität and Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Tjalf Ziemssen, MD	Department of Neurology, Center of Clinical Neuroscience, University Hospital, Dresden, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Alexander Emmer, MD	Department of Neurology, University Hospital, Halle, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Veit Rothhammer, MD	Department of Neurology, University Hospital, Erlangen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

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Appendix 1 *(continued)*

Name	Location	Contribution
Florian T. Nickel, MD	Department of Neurology, University Hospital, Erlangen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Klemens Angstwurm, MD	Department of Neurology, University Hospital, Regensburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Ralf Linker, MD	Department of Neurology, University Hospital, Regensburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Sarah A. Laurent, MD	Department of Neurology, University Hospital, Köln, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Clemens Warnke, MD	Department of Neurology, University Hospital, Köln, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Sven Jarius, MD	Department of Neurology, Molecular Neuroimmunology Group, University of Heidelberg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Mirjam Korporal-Kuhnke, MD	Department of Neurology, Molecular Neuroimmunology Group, University of Heidelberg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Brigitte Wildemann, MD	Department of Neurology, Molecular Neuroimmunology Group, University of Heidelberg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Stephanie Wolff, MD	Department of Neurology, University Hospital, Gießen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Maria Seipelt, MD	Department of Neurology, University Hospital, Marburg, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Yavor Yalachkov, MD	Department of Neurology, University Hospital, Frankfurt, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Nele Retzlaff, MD	Department of Neurology, University Hospital, Rostock, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Uwe K. Zettl, MD	Department of Neurology, University Hospital, Rostock, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Paulus S. Rommer, MD	Department of Neurology, Medical University of Vienna, Austria	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Markus C. Kowarik, MD	Department of Neurology, University Hospital, Tübingen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jonathan Wickel, MD	Section of Translational Neuroimmunology, Department of Neurology, Jena University Hospital, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Christian Geis, MD	Section of Translational Neuroimmunology, Department of Neurology, Jena University Hospital, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Martin W. Hümmert, MD	Department of Neurology, Hannover Medical School, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Corinna Trebst, MD	Department of Neurology, Hannover Medical School, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Makbule Senel, MD	Department of Neurology, University Hospital, Ulm, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Ralf Gold, MD	Department of Neurology, St. Josef-Hospital, Ruhr University Bochum, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Luisa Klotz, MD	Department of Neurology, University Hospital, Münster, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Christoph Kleinschnitz, MD	Center for Translational Neuro- and Behavioral Sciences, University Medicine Essen, University of Duisburg-Essen, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

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Appendix 1 *(continued)*

Name	Location	Contribution
Sven G. Meuth, MD, PhD	Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Orhan Aktas, MD	Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany	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
Achim Berthele, MD	Department of Neurology, School of Medicine and Health, Technical University of Munich, Klinikum rechts der Isar, Germany	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
Ilya Ayzenberg, MD	Department of Neurology, St. Josef-Hospital, Ruhr University Bochum, Germany	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

Appendix 2 Coinvestigators

Coinvestigators are listed at Neurology.org/N.

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