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Original research

Real-world multicentre cohort study on choices and effectiveness of immunotherapies in NMOSD and MOGAD

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ABSTRACT

Background Recurrent attacks in neuromyelitis optica spectrum disorders (NMOSDs) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) can lead to severe disability. We aimed to analyse the real-world use of immunotherapies in patients with NMOSD and MOGAD, focusing on changes in treatment strategies, effects on attack rates (ARR) and risk factors for attacks.

Methods This longitudinal registry-based cohort study included 493 patients (320 with aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive NMOSD (65%), 44 with AQP4-IgG seronegative NMOSD (9%) and 129 MOGAD (26%)) with 1247 treatments from 19 German and one Austrian centre from the registry of the neuromyelitis optica study group (NEMOS). We analysed unadjusted ARR and implemented survival analyses and Cox proportional hazard regression to assess efficiency and risk factors for subsequent attacks over time.

Results Rituximab and azathioprine are the most widely used immunotherapies in NMOSD as well as in MOGAD, with changes in distribution over the last decade. Immunotherapy demonstrated significant therapeutic effects in NMOSD but less pronounced effects in MOGAD. Risk factors for attacks included younger age and prior attacks under the same therapy. Efficacy varied among the different immunotherapies, with azathioprine, rituximab and eculizumab showing significant risk reductions in AQP4-IgG seropositive NMOSD.

Conclusions This study provides insights into the evolving treatment landscape and effectiveness of immunotherapies in NMOSD and MOGAD. Established

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Effective attack prevention in neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is essential to avoid the accumulation of severe disability. Despite the existence of established off-label therapies, as well as data regarding the use of recently approved immunotherapies in clinical practice, there is a lack of information regarding their real-world application and comparison of effectiveness.

WHAT THIS STUDY ADDS

⇒ Traditional off-label therapies continue to be used, while the newer approved therapies are becoming increasingly important. Immunotherapies show significant effectiveness in aquaporin 4 immunoglobulin G (AQP4-IgG) seropositive as well as seronegative NMOSD. Effectiveness in MOGAD is less pronounced.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the importance and complexity of tailored immunotherapy approaches in managing rare diseases like NMOSD and MOGAD and underscores the need for personalised treatment algorithms and further studies.

off-label therapies continue to play an important role, especially for patients with stable disease, with emerging evidence supporting newly approved therapies. Future studies are needed to refine treatment algorithms and address the ongoing uncertainties in MOGAD management.

INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSDs) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are rare neuroimmunological diseases.[1] The phenotypes may overlap when the diseases manifest with the most common clinical symptoms of optic neuritis and/or longitudinal transverse myelitis. The detection of aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) separates AQP4-IgG seropositive NMOSD from AQP4-IgG seronegative NMOSD.[2–4] MOGAD has been characterised as a disease entity of its own by the presence of myelin oligodendrocyte glycoprotein immunoglobulin G antibodies (MOG-IgG).[5 6]

Recurrent attacks with incomplete recovery can lead to severe permanent disability and reduced quality of life in NMOSD and MOGAD.[7–9] Based on case series and expert opinion, effective off-label therapies have been established to treat NMOSD, with rituximab becoming the treatment of choice in many countries.[10–12] Recently, eculizumab, inebilizumab, ravulizumab and satralizumab have been approved for the treatment of AQP4-IgG seropositive NMOSD,[13–17] but head-to-head comparisons among each other and with established off-label therapies are missing. The therapeutic strategies for MOGAD are even more uncertain due to limited evidence-based data and the absence of approved treatments. Evidence is growing that rituximab may be less effective in MOGAD,[18] favouring alternative therapies such as intravenous immunoglobulins (IVIG) or interleukin-6 inhibition.[19 20]

Data on the effectiveness of immunotherapies in real-world settings may help to overcome these knowledge gaps, but are scarce and, unfortunately, mainly derived from mixed cohorts in which AQP4-IgG seropositive and seronegative patients with NMOSD and MOGAD were investigated together. Therefore, the present study was designed to analyse the change in treatments during the last decade, the effect of immunotherapies on attacks and attack-free survival and predictors of attacks from a large cohort of well-defined NMOSD and MOGAD subgroups from the registry of the Neuromyelitis Optica Study Group (NEMOS).

METHODS

Study design and data collection

This longitudinal registry-based cohort study comprised data from 19 German and one Austrian NEMOS centres (www.nemos-net.de) between 1975 and database closure in October 2022; in cases with the last registry entry more than 365 days before the database closure, this entry was censored as the end of follow-up. Written informed consent was obtained from all patients before enrolment in the registry. Data were collected during regular clinical visits and included core demographic parameters (sex and year of birth), disease-specific characteristics (AQP4 and MOG-IgG serostatus, diagnostic criteria, year of manifestation and diagnosis), attacks (onset and clinical syndrome) and long-term treatment data (agent, start and end date). To ensure high-quality data, registry entries were exported and validated manually by two authors (AD and VH). Patients with a diagnosis of NMOSD according to the 2015 International Panel for NMO Diagnosis (IPND) criteria[2] or a diagnosis of MOGAD based on the presence of MOG-IgG in serum and at least one attack with a typical clinical syndrome were included in the study (diagnosis and database entry preceded the diagnostic criteria proposed by Banwell *et al*[5]). Standard testing for AQP4-IgG and MOG-IgG was performed with a cell-based assay (CBA)[21 22] in most patients (for AQP4-IgG: 74% CBA, 22% unknown and 4% other than CBA; and for MOG-IgG: 80% CBA, 16% unknown and 4% other). Patients with insufficient core datasets or incomplete treatment data were excluded from the analysis.

Statistical analysis

Descriptive data were summarised by either median with range or frequency according to the type of the data and tested for differences by Kruskal-Wallis or χ^2 test. We computed the unadjusted annualised attack rate (AAR) along with the corresponding 95% CI, assuming the number of attacks per year follows a negative binomial distribution. For further analysis, treatment episodes were defined as clinically meaningful stable treatment epochs, defined as the time between the first dose and either the assumed end of efficacy after the last dose (see online supplemental file for detailed information) or the last visit. For recurrent event analyses, these episodes were eventually split into separate periods at the date of attacks. Treatments with less than 30 cumulative patient years were excluded from the analysis. Survival analysis and calculation of attack-free rates were conducted using the Kaplan-Meier method, with concomitant steroid therapy considered a covariate in the subsequent analysis. To assess risk factors for attacks, we implemented a multivariate Cox proportional hazard regression model that included the patient ID as a cluster variable to account for the intraindividual correlation of observation. HRs and their 95% CI were computed. The p values <0.05 were considered statistically significant. Unless otherwise stated, all available episodes were included in the analysis of immunotherapies. All analyses were performed in R (V.4.3.1).

RESULTS

Description of the cohort

We screened 778 patients in the NEMOS database for eligibility (see online supplemental figure 1). After the exclusion of patients not fulfilling the 2015 IPND diagnostic criteria for NMOSD or not being classified as MOGAD or having incomplete or uncertain treatment data, 493 patients with 1247 treatments were included in the study. Of those, 320 patients were diagnosed with AQP4-IgG seropositive NMOSD, 44 with seronegative (AQP4-IgG/MOG-IgG) NMOSD and 129 with MOGAD (68.2% with >1 attack). Demographics varied significantly among the diagnostic groups but were typical for patients with AQP4-IgG seropositive and seronegative NMOSD and MOGAD (table 1). The median age at manifestation and diagnosis was higher in AQP4-IgG-positive NMOSD (43 and 48 years) than in double-negative NMOSD (35.5 and 39 years) and MOGAD (39 and 44 years). Similarly, the female sex constituted 88% of AQP4-IgG-positive patients with NMOSD, compared with only 40.9% in double-negative patients with NMOSD and 57.4% in patients with MOGAD. The most common syndrome at manifestation was transverse myelitis for AQP4-IgG-positive NMOSD (45.9%), followed by optic neuritis (35%). The occurrence of optic neuritis and myelitis in double-negative NMOSD was evenly distributed at 38.6% each, whereas in MOGAD, optic neuritis (45.7%) followed by myelitis (27.1%) was the most common manifestation. Other manifestations at disease

Table 1 Patient characteristics

	Statistics	AQP4-IgG seropositive NMOSD	AQP4-IgG seronegative NMOSD	MOGAD	P value
Number of patients	n	320	44	129	
Age at manifestation	Median (range)	43 (6-83)	35.5 (11-70)	32 (4-76)	<0.001*
Age at diagnosis	Median (range)	48 (6-85)	39 (17-71)	35 (10-79)	<0.001*
Sex					<0.001†
Male	n (%)	36 (11.2)	26 (59.1)	55 (42.6)	
Female	n (%)	284 (88.8)	18 (40.9)	74 (57.4)	
Attack type at initial diagnosis					0.007†
Optic neuritis	n (%)	112 (35)	17 (38.6)	59 (45.7)	
Transverse myelitis	n (%)	147 (45.9)	17 (38.6)	35 (27.1)	
Optic neuritis and transverse myelitis	n (%)	10 (3.1)	2 (4.5)	9 (7)	
Brainstem symptoms	n (%)	15 (4.7)	1 (2.3)	3 (2.3)	
Cerebral symptoms	n (%)	2 (0.6)	0 (0)	3 (2.3)	
Other	n (%)	29 (9.1)	5 (11.4)	20 (15.5)	
Unknown	n (%)	5 (1.6)	2 (4.5)	0 (0)	
Comorbid autoimmune disease					
Yes	n (%)	113 (35.3)	2 (4.5)	29 (22.5)	<0.001†
No	n (%)	186 (58.1)	38 (86.4)	94 (72.9)	
Unknown	n (%)	21 (6.6)	4 (9.1)	6 (4.7)	
Follow-up time (years)	Median (Range)	8.6 (0.1–52.4)	10.0 (0.8–27.3)	5.4 (0.1–48.4)	0.001*

Demography and basic clinical data of included patients.
*Kruskal-Wallis test.
†χ^2 test.
AQP4-IgG, aquaporin-4 immunoglobulin G ; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSD, neuromyelitis optica spectrum disorders.

onset were rare among all three groups. Comorbid autoimmune diseases were observed most frequently in AQP4-IgG-positive patients with NMOSD (35.3%), only rarely in double-negative patients with NMOSD (4.5%) and in 22.5% of the patients with MOGAD. Median follow-up time was 8.6 years in AQP4-IgG-positive NMOSD, 10 years in double-negative NMOSD and 5.4 years in MOGAD.

Immunotherapy characteristics and rates

Rituximab (348 treatment episodes in 301 patients for a total of 1110 patient years) and azathioprine (187 treatment episodes in 159 patients for a total of 678 patient years) were the most used immunotherapies in all three disease entities (online supplemental table 1). Similarly, rituximab, followed by azathioprine, was the most used first-line and second-line therapy. The choice of treatment was similar in AQP4-IgG seropositive and seronegative patients with NMOSD (rituximab 29.4% and 30.3%, azathioprine 13.7 and 13.8% of all treatment episodes, respectively). Looking at immunotherapies from the patient's perspective, approximately one-third of patients across all three disease entities received azathioprine during the course of disease, which was applied first-line in the majority of cases (table 2). Rituximab, on the other hand, was applied in 68% of the AQP4-IgG seropositive patients with NMOSD (55% first line), whereas only 57% of the AQP4-IgG seronegative NMOSD (44% first line) and 45% of the patients with MOGAD (55% first line) received this immunotherapy. In accordance with the approval, new therapies were rarely used in AQP4-IgG seronegative NMOSD or MOGAD, but in AQP4-IgG seropositive NMOSD (6% eculizumab; 2% each eculizumab combination therapy, satralizumab and satralizumab therapy; 1% inebelizumab). Combination therapies other than those listed separately were more frequently used in patients with comorbid autoimmune diseases (18.8%) than in those without (6.0%). A detailed description of frequencies, sequences and treatment durations per treatment is provided in table 2 and online supplemental table 1.

Changes in the therapeutic landscape over time

The use of different immunotherapies between 2010 and 2022 is shown in figure 1, online supplemental figure 2 and table 2. The therapeutic landscape changed remarkably over time. In 2010, classical therapies used in multiple sclerosis (MS) accounted for as many as one-fifth (20.1%) of the treatments and rituximab for less than one-third (29.2%). The utilisation of rituximab, both first line and overall, increased significantly over time, peaking in 2018 (60.1% overall). The use of disease-specific newly approved therapies has steadily increased since the first approval in 2019, reaching 12.3% in 2022. Classical MS drugs were no longer prescribed in 2022.

Looking at the different disease entities separately, the new therapies were only used in AQP4-IgG seropositive NMOSD as per approval, with a few exceptions. Interestingly, the use of rituximab decreased only slightly (61.3% in 2018, 55.0% in 2022) in AQP4-IgG seropositive NMOSD. Although first-line usage of rituximab is decreasing, it was still applied in 32% in the first line in 2022 (see online supplemental figure 2). However, in seronegative NMOSD, the proportion of rituximab decreased from its maximum of 73.1% in 2019 to 53.9%, in favour of azathioprine (30.8%) and tocilizumab (15.4%) in 2022. We observed similar effects for MOGAD, where the proportion of rituximab fell from 49.9% in 2018 to 37.3% in 2022.

Unadjusted efficacy of immunotherapies

The unadjusted AAR for all immunotherapies is presented in online supplemental table 1. The AAR for untreated episodes was 0.80 (95% CI 0.69 to 0.96); for AQP4-IgG seropositive NMOSD, it was 0.42 (95% CI 0.30 to 0.59) for seronegative NMOSD, it was 0.42 and 0.63 (95% CI 0.47 to 0.86)

Table 2 Immunotherapies

	AQP4-IgG seropositive NMOSD N (%)*	First line N (%)†	AQP4-IgG seronegative NMOSD N (%)*	First line N (%)†	MOGAD N (%)*	First line N (%)†
Azathioprine	98 (31)	69 (70)	15 (34)	10 (67)	46 (36)	33 (72)
Azathioprine and steroids	30 (9)	16 (53)	2 (5)	1 (50)	22 (17)	10 (45)
Classical multiple sclerosis	48 (15)	39 (81)	15 (34)	14 (93)	19 (15)	17 (89)
Combination therapy	35 (11)	4 (11)	2 (5)	0 (0)	11 (9)	0 (0)
Cyclophosphamide	17 (5)	8 (47)	0 (0)		0 (0)	
Eculizumab	18 (6)	8 (44)	0 (0)		0 (0)	
Eculizumab and other	7 (2)	0 (0)	0 (0)		0 (0)	
Inebilizumab	2 (1)	1 (50)	0 (0)		1 (1)	1 (100)
Intravenous immunoglobulin	10 (3)	4 (40)	0 (0)		8 (6)	4 (50)
Methotrexate	13 (4)	5 (38)	2 (5)	0 (0)	6 (5)	1 (17)
Mycophenolate mofetil	17 (5)	0 (0)	2 (5)	0 (0)	4 (3)	1 (25)
Other	21 (7)	8 (38)	2 (5)	1 (50)	4 (3)	1 (25)
Rituximab	218 (68)	120 (55)	25 (57)	11 (44)	58 (45)	32 (55)
Rituximab and other	40 (12)	1 (3)	5 (11)	0 (0)	17 (13)	2 (12)
Rituximab and steroids	29 (9)	12 41)	6 (14)	3 (50)	16 (12)	7 (44)
Satralizumab	7 (2)	0 (0)	0 (0)		0 (0)	
Satralizumab and other	7 (2)	0 (0)	0 (0)		0 (0)	
Oral steroids	34 (11)	14 (41)	7 (16)	4 (57)	18 (14)	16 (89)
Tocilizumab	17 (5)	2 (12)	3 (7)	0 (0)	5 (4)	0 (0)

Data presented as n (%).
*Percentage corresponds to the number of patients ever receiving the respective immunotherapy in AQP4-IgG seropositive, AQP4-IgG seronegative or patients with MOGAD.
†Percentage corresponds to how many of those received the respective immunotherapy first line.
AQP4-IgG, aquaporin-4 immunoglobulin G; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; NMOSDs, neuromyelitis optica spectrum disorders.

for MOGAD. We observed a trend towards higher AAR in AQP4-IgG seropositive NMOSD (1.32, 95% CI 0.90 to 1.96) as well as in seronegative NMOSD (1.36, 95% CI 0.82 to 2.28), not being evident in MOGAD (ARR 0.62 (95% CI 0.36 to 1.07)), for typical MS drugs in comparison to episodes with no treatment. Excluding classical MS therapies, the combined AAR for all drugs, compared with no treatment, was lower in AQP4-IgG seropositive NMOSD (AAR 0.48, 95% CI 0.41 to 0.56) as well as seronegative NMOSD (AAR 0.33, 95% CI 0.21 to 0.53) and remained nearly unchanged for MOGAD (AAR 0.67, 95% CI 0.52 to 0.88).

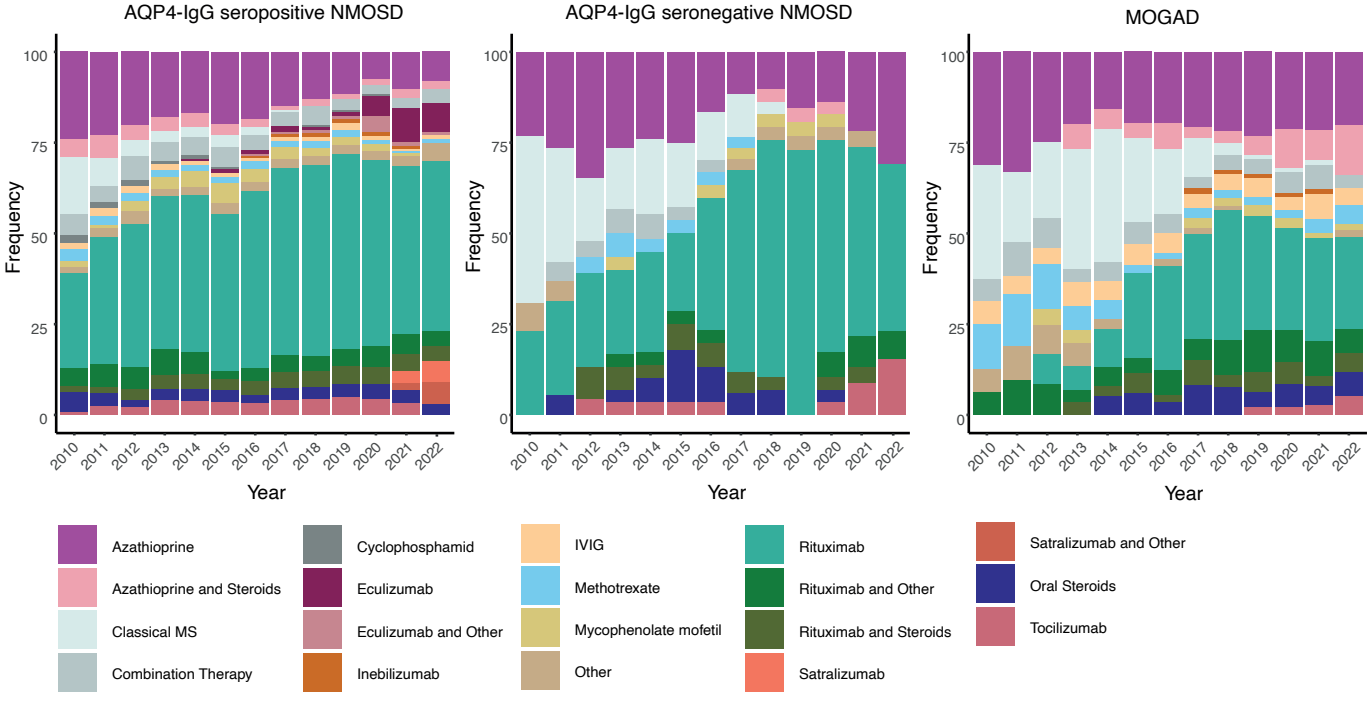

Figure 1 Change of the treatment landscape in the Neuromyelitis Optica Study Group cohort. Stacked bar plot illustrating the distribution of treatments for each year. AQP4-IgG, aquaporin-4 immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorders; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease.

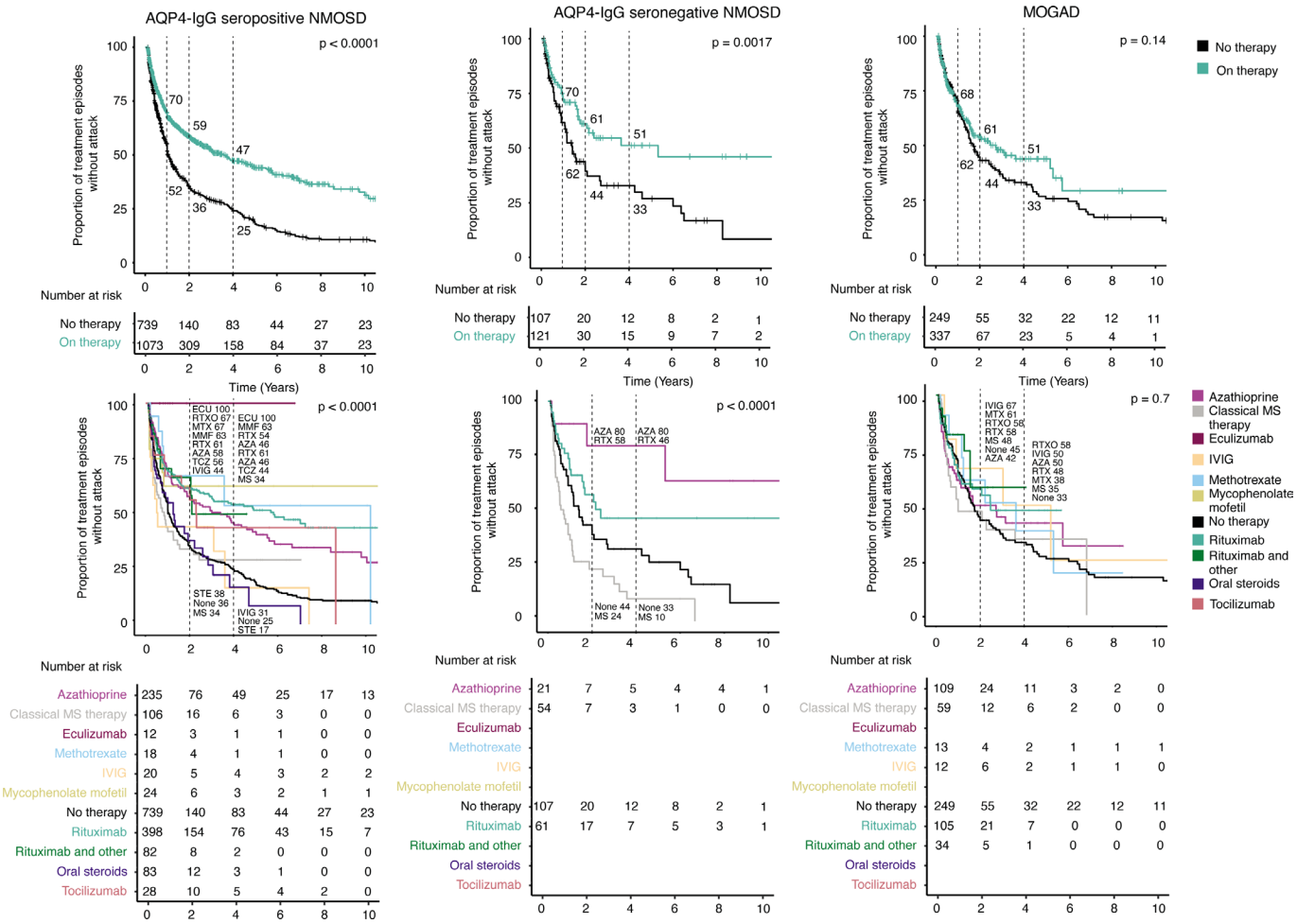

Figure 2 Unadjusted treatment effects in NMOSD and MOGAD. The unadjusted survival plots and their corresponding risk tables illustrate the risk for the next attack for all episodes (see methods for details). The dotted lines and the corresponding numbers highlight attack-free rates at 1, 2 and 4 years. The upper row compares any treatment (green, classic MS compounds excluded) with untreated episodes. The bottom row shows Kaplan-Meier curves for each compound separately. AQP4-IgG, aquaporin-4 immunoglobulin G; AZA, azathioprine; ECU, eculizumab; IVIG, intravenous immunoglobulins; MMF, mycophenolate mofetil; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MS, multiple sclerosis; MTX, methotrexate; NMOSD, neuromyelitis optica spectrum disorders; RTX, rituximab; RTXO, rituximab and other; STE, steroids; TCZ, tocilizumab.

Regarding the risk of suffering subsequent attacks, recurrent treatment episodes were computed, splitting the 1247 available treatment episodes in the event of an attack. This resulted in 1750 therapy episodes, of which 219 were classical MS treatments. Together with 1095 episodes without maintenance treatment, these were subjected to a survival analysis using the Kaplan-Meier method. We compared episodes without maintenance therapy to all episodes with therapy except classical MS drugs (figure 2) and observed a robust therapeutic effect in both AQP4-IgG seropositive NMOSD and seronegative NMOSD, with an increase of attack-free episodes of +18, +23 and +22 percentage points (AQP4-IgG seropositive) and +18, +17 and +18 percentage points (AQP4-IgG seronegative) at 1, 2 and 4 years, respectively. For MOGAD, in turn, the effect was less pronounced, with only +2, +9, and +12 percentage points at 1, 2 and 4 years.

Substances with a sufficient cumulative treatment duration (>30 patient years) were then examined individually (figure 2). In AQP4-IgG seropositive NMOSD, we found that most treatments led to increased attack-free survival at 2 and 4 years, namely azathioprine +22 and +21, eculizumab +64 and +75, methotrexate +31 and +28, mycophenolate mofetil +27 and +38, rituximab without (+25 and +29) or with additional immunosuppressive therapy (+31 and +25) and tocilizumab +20 and +19 percentage points, at 2 and 4 years, respectively, whereas oral steroid therapy had no conclusive effect (+2 increase of attack-free survival at 2 years and decrease of −8 at 4 years). In seronegative NMOSD, azathioprine (+36 and +47 percentage points) and less pronounced rituximab (+14 and +13 points) improved the attack-free survival at 2 and 4 years. For MOGAD, however, the rates of attack-free survival of the different immunotherapies differed only slightly from untreated episodes at 2 years. Azathioprine (−3 and +17 percentage points) and rituximab (+13 and +15 points) had a weaker attack-preventive effect than in both NMOSD subgroups at 2 and 4 years. Unadjusted HRs for the different immunotherapies are provided in online supplemental table 3.

Risk factors for subsequent attacks and effectiveness of immunotherapies

A multivariate Cox proportional hazard model was used to assess the risk for attacks, adjusting for the cofactors sex, age at attack, line of therapy, concomitant steroid use and prior attack under the same treatment (table 3). Overall, the risk of an attack was lower in MOGAD than in AQP4-IgG seropositive NMOSD (HR

Table 3 Risk for attacks in NMOSD and MOGAD

		N	All	P value	N	AQP4-IgG seropositive NMOSD	P value	N	AQP4-IgG seronegative NMOSD	P value	N	MOGAD	P
Antibody status	AQP4-IgG seropositive NMOSD	1745	Reference										
	AQP4-IgG seronegative NMOSD	270	0.93 (0.76–1.14)	0.466									
	MOGAD	615	**0.81 (0.66–1.00)**	**0.041**									
Sex	Female	2141	reference		1596	Reference		130	Reference		375	Reference	
	Male	490	**0.81 (0.68–0.96)**	**0.017**	131	**0.74 (0.59–0.93)**	**0.010**	140	1.05 (0.75–1.48)	0.778	206	0.72 (0.52–1.00)	0.051
Age	<30	511	reference		238	Reference		54	Reference		209	Reference	
	30–50	1181	**0.72 (0.61–0.84)**	**<0.001**	747	**0.69 (0.56–0.86)**	**0.001**	156	0.74 (0.52–1.05)	0.093	255	**0.66 (0.48–0.90)**	**0.009**
	>50	939	**0.50 (0.41–0.61)**	**<0.001**	742	**0.51 (0.40–0.64)**	**<0.001**	60	**0.34 (0.14–0.79)**	**0.012**	117	**0.45 (0.27–0.76)**	**0.003**
Line of therapy	First line	638	reference		398	Reference		70	Reference		144	Reference	
	Second line	352	1.05 (0.83–1.33)	0.665	212	0.98 (0.72–1.33)	0.895	38	1.29 (0.62–2.70)	0.495	91	1.12 (0.72–1.75)	0.619
	Third line	1641	1.21 (0.96–1.53)	0.108	1117	1.28 (0.96–1.72)	0.094	162	2.16 (0.96–4.84)	0.062	346	0.93 (0.61–1.41)	0.717
Concomitant steroids	No	2485	reference		1643	Reference		258	Reference		531	Reference	
	Yes	146	1.04 (0.72–1.49)	0.848	84	0.96 (0.63–1.45)	0.835	12	1.44 (0.51–4.05)	0.492	50	0.98 (0.46–2.12)	0.967
Prior attack under same therapy	No	1167	reference		740	Reference		126	Reference		271	Reference	
	Yes	1464	**1.5 (1.32–1.70)**	**<0.001**	987	**1.47 (1.26–1.72)**	**<0.001**	144	1.31 (0.82–2.09)	0.263	310	**1.52 (1.16–1.99)**	**0.002**
Treatment	No therapy	1095	Reference		739	Reference		107	Reference		249	Reference	
	Azathioprine	365	0.77 (0.59–1.01)	0.060	235	**0.72 (0.51–1.00)**	**0.049**	21	0.65 (0.09–4.55)	0.668	109	1.08 (0.66–1.75)	0.772
	Classical multiple sclerosis	219	**1.35 (1.04–1.76)**	**0.020**	106	1.35 (0.9–2.04)	0.148	54	**3.1 (1.69–5.60)**	**<0.001**	59	0.88 (0.50–1.53)	0.643
	Eculizumab	12	**<0.001 (NA)**	**<0.001**	12	**<0.001 (NA)**	**<0.001**						
	Intravenous immunoglobulin	31	1.03 (0.58–1.83)	0.914							13	0.53 (0.15–1.89)	0.325
	Methotrexate	38	0.82 (0.50–1.36)	0.448	20	0.54 (0.27–1.09)	0.084				12	1.06 (0.53–2.09)	0.872
	Mycophenolate mofetil	33	0.89 (0.39–2.02)	0.779	24	0.88 (0.32–2.47)	0.842						
	Rituximab	564	**0.71 (0.56–0.88)**	**0.002**	398	**0.66 (0.51–0.86)**	**0.002**	61	1.09 (0.53–2.22)	0.817	105	0.87 (0.55–1.40)	0.574
	Rituximab and other	122	0.72 (0.39–1.33)	0.291	82	0.70 (0.30–1.62)	0.406				34	0.87 (0.32–1.91)	0.589
	Steroids oral	116	1.17 (0.82–1.66)	0.381	83	1.20 (0.85–1.69)	0.300						
	Tocilizumab	36	0.59 (0.3–1.14)	0.118	28	0.68 (0.35–1.33)	0.256						

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

0.81, 95% CI 0.66 to 1.00, p=0.041), but the two NMOSD cohorts did not differ. Furthermore, we found that the attack risk decreased with age for all three subgroups (reference: <30 years; 30–50 years: HR 0.72, 95% CI 0.61 to 0.84, p<0.001 and >50 years: HR 0.50, 95% CI 0.41 to 0.61, p<0.001). A previous attack under the same immunotherapy increased the attack risk in AQP4-IgG seropositive NMOSD (HR 1.47, 95% CI 1.26 to 1.72, p<0.001) and MOGAD (HR 1.52, 95% CI 1.16 to 1.99, p=0.002), but not in AQP4-IgG seronegative NMOSD. Male sex decreased the attack risk in AQP4-IgG seropositive NMOSD (HR 0.74, 95% CI 0.59 to 0.93, p=0.010).

With regard to the effectiveness of immunotherapy, significant risk reduction for attacks was only seen in the largest group of AQP4-IgG seropositive NMOSD. The risk reduction was most pronounced for eculizumab monotherapy without any observed attacks (HR and CI not estimable, p<0.001). Furthermore, we observed a significantly reduced risk for rituximab (HR 0.66, 95% CI 0.51 to 0.86, p=0.002) and azathioprine (HR 0.72, 95% CI 0.51 to 1.00, p=0.049) in AQP4-IgG seropositive NMOSD. In seronegative NMOSD, risk reduction for azathioprine (HR 0.65, 95% CI 0.09 to 4.55, p=0.667) was not significant. For MOGAD, the HR was lowest for IVIG; nevertheless, it was not significantly reduced (HR 0.53, 95% CI 0.15 to 1.89, p=0.325), but only 13 patients were treated with IVIG. Interestingly, concomitant steroid therapy did not impact the risk reduction for all three entities (HR 1.04, 95% CI 0.72 to 1.49, p=0.848).

Treatment after failure of rituximab in AQP4-IgG-positive NMOSD

To identify treatments that were effective after rituximab has failed in AQP4-IgG-positive NMOSD, all immunotherapies used after a first attack while on rituximab for at least 60 days since its first dose were analysed using the Kaplan-Meier method (figure 3), irrespective of cumulative patient years. Attack-free rates after 2 and 4 years were higher for eculizumab (+36 and +46 percentage points) and for rituximab combined with another immunotherapy (+18 and +20 percentage points) compared with continuing rituximab monotherapy. Treatment with a monoclonal antibody against the interleukin-6-receptor (tocilizumab and satralizumab combined) did not show an effect (+3 and −2 percentage points attack-free survival). Using a multivariate Cox proportional hazard model, we observed a reduction in the risk of another attack for eculizumab only (p<0.001; online supplemental table 4).

DISCUSSION

In our registry-based real-world cohort, we showed that immunotherapy has a significant therapeutic effect in AQP4-IgG

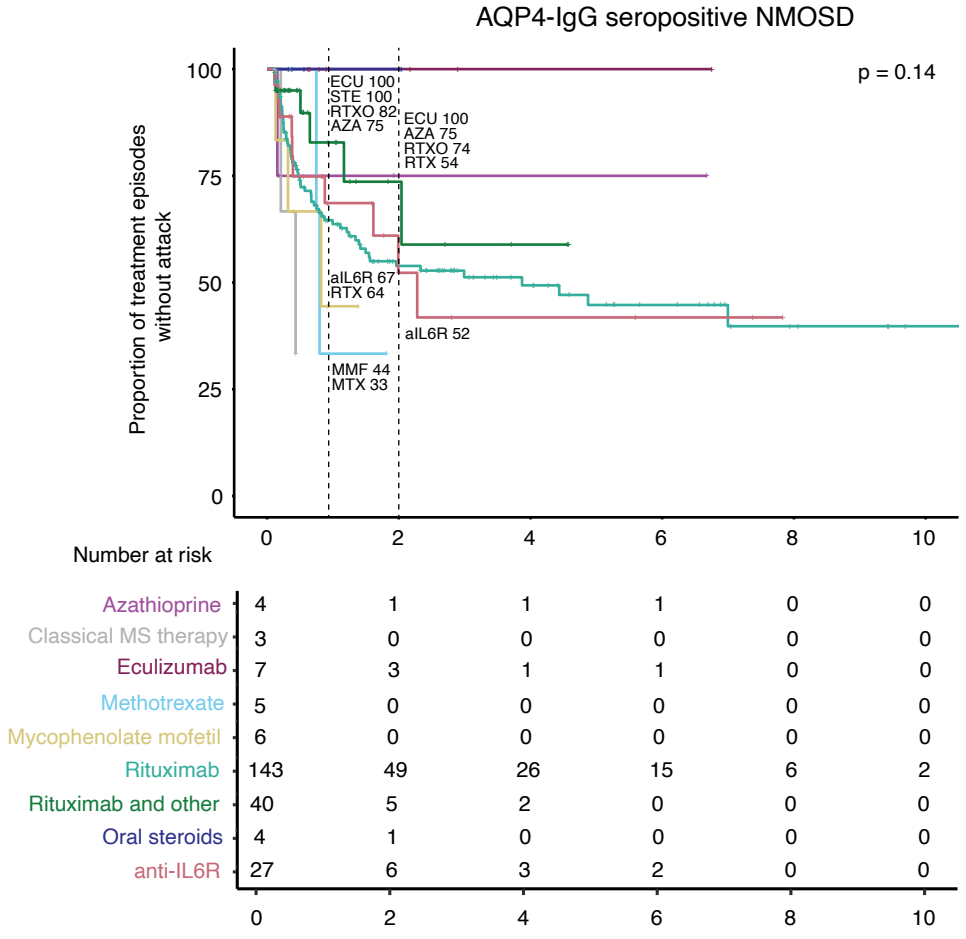

Figure 3 Unadjusted treatment effects after an attack under RTX in aquaporin-4 immunoglobulin G seropositive neuromyelitis optica spectrum disorders. The unadjusted survival plot and the corresponding risk tables illustrate the risk for the next attack under different treatments in episodes following an attack under RTX. The dotted lines and the corresponding numbers highlight attack-free rates at 1, 2 and 4 years. aIL6R, monoclonal antibodies against the interleukin-6 receptor (ie, tocilizumab and satralizumab); AZA, azathioprine; ECU, eculizumab; MMF, mycophenolate mofetil; MS, multiple sclerosis therapy; MTX, methotrexate; RTX, rituximab; RTXO, rituximab and other; STE, steroids.

seropositive NMOSD and seronegative NMOSD. This effect is less evident in MOGAD, however. We found that rituximab remains the most widely used immunotherapy in AQP4-IgG seropositive and seronegative NMOSD and MOGAD until 2022, demonstrating its continued valuation. Despite its off-label status, rituximab continues to be used not only in patients already receiving it for many years but also as first-line treatment in newly diagnosed AQP4-IgG seropositive patients. Possible reasons for this could be good long-term experience regarding efficacy and safety, as well as treatment costs.[8]

From the medical perspective, there is a lack of data from large cohorts that compare the effectiveness of currently available and recommended[23] immunotherapies in AQP4-IgG seropositive NMOSD in a real-world setting. However, some studies showed that treatment with monoclonal antibodies with an assumed high efficacy was superior to classical immunosuppressant treatment in NMOSD.[24–26] Although the numbers for immunotherapies other than rituximab and eculizumab were relatively small in our study, we could support this observation and validate these findings for NMOSD in our multivariate model for rituximab and eculizumab. However, recent data raised some safety concerns about fatal outcomes as well as attacks occurring in close temporal association with meningococcal vaccinations, which are mandatory for patients treated with complement inhibitors.[27] Main concerns regarding anti-CD20 therapy include hypogammaglobulinaemia which may increase infection risks in vulnerable patients.[28] Notably, only azathioprine, rituximab and eculizumab showed a significant risk reduction in AQP4-IgG-positive NMOSD in our cohort, which may be too small to prove the effectiveness of other drugs (particularly the other newly approved drugs, inebilizumab and satralizumab).

Regarding further attacks, younger age and a prior attack on the same therapy are risk factors in all three disease entities; female sex increased the risk only in AQP4-IgG seropositive NMOSD and MOGAD. The increased risk with continued therapy in the multivariate model supports the recommendation to switch to another drug as soon as possible, ideally to a different monoclonal antibody.[23 29] In our cohort, eculizumab or add-on immunosuppressants to rituximab were therapeutic alternatives after rituximab failure in AQP4-IgG seropositive NMOSD. Surprisingly, add-on steroids failed to be protective, which has been suggested before[30] and might be caused by the exclusion of short-term steroid therapies <60 days in our study. In addition, we may have missed the benefits of long-term concomitant steroid therapy in our patients because the doses administered may have been too low, which we cannot rule out because long-term steroid doses were not consistently recorded.

In addition to effectiveness in AQP4-IgG seropositive patients with NMOSD, we were able to validate the efficacy of immunotherapy in a truly, that is, AQP4-IgG and MOG-IgG seronegative, NMOSD cohort. Regarding the controversy as to whether AQP4-IgG seronegative NMOSD exists as a single entity or rather represents a heterogeneous subgroup of different diseases,[31] it is crucial to recognise that many studies on this topic are probably confounded by the enrolment of patients with MOGAD.[32 33] In our AQP4-IgG seronegative NMOSD cohort, we observed that azathioprine and rituximab were efficacious, although the effectiveness of rituximab was rather low in our multivariate model after correction for cofactors.[30]

The data on patients with MOGAD, on the other hand, is difficult to interpret. It is already known that the drugs used in NMOSD, particularly rituximab, are less effective.[18 34 35] Our study, however, found an even higher AAR for rituximab compared with untreated patients. Only after correction for cofactors, the observed effect attenuated, persisting as less favourable compared with other studies. However, it should be noted that we did not compare the difference in AAR before and after the initiation of rituximab, as a number of studies indicated a considerable decrease in AAR after the initiation of rituximab. Furthermore, at least 20% of patients with MOGAD exhibit a monophasic course,[5 36] depending on the observation period, which might also influence the effectiveness of immunotherapy. The risk factors for a relapsing or severe course are currently under discussion. Additionally, in MOGAD, it is common practice to not initiate immunotherapy after the first attack, likely introducing a bias towards more severe courses, but early oral steroid therapy in an adequate dose might be important.[37] While it is beyond the scope of this manuscript to address this issue separately, further studies are urgently needed. Moreover, a thorough comparison with the currently preferred treatments IVIG and tocilizumab[19 20] is still pending.

Limitations

This study has several limitations. The retrospective design may introduce biases related to data collection and selection, and, since most NEMOS centres are tertiary care centres, there might be a recruitment bias. Moreover, our cohort under-represents children, which is important in MOGAD. Regarding treatments, missing randomisation most likely leads to the assignment of treatments with a presumed higher effectiveness to patients with a more aggressive disease course and vice versa, which causes both overestimation and underestimation of the potency of the different treatments. Moreover, the lengthy observational period, spanning from 1975 to 2022, encompasses a period of significant change in diagnostic tools and criteria, as well as the treatment landscape. This complexity makes it challenging to interpret the results. While the study includes a large cohort from multiple centres, the sample size of some treatments is small. This is particularly true for the newly approved inebilizumab and satralizumab and therapies such as IVIG and tocilizumab to treat MOGAD. Finally, we did not assess safety or tolerability, both of which have an impact on treatment effectiveness.

CONCLUSION

This study provides valuable insights into the real-world effectiveness of immunotherapies in NMOSD and MOGAD in a changing treatment landscape. The newly approved therapies, as well as established off-label treatment, facilitate effective attack prevention in AQP4-IgG seropositive NMOSD. The future usage of these therapies with rituximab is still being most often applied, but with an obvious trend towards newer therapies, it indicates the need to further optimise treatment concepts. Further studies are needed to address the comparative effectiveness as well as the safety and tolerability of these immunotherapies to evolve stepwise therapeutic algorithms. In MOGAD, the treatment of choice remains less clear. Although some effects of rituximab as well as azathioprine can be assumed, it seems to be less effective than in NMOSD; for other therapeutic alternatives, only small case series[19 20] or data in significantly younger populations are available. Further treatment studies are urgently needed, ideally in a prospective, randomised setting.

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