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Comparative Effectiveness of Disease-Modifying Treatments in Double Seronegative Neuromyelitis Optica Spectrum Disorder

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Abstract

Background and Objectives

Double seronegative NMOSD (DS-NMOSD) lacks approved disease-modifying treatments, and limited data exist on optimal relapse-prevention strategies. In this multicenter, international, retrospective cohort study, we sought to compare the real-world effectiveness of anti-CD20 agents vs nonspecific immunosuppressants as disease-modifying strategies for relapse prevention in DS-NMOSD.

Methods

A retrospective cohort database was constructed using standardized data collection from medical records across collaborating centers in the United States, Brazil, the United Kingdom, Thailand, Turkiye, and China. Patients meeting IPND-2015 NMOSD criteria with negative serum aquaporin-4 and myelin oligodendrocyte glycoprotein antibody testing via cell-based assays and at least 12 months of follow-up were reviewed. The primary outcome was the incidence rate ratio (IRR) of relapses; secondary outcomes included the annualized relapse rate (ARR) and time to relapse.

Results

A total of 103 patients with DS-NMOSD met study criteria, with a median follow-up of 6 years. Anti-CD20 therapy was associated with a significantly lower IRR (0.02, 95% CI 0.01–0.04) and ARR (0.17, 95% CI 0.07–0.40) compared with nonspecific immunosuppressants (0.76, 95% CI 0.40–1.43) after adjusting for covariates. Survival analysis demonstrated a prolonged relapse-free interval with anti-CD20 agents.

Discussion

Our findings support the use of B-cell depletion as a potentially superior relapse-prevention strategy in DS-NMOSD, highlighting its potential as a first-line therapy.

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Class of Evidence
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Supplementary Material

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Glossary

AQP4 = aquaporin-4; **ARR** = annualized relapse rate; **CBA** = cell-based assay; **DMT** = disease-modifying therapy; **DS-NMOSD** = double seronegative NMOSD; **HR** = hazard ratio; **IQR** = interquartile range; **IRR** = incidence rate ratio; **IVIg** = IV immunoglobulin; **MOG** = myelin oligodendrocyte glycoprotein; **MOGAD** = myelin oligodendrocyte glycoprotein antibody–associated disease; **NMOSD** = neuromyelitis optica spectrum disorder; **OCB** = oligoclonal band; **ON** = optic neuritis; **TM** = transverse myelitis.

Classification of Evidence

This study provides Class IV evidence that, in patients with DS-NMOSD, treatment with a DMT reduces relapse incidence rate ratio compared with no treatment and anti-CD20 DMTs are associated with a lower relapse incidence rate ratio compared with nonspecific immunosuppressants.

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a disabling, relapsing, autoimmune disease that targets the CNS. Characteristic attacks include severe optic neuritis (ON); longitudinally extensive transverse myelitis (TM); and cerebral, brainstem, and diencephalic syndromes.[1]

Worldwide, 65–73% of patients with NMOSD are seropositive for a circulating antibody that targets aquaporin-4 (AQP4),[2,3] the most abundant astrocytic water channel protein in the CNS. Among AQP4-IgG–seronegative patients with non-MS CNS demyelinating disease and syndromes typical of NMOSD, an antibody-targeting myelin oligodendrocyte glycoprotein (MOG) is present in approximately 40%.[3] Roughly 12–16% of patients with a clinical diagnosis of NMOSD remain seronegative for both AQP4 and MOG autoantibodies, despite testing via highly accurate antibody detection methods such as live cell-based assays (CBAs).[2,4,5]

Currently, patients diagnosed with double seronegative NMOSD (DS-NMOSD) have no approved disease-modifying therapies (DMTs) and lack considerable natural history and treatment efficacy data. Notably, a portion of the literature about AQP4-IgG–seronegative NMOSD was published prior to the recognition of clinically relevant MOG-IgG autoantibodies and the commercial availability of live CBAs.[6] While some NMOSD clinical trials, such as those using satralizumab[7] and inebilizumab,[8] included a small subset of patients with DS-NMOSD, the efficacy of these drugs in the seronegative group could not be fully ascertained because of limited sample sizes or lack of testing for MOG-IgG.[9]

In this study, we determined the efficacy of different classes of DMTs for relapse prevention in an international retrospective cohort of well-characterized patients with DS-NMOSD.

Methods

Ethical Approval and Reporting Guidelines

This study received institutional review board approval at each participating institution. Informed consent was waived because of the deidentified and retrospective nature of the acquired data. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[10] guidelines were followed.

Study Population

Patients were included if they fulfilled IPND-2015 AQP4-IgG–seronegative NMOSD criteria (i.e., 2 clinical core syndromes, at least one supporting neuroimaging feature, and no alternative diagnosis) and tested negative for serum MOG-IgG and AQP4-IgG through a cell-based assay at least once. Subsequent testing must also have been consistently negative. All patients included were older than 18 years at the time of data collection. Patients with fewer than 12 months of follow-up, with missing treatment data, undergoing combination therapy with 2 or more DMTs, or with documented medication adherence concerns were excluded. The 12-month cutoff was used to ensure sufficient diagnostic certainty and opportunity to capture events. Senior neuroimmunologists at expert centers reviewed patient charts to confirm that the leading diagnosis was DS-NMOSD at the last follow-up, and suspicion for mimics (e.g., atypical MS) was not a concern. Data collection was performed from December 2023 to November 2024.

Data Acquisition and Clinical Definitions

Retrospective data from patients fulfilling all inclusion criteria from participating institutions were collected from medical records using a standardized REDCap[11,12] survey form. Partial dates registered in charts were rounded to the first day of the month for quantitative analysis (e.g., "Optic Neuritis in January 2017" was rounded to January 1, 2017). Individual attacks were defined as new clinical symptoms or signs consistent with an acute inflammatory demyelinating event in the CNS, lasting at least 24 hours, in the absence of fever or infection, with or without supporting neuroimaging at the time of the attack, as previously established.[13,14] Neuroimaging was not required for attack adjudication/definition. We extracted clinical details of attacks as documented by treating physicians and considered those occurring within 30 days of each other as a single polyphasic attack.[15] Information on clinical features suggestive of myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD)–like presentations

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(i.e., presence of leptomeningeal enhancement, spinal cord H-sign, and complete recovery with steroids)[16] was also included.

DMTs were grouped according to their class effect to enhance statistical power. The "anti-CD20" group included rituximab and ocrelizumab. "Nonspecific immunosuppressants" (NSISs) included azathioprine, mycophenolate, methotrexate, mitoxantrone, and cyclophosphamide. "Multiple Sclerosis (MS) drugs" included any DMT approved for MS except for B-cell depletion (e.g., interferons, teriflunomide, glatiramer, fumarates, and natalizumab). Acute administration of steroids or IV immunoglobulin (IVIg) was not considered DMT. Because maintenance oral corticosteroid regimens were highly variable in drug, dose, and documentation quality, person-time on chronic steroids was excluded from exposure modeling, whereas maintenance IVIg was retained as a discrete DMT category owing to its uniform and well-defined start/stop dates. Treatment periods were extracted as the interval between the first and last prescription date available in charts.

The primary outcome was the incidence rate ratio (IRR) of attacks when comparing treatment periods. Secondary outcomes included the adjusted annualized relapse rate (ARR) and hazard ratios (HRs) for attacks.

Statistical Analysis

Demographic data were described through counts and frequencies, as well as medians and interquartile ranges where applicable. ARR was calculated by dividing the number of relapses by person-years.[17]

We used a negative binomial mixed-effects regression model to assess factors associated with the rate of attacks on different treatments. Attack frequency was modeled as a function of DMT modality, age at onset, sex, race, ethnicity, clinician suspicion for MOGAD, onset clinical presentation (e.g., optic neuritis and transverse myelitis), and time to DMT initiation. A random intercept for each participant was included to account for repeated measures, and we included DMT duration as an offset variable. Race and ethnicity were binarized to improve multivariate regression performance and reduce collinearity. Covariates were selected after repeated model iterations of the most clinically relevant variables, optimizing for the lowest possible Akaike information criterion.[18]

Exposure to DMTs was modeled as a time-varying categorical variable. All person-time that accrued before the first dose of any chronic DMT, together with the complete follow-up of the 6 participants who never initiated treatment, was pooled into a single "pretreatment" category. Relapses observed during this pooled interval generated the baseline ARR, which served as the reference level in the negative-binomial mixed-effects model. Subsequent person-time was allocated to the relevant DMT category according to start and stop dates recorded in the chart. We reported incidence rate ratios (exponentiated coefficients) with 95% confidence intervals to facilitate the interpretation of effect sizes.

We computed marginal means to estimate the predicted ARRs through our adjusted model, obtaining model-based rate estimates for each treatment period. Pairwise comparisons were then performed, and the Bonferroni correction was applied to adjust for multiple comparisons.

In addition, we performed a Cox proportional hazards analysis to evaluate the association between treatments and HRs of attacks, adjusting for covariates. Covariates such as age at onset, sex, race, ethnicity, clinical suspicion for MOGAD, and lag time to treatment initiation were incorporated into the model. HRs with 95% CIs were calculated for each covariate. Survival curves were generated using the Kaplan-Meier method. p Values were calculated using a univariate log-rank test.

We considered a p value <0.05 as significant. All statistical analyses were performed in RStudio 4.4.2.

Data Availability

Anonymized data not published within this article may be made available by request from a qualified investigator to the corresponding author.

Results

Patient Population

The records of 124 patients with DS-NMOSD who fulfilled the inclusion criteria were screened for eligibility. Twenty-one patients were excluded. Reasons for exclusion included short follow-up, combination therapy, concerns for medication adherence, and missing data (eFigure 1). Data from 103 patients were extracted and reviewed. Patients in the study originated from the United States, Brazil, United Kingdom, Thailand, Turkiye, and China. Sex distribution was similar across countries, with an overall female-to-male ratio of 2.8, similar to previously reported rates.[19] Racial and ethnic compositions varied by region. A summary of demographic and clinical characteristics is given in Table 1.

The median follow-up duration was 6 years (interquartile range [IQR] 4.1–10.9), and the median age at the first attack was 35 years (IQR 24–44). Eight patients had their first attack before the age of 18. Relapsing disease was documented in 82 patients (79.6%). Transverse myelitis (58.2%) and optic neuritis (53.3%) were the most frequent initial clinical syndromes, while simultaneous (or polyphasic) ON and TM occurred in 20.3% of patients. Area postrema syndrome was documented in 11.6% of patients. Brainstem syndrome (without area postrema involvement) also occurred in 11.6% of patients. Cerebral attacks were rare, occurring in 4 patients (3.9%).

Clinician suspicion for a MOGAD-like presentation was noted in 7 patients (6.7%). The most common reason for this was a clinical event of acute disseminated encephalomyelitis,

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Table 1 Cohort Characterization

Demographic characteristics	Total N = 103	United States N = 40	Brazil N = 23	United Kingdom N = 19	Thailand N = 16	Turkiye N = 3	China N = 2
Sex, n (%)							
Male	27 (26.2)	9 (22.5)	5 (21.7)	8 (42.1)	3 (18.7)	2 (66.6)	0 (0)
Female	76 (73.7)	31 (77.5)	18 (78.2)	11 (57.8)	13 (81.2)	1 (33.3)	2 (100)
Race, n (%)							
White	48 (46.6)	23 (57.5)	8 (34.8)	14 (73.7)	0 (0.0)	3 (100.0)	0 (0.0)
Black/African American	12 (11.7)	6 (15.0)	6 (26.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	22 (21.4)	3 (7.5)	0 (0.0)	1 (5.3)	16 (100.0)	0 (0.0)	2 (100.0)
Other	19 (18.4)	6 (15.0)	9 (39.1)	4 (21.1)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown/undeclared	2 (1.9)	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)							
Latino	28 (27.1)	6 (15)	22 (95.6)	0 (0)	0 (0)	0 (0)	0 (0)
Non-Latino	75 (72.8)	34 (85)	1 (4.3)	19 (100)	16 (100)	3 (100)	2 (100)
Age at onset[a]	35 (24, 44)	36 (25, 46)	31 (21, 40)	40 (27, 50)	36 (24, 40)	29 (22, 50)	39 (22, 56)
Follow-up duration (y)[a]	6.0 (4.1, 10.9)	5.3 (3.2, 7.4)	6.3 (4.7, 13.5)	6.0 (5.1, 10.1)	10.0 (6.7, 12.1)	2.8 (1.0, 19.6)	2.0 (1.6, 2.5)
Relapsing disease	82 (79.6)	27 (67.5)	22 (95.6)	16 (84.2)	15 (93.7)	2 (66.6)	0 (0)
MOGAD-like features	7 (6.7)	6 (15)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50)
Clinical syndrome at onset, n (%)							
ON	55 (53.3)	21 (52.5)	11 (47.8)	10 (52.6)	8 (50)	3 (100)	2 (100)
TM	60 (58.2)	23 (57.5)	11 (47.8)	15 (78.9)	8 (50)	1 (33.3)	2 (100)
Simultaneous ON and TM	21 (20.3)	8 (20)	1 (4.3)	7 (36.8)	2 (12.5)	1 (33.3)	2 (100)
Area postrema syndrome	12 (11.6)	3 (7.5)	3 (13)	1 (5.2)	3 (18.7)	0 (0)	2 (100)
Brainstem syndrome	12 (11.6)	1 (2.5)	4 (17.3)	3 (15.7)	4 (25)	0 (0)	0 (0)
Cerebral syndrome	4 (3.9)	4 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Treated with a DMT	97 (94.1)	39 (97.5)	23 (100)	17 (89.4)	15 (93.7)	2 (66.6)	1 (50)
Nonspecific immunosuppressants	66 (64)	11 (27.5)	22 (95.6)	16 (84.2)	15 (93.7)	2 (66.6)	0 (0)
Azathioprine	50 (48.5)	2 (5.0)	21 (91.3)	13 (68.4)	12 (75)	2 (66.6)	0 (0)
Mycophenolate	27 (26.2)	7 (17.5)	3 (13)	8 (42.1)	8 (50)	1 (33.3)	0 (0)
Cyclophosphamide	8 (7.8)	4 (10)	3 (13)	1 (5.2)	0 (0)	0 (0)	0 (0)
Methotrexate	3 (2.9)	2 (5.0)	0 (0)	1 (5.2)	0 (0)	0 (0)	0 (0)
Mitoxantrone	1 (0.9)	0 (0)	1 (4.3)	0 (0)	0 (0)	0 (0)	0 (0)
Anti-CD20	53 (51.4)	34 (85)	11 (47.8)	7 (36.8)	0 (0)	0 (0)	1 (50)
Rituximab	52 (50.4)	33 (82.5)	11 (47.8)	7 (36.8)	0 (0)	0 (0)	1 (50)
Ocrelizumab	2 (1.9)	2 (5.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Traditional MS drugs	7 (6.8)	4 (10)	0 (0)	1 (5.2)	2 (12.5)	0 (0)	0 (0)
Interferon-beta	2 (1.9)	0 (0)	0 (0)	0 (0)	2 (12.5)	0 (0)	0 (0)
Glatiramer	3 (2.9)	3 (7.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fumarates	1 (1.0)	1 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Alemtuzumab	1 (1.0)	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)	0 (0)

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Table 1 Cohort Characterization *(continued)*

Demographic characteristics	Total N = 103	United States N = 40	Brazil N = 23	United Kingdom N = 19	Thailand N = 16	Turkiye N = 3	China N = 2
Others	6 (5.8)	5 (12.5)	0 (0)	1 (5.2)	0 (0)	0 (0)	0 (0)
IVIG	3 (2.9)	2 (5.0)	0 (0)	1 (5.2)	0 (0)	0 (0)	0 (0)
Tocilizumab	2 (1.9)	2 (5.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eculizumab	1 (1.0)	1 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: DMT = disease-modifying therapy; IVIg = IV immunoglobulin; NSIS = nonspecific immunosuppressant.
Categorical data expressed in counts and percentages.
[a] Median (Q1, Q3).

occurring in 4 patients. Transverse myelitis involving the conus medullaris was documented in 2 cases. One patient with TM had a spinal cord H-sign, and one demonstrated leptomeningeal enhancement in the cauda equina. Complete recovery with steroids alone was noted in one patient. Despite these features, each of these patients tested negative for serum MOG-IgG.

Presence of oligoclonal bands (OCBs) was assessed in 75 patients and was positive in 13 (17.3%). The median number of unique CSF bands was 2.5, and their distribution ranged from 2 to 9. Chest imaging was available in 72 (69.9%), and only one had hilar lymphadenopathy, which was deemed inconsistent in distribution and appearance with sarcoidosis. Neuroimaging revealed longitudinally extensive myelitis (3 or more vertebral segments) in 76 (73.8%), longitudinally extensive optic neuritis (more than half of the optic nerve extension) in 53 (51.4%), and periependymal brainstem lesions in 25 (24.3%). Nonspecific brain lesions were found in 58 (56.3%). At the time of attacks, MRI was pursued in 155 of 260 documented attacks. A new T2/FLAIR or new enhancing lesion was documented in 137 events (88.4%). In 18 events (11.6%), no new lesions were detected.

Participants were tested for both MOG-IgG and AQP4-IgG a median of 2 times (IQR 1–3). Forty-seven were tested at least twice for MOG-IgG and 62 for AQP4-IgG. The median time from first clinical symptom to antibody testing was 33.6 months (IQR 8.1–94.0) for AQP4-IgG and 47.1 months (IQR 9.4–118.0) for MOG-IgG, with 28 patients (27%) tested before starting any DMT. A histogram depicting the distribution of the lag time from clinical onset to the first cell-based assay serum testing is presented in eFigure 2.

Most patients (94.1%) received a DMT (Figure 1). The most frequent DMT modality was nonspecific immunosuppression (64%), with azathioprine (48.5%) and mycophenolate (26.2%) being the most common. Anti-CD20 agents were used in 51.4% of patients, most of whom received rituximab (50.4%). Seven patients (6.8%) received DMTs classically used in the treatment of MS (interferon-beta, n = 2; glatiramer acetate, n = 3; fumarates, n = 1; alemtuzumab, n = 1). Other drugs less frequently used included IVIg (n = 3), tocilizumab (n = 2), and eculizumab (n = 1). No relapses were captured in patients receiving tocilizumab or eculizumab. One relapse occurred in a patient receiving IVIg. None of the patients who received MS DMTs exhibited a clinic-radiologic phenotype consistent with MS, and only 3 had OCBs in their CSF. Additional demographic information, raw relapse data, and person-years of treatment exposure by DMT category are given in eTable 1.

Seventy-four patients (72%) were tested for serum MOG-IgG with a live CBA and 24 (23%) with fixed CBAs. A minority of the tests were performed in-house, with most being performed at reference laboratories associated with Mayo Clinic, Tohoku University, and Oxford University (69%). Twenty-eight patients (27%) were tested for MOG-IgG and AQP4-IgG before the start of any DMTs.

One patient was tested for MOG-IgG before any confirmed attacks, lacking sufficient clinical and imaging criteria to establish an index event at that time. Three patients were tested after their last follow-up at external institutions, where only laboratory results were available without clinical records.

Nonspecific immunosuppressants achieved relapse-free status in approximately half of treatment courses. Anti-CD20 therapies demonstrated over 85% of relapse-free intervals. A breakdown of relapse-free status is given in eTable 2.

Among NSIS exposures, discontinuations were relatively common and were primarily driven by relapses (46%), adverse events (29%), and pregnancy planning (14%). By contrast, anti-CD20 agents were rarely stopped, limiting our ability to compare discontinuation reason rates meaningfully across classes. Discontinuation data are summarized in eTable 2.

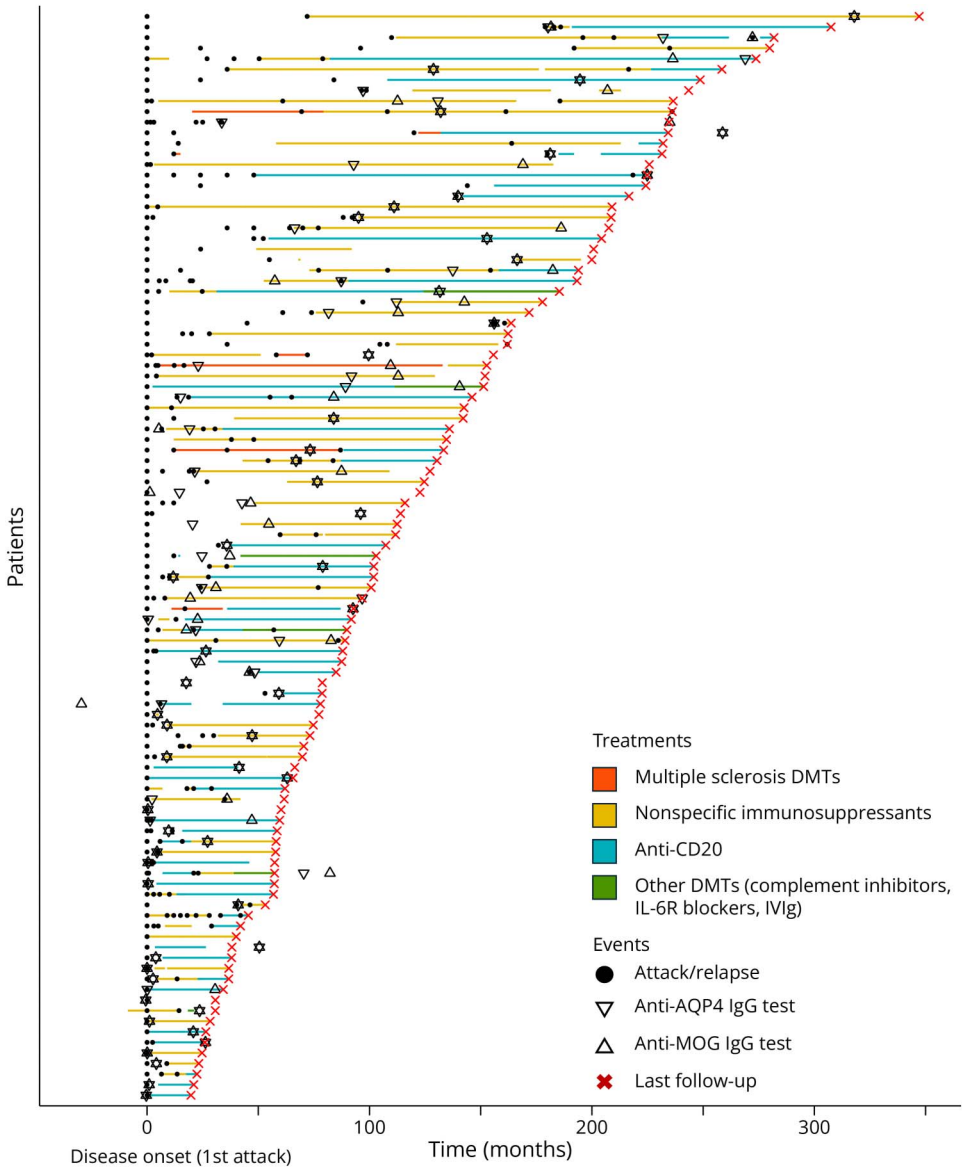
Autoimmune comorbidities were observed in 13 of 103 patients (12.6%), most commonly Hashimoto thyroiditis (n = 3, 2.9%) and psoriasis with or without arthritis (n = 3, 2.9%).

Relapse Incidence Rate Ratios of Different DMTs

The negative binomial model (Table 2) included all 103 patients who underwent 214 treatment periods, with 260

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Figure 1 Patient Disease Course Time Lines



The longitudinal disease course in our cohort is demonstrated. Each row represents an individual patient, with the horizontal axis marking the time from disease onset. As displayed, there is marked heterogeneity in disease trajectories among patients, with some exhibiting rapid, clustered relapses soon after disease onset while others experience more protracted courses. Twenty-eight patients (27%) were tested for MOG-IgG and AQP4-IgG before the start of any DMTs. The first documented attack date was normalized to time zero. Colored segments represent periods of DMT administration. Attacks, testing dates, and the last in-person follow-up are annotated as individual symbols. Superimposed triangles signal simultaneous testing for AQP4-IgG and MOG-IgG. Some test dates were not plotted when the exact testing date was not available. One patient was taking a DMT for a comorbid condition before disease onset. AQP4 = aquaporin-4; DMT = disease-modifying therapy; IgG = immunoglobulin G; IL6R = interleukin-6 receptor; MOG = myelin oligodendrocyte glycoprotein.

attacks recorded. After adjusting for covariates and setting the attack rate during the pretreatment period (i.e., time between disease onset and first DMT administration) as reference, all DMT groups were associated with a significantly lower relapse IRR than the pretreatment period (MS IRR = 0.13, 95% CI 0.06–0.30; NSIS IRR = 0.09, 95% CI 0.07–0.13; anti-CD20 IRR = 0.02, 95% CI 0.01–0.04; $p < 0.001$). Immunomodulatory medications used for MS (e.g., interferon, glatiramer, and alemtuzumab) did not appear to be as harmful as they are for AQP4-seropositive NMOSD.[20-24] Notably, anti-CD20 DMTs were associated with lower IRRs compared with either MS medications or NSISs (Figure 2).

Additional covariates, including sex, race, ethnicity, age at onset, clinician suspicion for MOGAD, or type of clinical syndrome at onset, were not associated with treatment response. Longer delay between disease onset and DMT initiation was associated with a lower IRR (0.98, 95% CI 0.98–0.99, $p < 0.001$). A forest plot containing the effect sizes and confidence intervals for the IRRs of DMTs and model covariates is shown in Figure 2.

Using estimated marginal means derived from the negative binomial model—adjusting for race, ethnicity, sex, suspicion for MOGAD, time to DMT initiation, and clinical onset syndrome—we observed that patients on anti-CD20 therapy had the lowest ARR (CD20 ARR = 0.17, 95% CI 0.07–0.40). By contrast, those treated with NSISs had an estimated ARR of 0.76 (95% CI 0.40–1.43), while those receiving MS DMTs had an estimated ARR of 1.07 (95% CI 0.39–2.93). Pairwise, Bonferroni-corrected, comparisons indicated that anti-CD20 DMTs were associated with significantly lower ARRs

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Table 2 Incidence Rate Ratios of Relapse Risk

Effect variables	IRR	95% CI	*p* Value
Treatment period			<0.001
Pretreatment (ref)	—	—	
NSIS	0.09	0.07–0.13	
MS DMTs	0.13	0.06–0.30	
Anti-CD20	0.02	0.01–0.04	
Race			0.69
Non-White (ref)	—	—	
White	0.94	0.71–1.3	
Ethnicity			
Latino (ref)	—	—	0.34
Non-Latino	0.86	0.63–1.2	
Sex			0.42
Male (ref)	—	—	
Female	0.87	0.61–1.2	
Suspicion for MOGAD			0.7
No (ref)	—	—	
Yes	1.1	0.58–2.3	
Onset clinical syndrome			
ON			0.104
No (ref)	—	—	
Yes	1.7	0.90–3.2	
TM			0.197
No (ref)	—	—	
Yes	1.5	0.81–2.8	
Simultaneous ON and TM			0.6
No (ref)	—	—	
Yes	0.47	0.21–1.1	
APS			0.577
No (ref)	—	—	
Yes	1.2	0.66–2.1	
BS			0.534
No (ref)	—	—	
Yes	1.2	0.72–1.9	
Cerebral syndrome			0.19
No (ref)	—	—	
Yes	1.9	0.72–5.0	
Pretreatment duration	0.98	0.98–0.99	<0.001
Presence of oligoclonal bands	1.1	0.69–1.7	0.698
Age at onset	1.0	0.99–1.0	0.467

Abbreviations: APS = area postrema syndrome; BS = brainstem syndrome; DMT = disease-modifying therapy; IRR = incidence rate ratio; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; NSIS = nonspecific immunosuppressant; ON = optic neuritis; ref = reference; TM = transverse myelitis.

compared with both MS DMTs ($p = 0.002$) and NSIS ($p = 0.003$). By contrast, the difference between MS DMTs and NSISs was not statistically significant (Figure 3).

Survival Analysis

The Cox proportional hazards model adjusted for the same covariates revealed that, compared with the MS treatment periods, the time-to-relapse hazard ratio was not statistically different in the NSIS group (HR = 0.35, 95% CI 0.12–1.04, $p = 0.059$) but was markedly lower in the CD20 group (HR = 0.06, 95% CI 0.02–0.24, $p < 0.001$). Kaplan-Meier curves (Figure 4) further visually demonstrated that relapse-free survival was substantially longer in patients receiving anti-CD20 drugs relative to those receiving NSIS-based regimens (log-rank p value = 0.0001).

Sensitivity Analysis

Next, we performed a sensitivity analysis to assess whether the individual breakdown of the most frequently administered DMTs would reveal additional differences in relapse rates. A Kaplan-Meier plot was constructed using data from treatment periods in which rituximab, azathioprine, or mycophenolate were administered (eFigure 3). Survival curves were markedly different (log-rank p value = 0.0000734). Relapse-free status occurred in 84.6% (n = 44/52) of patients receiving rituximab, 74.1% (n = 20/27) of patients receiving mycophenolate, and 46% (n = 23/50) of patients receiving azathioprine (Chi-squared = 17.994, p value = 0.00012).

Univariate Cox proportional hazards revealed that, when compared with rituximab, azathioprine led to a higher HR (HR = 4.95, 95% CI 2.16–11.38, p value = 0.00016) while mycophenolate did not achieve statistical significance (HR = 2.03, 95% CI 0.71–5.79, p value = 0.18). Compared with azathioprine, mycophenolate yielded a lower relapse rate (HR = 0.41, 95% CI 0.18–0.94, p value = 0.03).

Furthermore, we investigated whether early, first-line administration of rituximab would result in different relapse rates when compared with late (second-line or after) prescription. A Kaplan-Meier curve is demonstrated in eFigure 4. No differences were seen when both groups were compared using a univariate Cox proportional hazards model (HR = 1.28, 95% CI 0.3–5.4, p value = 0.73).

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Figure 2 Forest Plot of Incidence Rate Ratios From the Negative Binomial Regression Model

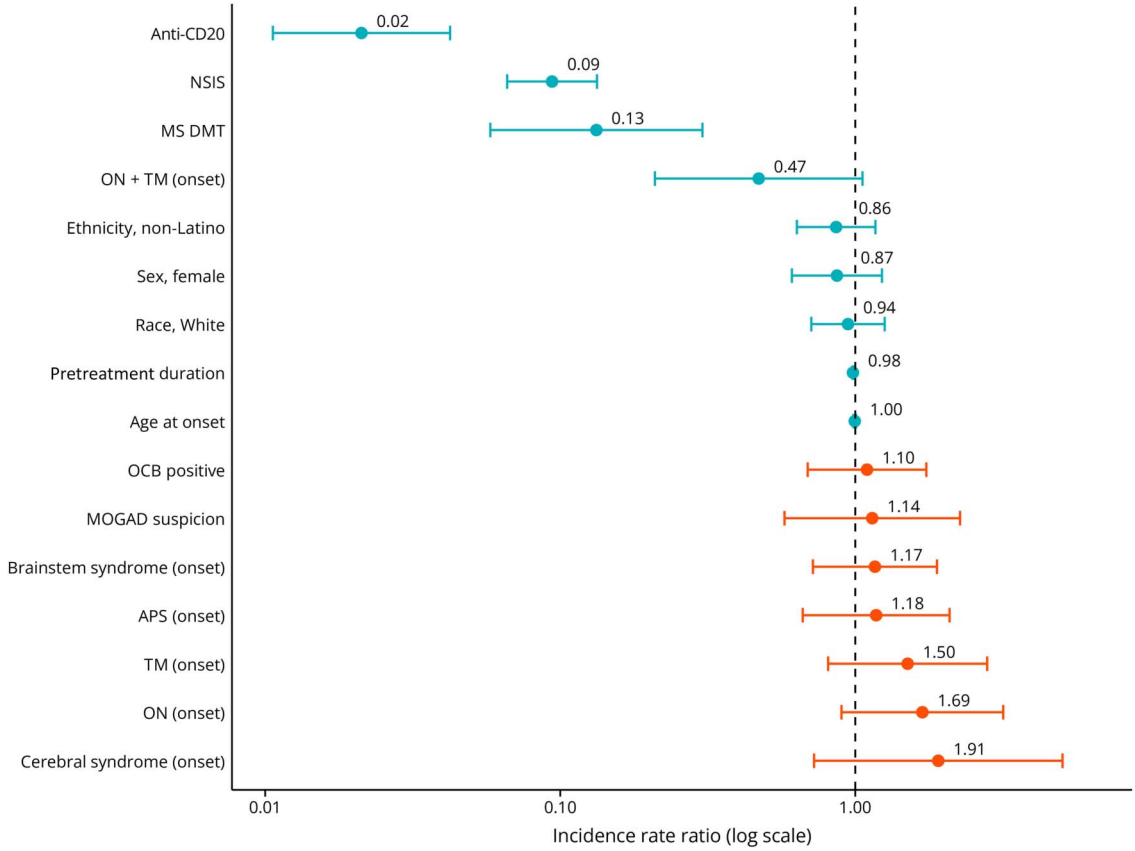


Figure 2 depicts a forest plot with the IRRs of negative binomial regression variates and covariates. IRRs for anti-CD20 agents, NSISs, and MS DMTs were plotted relative to the pretreatment period. IRRs of clinical onset presentations are relative to the absence of the respective presentation. Female IRR is relative to male IRR. White IRR is relative to non-White IRR. Non-Latino IRR is relative to Latino IRR. APS = area postrema syndrome; BS = brainstem syndrome; DMT = disease-modifying therapy; IRR = incidence rate ratio; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; MS = multiple sclerosis; NSIS = nonspecific immunosuppressants; ON = optic neuritis; TM = transverse myelitis.

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Classification of Evidence

This study provides Class IV evidence that, in patients with DS-NMOSD, treatment with a DMT reduces relapse incidence rate ratio compared with no treatment and anti-CD20 DMTs are associated with a lower relapse incidence rate ratio compared with nonspecific immunosuppressants.

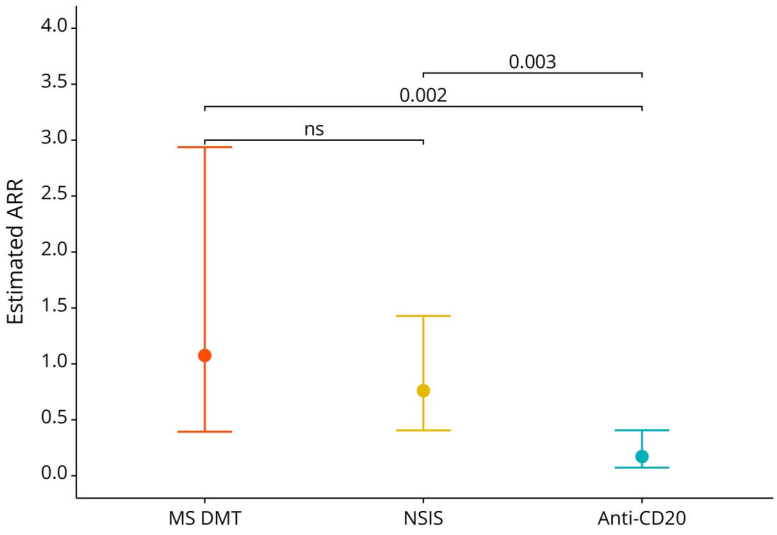
Discussion

In this retrospective, multicenter, international, DS-NMOSD observational cohort, anti-CD20 therapy was associated with a significantly lower risk of relapse and a lower relapse rate compared with nonspecific immunosuppression, even after extensive control for demographic and clinical confounding factors. Moreover, treatment modality was the only consistent factor associated with changes in relapse rates across different statistical models (negative binomial regression, ARR estimated marginal means, and survival analysis).

Post hoc sensitivity analysis further indicated that relapse rates were significantly different when individually comparing rituximab, mycophenolate, and azathioprine, the most frequently used DMTs in our cohort. Although pairwise comparisons with mycophenolate did not yield statistical differences, likely because of the limited number of patients, it appears to promote a lower relapse rate than azathioprine, but a higher rate than rituximab.

Of interest, the time between disease onset and DMT initiation was associated with a lower IRR, likely reflecting that patients with milder disease are more likely to receive a DMT later (IRR = 0.98, 95% CI 0.98–0.99, $p < 0.001$). This inverse association between DMT latency and relapse risk almost certainly represents confounding by indication rather than a true benefit of delaying therapy. Patients presenting with severe or clustered attacks might be prescribed DMTs earlier, falsely associating early DMT introduction with a higher relapse risk. This artifact has been documented in several

Figure 3 Estimated Annualized Relapse Rates by DMT Modality



The predicted ARRs and confidence intervals by DMT modality are demonstrated. Pairwise comparisons were performed with Bonferroni-corrected *p* values. ARR = annualized relapse rate; DMT = disease-modifying therapy; MS = multiple sclerosis; ns = nonsignificant; NSIS = nonspecific immunosuppressant.

NMOSD registries[25,26] but is absent from prospective clinical trials in NMOSD.[8] Thus, it should not be interpreted as evidence to postpone DMTs.

Whether the superiority of B-cell depletion is due to a targeted immunologic effect or simply due to facilitated medication adherence (i.e., infusion every 6 months vs daily oral pills) remains unknown. Mechanistically, we speculate that the versatile effects of rituximab and other B cell–targeting DMTs may be due to their ability to cull the memory B-cell compartment[27] through both complement and antibody-dependent cellular cytotoxicity,[28] leading to impaired autoantibody production and plasmablast differentiation, as well as a decreased CD80/86-dependent and CD40/40L-dependent antigen presentation to $CD4^+$ T cells.[29-31] A reduction in IL-17a and IL-23 secretion by peripheral blood mononuclear cells of patients with AQP4+ NMOSD after rituximab infusion has also been observed, implicating a crosstalk between $CD20^+$ cells and the Th17 axis.[32] Moreover, a comparative analysis has shown that early rituximab initiation is more cost effective than starting nonspecific immunosuppressants in AQP4-IgG NMOSD.[33]

In addition, the frequency of comorbid autoimmune conditions (12.6%) was lower in our cohort than expected for the

Figure 4 Kaplan-Meier Curve of Time to Relapse After DMT Introduction

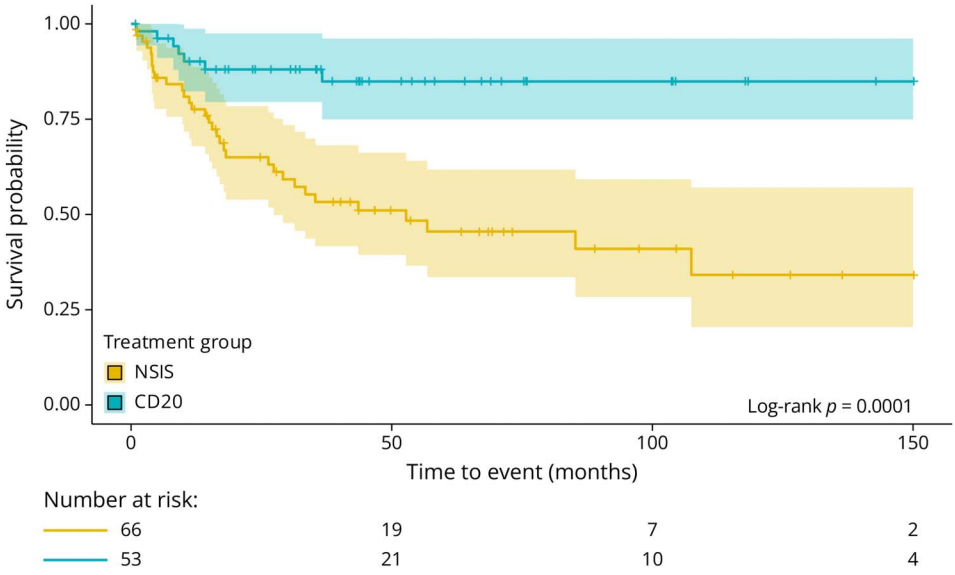


Figure 4 represents Kaplan-Meier survival curves of time to relapse after DMT initiation, by DMT modality. A univariate log-rank test comparing both DMTs is annotated. CD20 = anti-CD20 drugs; DMT = disease-modifying therapy; NSIS = nonspecific immunosuppressant.

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AQP4-IgG–positive counterpart and more similar to MOGAD. For instance, a retrospective study demonstrated a 33.5% frequency of comorbid autoimmune diseases in patients with AQP4-IgG+ NMOSD, whereas the frequency in patients with MOGAD was 12.2%.[34] No cases of anti-NMDAr (N-methyl-D-aspartate receptor) encephalitis were seen, the autoimmune comorbidity most frequently seen in MOGAD.[35] The absence of large, well-defined cohorts of DS-NMOSD and the exclusion of this patient population from several clinical trials[36-38] may result in diagnostic delays and inappropriate extrapolation of clinical management principles from studies of AQP4-IgG–seropositive patients, potentially leading to suboptimal patient care. In NMOSD, a poorly managed relapse can cause significant, permanent disability—such as blindness or paralysis—and in severe cases, death.[25,39] Thus, the description of natural history, clinical outcomes, relapse risk factors, and treatment efficacies in this population is of utmost importance.

The N-MOmentum RCT of inebilizumab[8]—a B cell–depleting anti-CD19 monoclonal antibody—enrolled 9 patients with DS-NMOSD, with 3 allocated to placebo and 6 to the study drug. Of interest, the trial observed no relapses after 2 infusions in the intervention group. Statistical significance was not attained because of the small sample size. However, a post hoc analysis revealed that the DS-NMOSD subpopulation had a mean pretrial ARR of 1.60 (95% CI 1.02–2.38), which decreased to 0.051 (95% CI 0.013–0.204) in those receiving inebilizumab. Aligned with our study, these findings further suggest that targeting B cells effectively reduces relapse risk in patients with DS-NMOSD.

Our study has several strengths. Notably, this is, to our knowledge, the most extensive patient characterization of DS-NMOSD. Given its rarity, this was only attainable as a multicenter collaboration. In addition, inclusion for analysis required strict diagnostic criteria (IPND-2015)[40] and negative testing with the most sensitive antibody detection assays (e.g., CBAs),[41] most of which were live CBAs. The strict inclusion criteria ensured a homogeneous cohort and reduced contamination by highly active or atypical forms of MS or other CNS inflammatory disorders (e.g., neurosarcoidosis). The low frequency of positive OCBs (17.3%) and hilar lymphadenopathy further strengthen our conclusions. Although nonspecific, OCBs are detected in more than 90% of patients with MS.[14] Moreover, none of the patients who were prescribed MS DMTs exhibited a phenotype consistent with MS, and only 3 had detectable oligoclonal bands.

Some limitations limit the generalizability of our work. First, given its retrospective nature, it is possible that residual confounding is present despite extensive control for clinical and demographic variables in our models. Second, selection bias due to the requirement of seronegative NMOSD to have 2 core clinical syndromes for diagnosis likely skewed this population toward relapsing presentations of this syndrome. Thus, our findings are not directly applicable to monophasic patients unless they had a criteria-fulfilling polyphasic attack. Exclusion of patients receiving combination therapies, on the contrary, could have skewed the cohort toward milder phenotypes.

Third, we did not include corticosteroids in our treatment analysis. Corticosteroids are widely used worldwide for seronegative diseases, with varying doses and titrations that complicate statistical analyses. Compliance with oral or self-injection medications could not be confirmed with certainty from medical records. Acute rescue therapies (e.g., high-dose corticosteroids and plasma exchange) were documented inconsistently—often lacking exact doses, or number of sessions—to support reliable time-varying modeling. Despite some evidence that these interventions can offer benefits for up to 3 months after administration,[42-44] the lack of data granularity impairs statistical modeling due to risk of introducing substantial misclassification bias.

Neuroimaging was not required for attack characterization. While this may reduce the methodological specificity due to potential inclusion of pseudorelapses, this was mitigated by ensuring that the history, presentation, and examination at the time of an event fulfilled McDonald 2017 attack criteria[14] and was adjudicated a posteriori by experienced neuroimmunologists at each center. MRI at the time of attacks was available in roughly 60% of events. In 11.6%, no new lesions were detected. Whether these MRI-negative events represent pseudorelapses or reflect the radiologic lag between symptom onset and detection of MRI abnormalities remains unknown. Clinic-radiologic dissociation has been well established in MOGAD and has been reported to occur in up to 10% of attacks; of interest, MRI-negative attacks have also been reported.[45,46] Although the overall availability of MRI during attacks was low in our cohort (60%), pseudorelapses in NMOSD are infrequent.[15] Nonetheless, the impact of the potential inclusion of pseudorelapses in the observed effect of anti-CD20 drugs is likely minimal, given the reduction of 98% in the incidence rate ratio of relapses and the requirement for symptoms to last more than 24 hours in the absence of fever and infection for data capturing.

Finally, although most of the cohort was tested with live CBAs, roughly 23% were tested using fixed CBAs, limiting sensitivity in a minority of individuals, because live CBAs are known to display superior sensitivity for both AQP4-IgG and MOG-IgG compared with its fixed counterpart.[47] Thus, despite our efforts to minimize it, we cannot rule out with complete confidence the possibility of cases of MOG-IgG in the cohort. For instance, MOG-IgG titers are known to serorevert with immunotherapy,[48] in contrast to AQP4-IgG,[49] which stays positive in more than 90% of patients. Only 27% of our patients were tested before the initiation of any DMT. Moreover, up to 10% of patients with MOGAD may harbor isolated MOG-IgG in the CSF,[50-52] which was assessed in a single patient. The median time from onset until testing was overall long and can reduce sensitivity for antibody detection,

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in particular MOG-IgG. This likely stems from the fact that several patients had an initial attack before the availability of MOG testing in their respective institutions. Despite this limitation, the median number of tests for both AQP4-IgG and MOG-IgG was 2, and some patients maintained persistent seronegativity even during new relapses (Figure 1). Moreover, despite some degree of etiologic uncertainty, our study aimed to provide pragmatic guidance for relapse prevention in patients presenting with an NMOSD-like phenotype, who persistently test negative for the most common antibodies, regardless of the true underlying disease mechanism.

Despite the inherent limitations of a retrospective design, our analysis indicates that, in a real-world setting, patients whose phenotypes satisfy the 2015 IPND diagnostic criteria for NMOSD and are seronegative for both AQP4-IgG and MOG-IgG via CBAs experience fewer relapses when treated with B-cell depletion. Because disability in NMOSD is largely driven by attacks,[53] therapies that offer superior relapse suppression, particularly anti-CD20 agents, are likely to mitigate long-term disability accumulation and improve clinical outcomes. Thus, even in the absence of prospective data, it is reasonable to initiate high-efficacy disease-modifying therapy as soon as double-seronegative NMOSD is deemed the most probable diagnosis, paralleling the high-efficacy–first treatment paradigm now common in MS care.[54,55] In conclusion, our study suggests that B-cell depletion as a relapse-prevention strategy may be more effective than conventional immunosuppression in DS-NMOSD, argues for its use as first-line therapy, and lays the groundwork for a clinical trial in this patient population.

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J.V. Mahler: 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. G.B. Vallejos: 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. T. Mikami: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. P.A. Bilodeau: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M. Anderson: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. N. Drosu: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. N. Bobrowski-Khoury: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. G.D. Silva: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M. Solti: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. S.L. Apóstolos-Pereira: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. D. Callegaro: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. B. Leles Vieira de Souza: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. G.S. Manzano: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Vishnevetsky: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. R. Gillani: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. O. Pasquale: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Kim: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. R. Vij: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. I. Kister: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. E.L. Gibbons: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Jacob: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S. Huda: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. Y. Said: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J.D. Krett: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. E.S. Sotirchos: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. M. Ramprasad: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. H. Abboud: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. V.T.C. Crelier: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. G. dos Santos: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. E. Uawithya: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S. Siritho: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Sezen: drafting/revision

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