Original Investigation

Comparison of Relapse and Treatment Failure Rates Among Patients With Neuromyelitis Optica
Multicenter Study of Treatment Efficacy

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IMPORTANCE Neuromyelitis optica (NMO) is an inflammatory disease of the optic nerves and spinal cord that leads to blindness and paralysis. Effective immunosuppression is the standard of care for relapse prevention.

OBJECTIVE To compare the relapse and treatment failure rates among patients receiving the 3 most common forms of immunosuppression for NMO: azathioprine, mycophenolate mofetil, and rituximab.

DESIGN, SETTING, AND PARTICIPANTS We performed a retrospective, multicenter analysis of relapses in 90 patients with NMO and NMO spectrum disorder treated with azathioprine, mycophenolate, and/or rituximab at the Mayo Clinic and the Johns Hopkins Hospital during the past 10 years.

MAIN OUTCOME AND MEASURE Annualized relapse rates.

RESULTS Rituximab reduced the relapse rate up to 88.2%, with 2 in 3 patients achieving complete remission. Mycophenolate reduced the relapse rate by up to 87.4%, with a 36% failure rate. Azathioprine reduced the relapse rate by 72.1% but had a 53% failure rate despite concurrent use of prednisone.

CONCLUSIONS AND RELEVANCE Initial treatment with rituximab, mycophenolate, and, to a lesser degree, azathioprine significantly reduces relapse rates in NMO and NMO spectrum disorder patients. Patients for whom initial treatment fails often achieve remission when treatment is switched from one to another of these drugs.

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Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the central nervous system (CNS) distinct from multiple sclerosis (MS). It is characterized by optic neuritis (ON), longitudinally extensive transverse myelitis (TM), and, in approximately 70% of cases, the presence in serum of IgG antibodies that target aquaporin 4 (AQP4-IgG; also known as NMO-IgG). Patients with neuromyelitis optica spectrum disorder (NMOSD) are seropositive for AQP4-IgG and have evidence of an inflammatory event consistent with NMO, including TM, ON, or brainstem inflammation. Disease-modifying treatment for relapse prevention in patients with NMO and NMOSD requires immunosuppression because some immunomodulatory therapies used for MS appear to aggravate NMO.[1-3] Although no placebo-controlled or comparative randomized controlled trials of immunosuppressive therapies have been conducted for NMO and there is no consensus on how to select initial therapy, there is evidence that azathioprine, mycophenolate mofetil, and rituximab are effective in reducing relapse rates.[4-10] We conducted this retrospective study to compare relapse and treatment failure rates among NMO and NMOSD patients who received azathioprine, mycophenolate, or rituximab as their initial long-term immunosuppressive therapy at the Johns Hopkins Hospital and Mayo Clinic.

Methods

Institutional review board approval was obtained from the Johns Hopkins University and Mayo Clinic. Deidentified data were used; therefore, patient consent was not required. Patients were included if they were diagnosed as having NMO

Table 1. Demographic Characteristics of the Study Participants

Initial Treatment	No. (%) of Study Participants[a]		
	Azathioprine (n = 32)	Mycophenolate Mofetil (n = 28)	Rituximab (n = 30)
Diagnosis			
NMO	23 (72)	18 (64)	19 (63)
Seropositive NMO	16	17	15
Seronegative NMO	7	1	2
Unknown	0	0	2
NMOSD	9 (28)	10 (36)	11 (37)
Mean age at onset, y	39.1	38.5	43.7
Median age (range), y	39.5 (3-70)	36.1 (19-74)	44.9 (13-79)
Female sex	29 (91)	26 (93)	25 (83)
Race			
White	14 (44)	10 (36)	14 (47)
African American	8	16	16
Asian	4	1	0
Latin American	2	1	0
Native American	4	0	0
Previous treatment			
Prednisone	1 (3)	2 (7)	1 (3)
β-Interferons	3 (9)	5 (18)	2 (7)
Glatiramer acetate	1 (3)	2 (7)	3 (10)
Intravenous immunoglobulins	0	1 (4)	1 (3)

Abbreviations: NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder.

[a] Data are presented as number (percentage) of study participants unless otherwise indicated.

based on the 2006 revised NMO criteria that require occurrence of both ON and TM, along with 2 of the 3 following supportive features: (1) longitudinally extensive spinal cord lesion (≥3 vertebral segments), (2) magnetic resonance imaging of the brain nondiagnostic for MS, and (3) AQP4-IgG seropositivity.[11] We defined NMOSD as TM, ON, or brainstem inflammation associated with serum AQP4-IgG.[12] Only NMO and NMOSD patients who received azathioprine or mycophenolate for at least 6 months or rituximab for at least 1 month were included. Patients who were taking azathioprine, mycophenolate, or rituximab and then switched to another 1 of these 3 therapies were included if the final therapy was used for at least 6 months with azathioprine or mycophenolate or at least 1 month with rituximab regardless of duration of initial therapy. Patients who had previously been receiving immunomodulatory therapies, including glatiramer acetate, β-interferons, prednisone monotherapy, or hydroxychloroquine sulfate, were included as indicated in **Table 1**. Exposure to another general immunosuppressive agent, including cyclophosphamide, methotrexate, and mitoxantrone, was an exclusion criterion. Patients who were concurrently receiving more than 1 of the medications being analyzed in this analysis were also excluded.

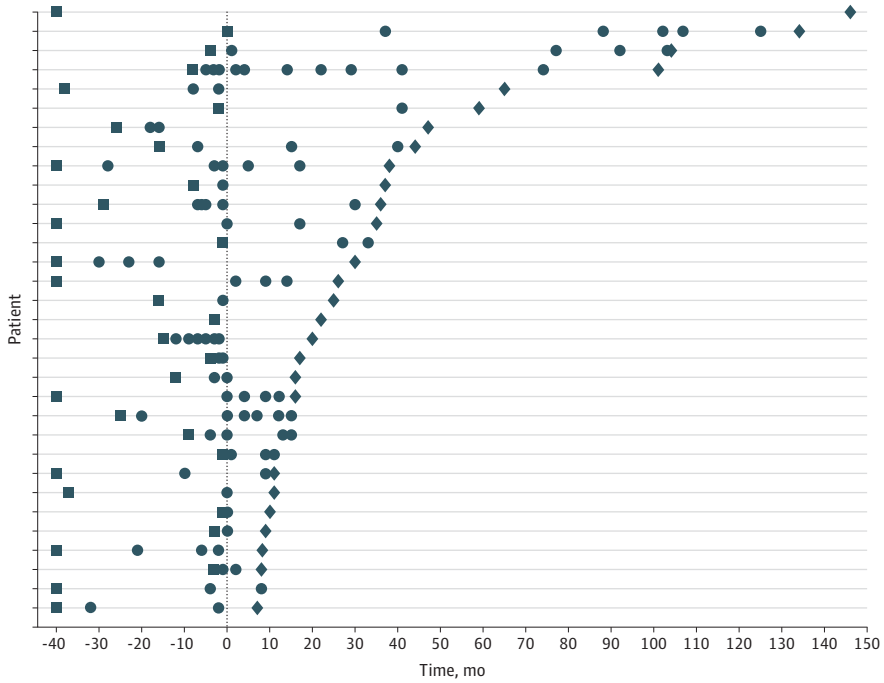
For the purpose of this analysis, medication failure was defined as any new inflammatory CNS event that occurred despite immunosuppressive treatment. Relapses were defined as new CNS symptoms and signs that lasted longer than 24 hours, with or without an associated new lesion on gadolinium-enhancing magnetic resonance imaging. Medication regimens were categorized as optimal or suboptimal based on dosing and duration of treatment. The purpose of these definitions is to divide treatment failures into those that occur because of insufficient treatment and those that occur despite optimal medication use. For the purpose of this analysis, azathioprine treatment was suboptimal if the relapse occurred within 6 months of drug therapy initiation or if the dosage was less than 2 mg/kg/d. Criteria for optimal dosing of azathioprine have not been established and were not standardized among centers. Suboptimal treatment with mycophenolate was defined as duration of therapy of less than 6 months or a dose that did not lower the absolute lymphocyte count to less than 1500/μL (to convert to $\times 10^9$/L, multiply by 0.001) (up to 3000 mg/d). Suboptimal dosing for rituximab was defined as a duration of less than 1 month or greater than 5 months or as the presence of CD19 cells in circulation (>0.1% of total lymphocytes).

Annualized relapse rates (ARRs) on retrospective data were calculated as number of relapses per year and only included patients who were followed up after treatment for at least 6 months. Relapses were analyzed for up to 40 months before initiation of therapy and for the duration of the time undergoing therapy. Cox regression analysis was used for the first relapse-free survival and repeated relapse survival. Repeated relapse survival was modeled by assuming a patient was at risk for a subsequent relapse only if a previous relapse already occurred. $P < .05$ was considered statistically significant. Statistical calculations were implemented with SAS statistical software, version 9.3 (SAS Institute Inc).

Results

We reviewed the records of the first 90 NMO and NMOSD patients seen at the Johns Hopkins Hospital or Mayo Clinic who

Figure 1. Relapses in Patients With Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD) Before and After Azathioprine Treatment



Thirty-two patients with NMO and NMOSD were prescribed azathioprine at time 0. The initial attack was marked with a solid square unless it occurred more than 40 months before starting therapy. Solid circles identify relapses before starting azathioprine treatment and occurring after starting azathioprine treatment. A solid diamond marks the end of azathioprine therapy for each patient. Only patients who took azathioprine for a minimum of 6 months were included in this analysis. In 17 patients (53%), azathioprine treatment failed, defined as any clinical relapse of transverse myelitis and/or optic neuritis while taking azathioprine. The relapse rate decreased with azathioprine from 2.26 to 0.63 (P = .004).

Table 2. Treatment-Associated Annualized Relapse Rates (ARRs) and Hazard Risks Relative to Rituximab

Medication	Pretreatment ARR	Posttreatment ARR	Change From Pretreatment to Posttreatment, %	Hazard Risk Relative to Rituximab (95% CI)	*P* Value
Azathioprine	2.26	0.63	72.1	2.12 (1.12- 4.01)	.02
Mycophenolate mofetil					
Total	2.61	0.33	87.4	1.48 (0.75-2.93)	.26
Optimal dosing	2.55	0.25	90.2		
Rituximab					
Total	2.89	0.33	88.6	1 [Reference]	
Optimal dosing	3.25	0.20	93.9		
Switch treatments	1.03	0.14	86.4		.054

met the inclusion criteria. Thirty-two patients taking azathioprine, 28 patients taking mycophenolate, and 30 patients taking rituximab were included for individual analysis. No difference was found in the pretreatment relapse risk among the 3 treatments with or without adjustment for the clinical center (P = .58 [.25 adjusted for center] and .17 [.86 adjusted for center] for mycophenolate and rituximab, respectively). Eighteen patients for whom primary therapy failed were switched to another treatment during this period: 4 patients switched from azathioprine to mycophenolate, 4 patients from azathioprine to rituximab, 4 patients from rituximab to mycophenolate, and 6 patients from mycophenolate to rituximab.

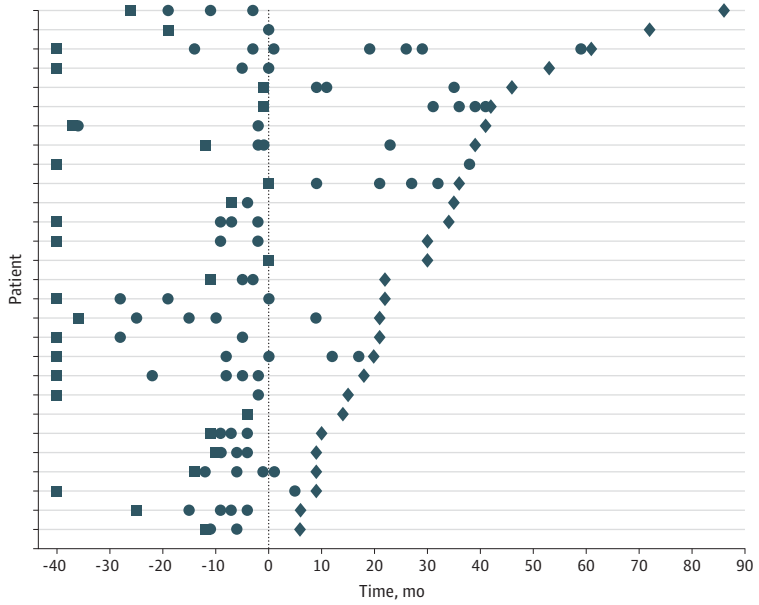
Azathioprine

Thirty-two patients were prescribed azathioprine as their initial immunosuppressive agent (NMO patients, 72% [of whom 70% were AQP4-IgG positive]; NMOSD patients, 28%). The initial dosage of azathioprine used for this patient population was 2 to 3 mg/kg/d. Azathioprine patients were treated with concomitant prednisone at a dose range of 5 to 60 mg for a median duration of 6 months (range, 0-122 months). Seventeen patients (53%) had at least 1 relapse while undergoing therapy, with a total of 43 relapses among them (**Figure 1**). The ARR within the 40 months before therapy was 2.26, and after a median duration of therapy of 23.5 months (range, 7-148 months), the ARR decreased to 0.63, a reduction of 72.1% (P = .004) (**Table 2**). Twenty-three of the azathioprine relapses occurred among 9 patients despite concurrent prednisone treatment.

Mycophenolate

Twenty-eight patients were prescribed mycophenolate as their initial immunosuppressive agent (NMO patients, 64% [of whom 94% were AQP4-IgG positive]; NMOSD patients, 36%). The initial dose of mycophenolate mofetil used was 1000 to 2000 mg/d

Figure 2. Relapses in Patients With Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD) Before and After Mycophenolate Mofetil Treatment



Twenty-eight patients with NMO and NMOSD were prescribed mycophenolate at time 0. The initial attack was marked with a solid square unless it occurred more than 40 months before starting therapy. Solid circles identify relapses before starting mycophenolate treatment and occurring after starting mycophenolate treatment. A solid diamond marks the end of mycophenolate therapy for each patient. Only patients who took mycophenolate for a minimum of 6 months were included in this analysis. In 10 patients (36%), mycophenolate treatment failed, defined as any clinical relapse of transverse myelitis and/or optic neuritis while taking mycophenolate. The relapse rate decreased with mycophenolate from 2.61 to 0.33 ($P < .001$).

and titrated according to laboratories as outlined in Table 1. Ten patients (36%) had at least 1 relapse while undergoing therapy, with a total of 23 relapses among them, whereas 18 (64%) were relapse free (**Figure 2**). The ARR in the 40 months before initiating mycophenolate therapy was 2.61, and after a median duration of therapy of 26 months (range, 6-86 months), the ARR decreased to 0.33, a reduction of 87.4% (Table 2). Seven patients (25%) had at least 1 relapse despite optimal dosing of a mycophenolate regimen as defined in Table 1. The ARR for patients receiving an optimal mycophenolate regimen decreased from 2.55 to 0.25, a reduction of 90.2% ($P < .001$). Thirteen patients were cotreated with prednisone, starting at initiation of therapy with a dose range of 15 to 40 mg for a median duration of 3 months (range, 0-68 months). Six of the mycophenolate relapses occurred among 6 patients despite concurrent prednisone treatment.

Rituximab

Thirty patients were prescribed rituximab as their initial immunosuppressive agent (NMO patients, 63% [of whom 79% were AQP4-IgG positive]; NMOSD patients, 37%). The dose for rituximab was 1000 mg intravenously, with a premedication dose of 100 mg of methylprednisolone, and the dosage repeated 2 weeks later. CD19 cell counts were tested monthly, and repeat paired rituximab dosing was scheduled on detection of a CD19 population greater than 0.1% of total lymphocytes or at regular 6-month intervals. Ten patients (33%) had at least 1 relapse while undergoing rituximab therapy, with a total of 13 relapses among them, and 20 patients (67%) were relapse free (**Figure 3**). The ARR in the 40 months before initiating rituximab therapy was 2.89, and after a median duration of therapy of 20 months (range, 5-83 months), the ARR decreased to 0.33, a reduction of 88.6% (Table 2). Five patients (17%) had a single relapse despite optimal rituximab dosing (Table 1). The ARR for patients receiving an optimal rituximab medication regimen decreased from 3.25 to 0.20, a 93.9% reduction ($P = .02$).

Compared with rituximab, azathioprine therapy in NMO increases the risk of relapse by more than 2-fold (**Table 3**). Efficacy with mycophenolate is not statistically different from rituximab.

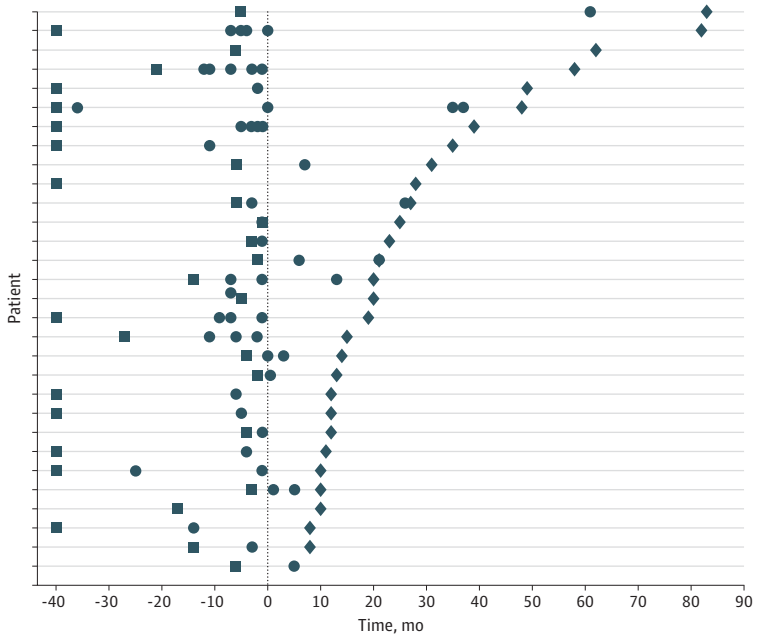
Switched Treatments

Eighteen patients (NMO patients, 78% [of whom 73% were AQP4-IgG positive]; NMOSD patients, 22%) began therapy with azathioprine, mycophenolate, or rituximab and then switched to either mycophenolate or rituximab because of treatment failure. One patient was switched from azathioprine to mycophenolate because of concerns of rare cancer risk. No patients switched therapies because of drug tolerability issues. In 4 of the 18 patients (22%), 2 therapies failed: both mycophenolate and rituximab therapy failed in 3 patients, and both azathioprine and rituximab therapy failed in 1 patient (**Figure 4**). The ARR in the 40 months while taking the first drug before switching treatments was 1.03. After a median duration of new therapy of 20 months (range, 6-97 months), the ARR decreased to 0.14, a reduction of 86.4% but did not meet statistical significance ($P = .054$). The efficacy of the second drug was not compared with untreated ARR because of concern of immunologic effects of the intervening first drug. Overall, 2 therapies have thus far failed in only 4 of 90 NMO and NMOSD patients (4%).

Interpretation

Since the initial 7-patient trial of azathioprine in NMO in 1998,[4] a total of 15 treatment studies in NMO have been published on the use of azathioprine (5 studies), mycophenolate (1 study), rituximab (6 studies), methotrexate (1 study), corticosteroids

Figure 3. Relapses in Patients With Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD) Before and After Rituximab Treatment



Thirty patients with NMO and NMOSD were prescribed rituximab at time 0. The initial attack was marked with a solid square unless it occurred more than 40 months before starting therapy. Solid circles identify relapses before starting rituximab treatment and occurring after starting rituximab treatment. A solid diamond marks the end of rituximab therapy. In 10 patients (33%), rituximab treatment failed, defined as any clinical relapse of transverse myelitis and/or optic neuritis while taking rituximab. The relapse rate decreased with rituximab from 2.89 to 0.33 (P = .004).

Table 3. Failure Rates With Azathioprine, Mycophenolate Mofetil, and Rituximab

Medication	Failure Rate, %
Azathioprine	53
Mycophenolate mofetil	
Total	36
Optimal dosing	25
Rituximab	
Total	33
Optimal dosing	17
Switched treatments	22

(1 study), and mitoxantrone (2 studies).[10] All the immunosuppressants have shown some benefit in reducing relapse rates in NMO patients, but even 1 treatment failure, defined as an inflammatory CNS event while undergoing treatment, is potentially devastating. For this reason, we provide a comparative analysis of the 3 most widely used NMO treatments in the United States (azathioprine, mycophenolate, and rituximab) in terms of reduction in relapse and treatment failure rates, as well as the beneficial effects of optimal dosing.

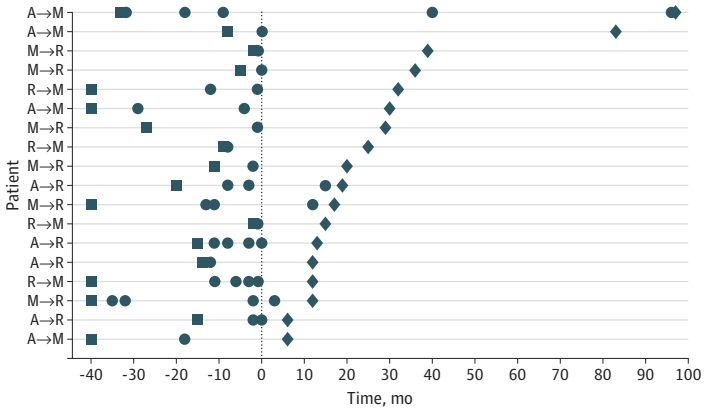
Similar to previous studies,[4-10] we found a reduction in relapse rates in NMO patients with all 3 immunosuppressants. Azathioprine treatment provides a reduction in relapse rate of 72.1%. Compared with mycophenolate and rituximab, which demonstrate better reductions in relapse rates of up to 90.2% and 97.9%, respectively, when dosed optimally, azathioprine treatment carries a higher risk of relapse. The failure rate with azathioprine is 53%, significantly higher compared with optimally dosed mycophenolate (failure rate of 25%) and rituximab (failure rate of 17%). Even when optimal dosing of mycophenolate and rituximab is not considered, their failure rates of 36% and 33% are still lower than the failure rate with azathioprine.

Our report on azathioprine is supported by data from Costanzi et al,[5] which found that NMO relapses in patients taking azathioprine occurred in 66% of patients. The authors also noted that 22% of patients discontinued use of the medication and 3% developed lymphomas, suggesting that azathioprine has additional safety risks and tolerability concerns. Azathioprine therapy for NMO has not been studied without concurrent prednisone, whose adverse effects include hypertension, hyperglycemia, mood disturbances, glaucoma, and bone density loss.[12]

Rituximab is an effective treatment option for NMO, with the greatest reduction in relapse rate and lowest failure rate of the 3 medications examined in our study. With close monitoring of CD19 and CD20 cell counts, the failure rate of rituximab in NMO patients is only 17%. No significant difference was found in the age, sex, race, or AQP4-IgG serostatus among the 5 optimally dosed rituximab failures. Infusion-related reactions associated with rituximab are routinely managed with methylprednisolone, and other adverse effects from rituximab are rare.[9] The estimated risk of progressive multifocal leukoencephalopathy is 1:25 000 among all patients treated with rituximab,[13] and no patient with MS or NMO treated with rituximab has yet developed progressive multifocal leukoencephalopathy.

Mycophenolate is also an effective treatment option in NMO. With close monitoring of lymphocyte counts and optimizing the dose to achieve suppression of less than 15 000/μL, the failure rate with mycophenolate was 25%. No significant difference was seen in age, sex, race, or AQP4-IgG serostatus among the 7 optimally dosed patients in whom treat-

Figure 4. Relapses in Patients With Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD) Before and After Switching Immunosuppressive Treatment



Eighteen patients with NMO and NMOSD were switched from azathioprine (A), mycophenolate mofetil (M), or rituximab (R) to mycophenolate or rituximab at time 0. The initial treatment start date is marked with a solid square unless it occurred 40 months or more before switching therapies. Solid circles identify relapses before switching and occurring after switching. A solid diamond marks the end of the second medication period. In 4 patients (22%), 2 therapies failed, defined as any clinical relapse of transverse myelitis and/or optic neuritis while taking the second medication. The relapse rate decreased with switching therapies from 1.03 to 0.14 but did not reach statistical significance (P = .054).

ment failed. Patients in whom mycophenolate treatment fails tend to relapse often. Consequently, patients in whom mycophenolate treatment fails should be switched to another medication as soon as possible. Similar to azathioprine, concurrent prednisone is recommended for the first 6 months of mycophenolate treatment, adding similar risks associated with prolonged corticosteroid therapy.[11]

Conclusions

Patients who switched immunosuppressive therapy because of treatment failure generally responded well to the new therapy. Among 18 patients in whom initial therapy with azathioprine, mycophenolate, or rituximab failed, 14 patients were successfully switched to either mycophenolate or rituximab. Two treatment options failed in only 4 patients, including 3 patients in whom both mycophenolate and rituximab treatment failed. For these few, additional options may include experimental immunotherapies with drugs such as cyclophosphamide[14] or methotrexate.[15] Recently, eculizumab, a C5a complement inhibitor, minimized disease activity in 12 of 14 NMO patients, most of whom had undergone failed first-line treatment.[16] A phase 3 trial of eculizumab in NMO patients is currently in preparation and may be available to patients for whom standard therapy fails.

This study is limited by the biases inherent to retrospective study design. Patients who were seen before the seminal rituximab and mycophenolate studies[6,7] in NMO were more likely to be treated with azathioprine, which was the most common treatment option at the time. Although patients at our centers were offered all 3 treatment options, patients evaluated more recently were more likely to initiate mycophenolate or rituximab as their first-line therapy. Between mycophenolate and rituximab, there were other biases that relate to potential adverse effects, route of therapy, need for concurrent prednisone treatment, and perceived long-term safety.

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Study concept and design: Wingerchuk, Palace, Greenberg, Levy.
Acquisition of data: Mealy, Wingerchuk, Greenberg, Levy.
Analysis and interpretation of data: Mealy, Wingerchuk, Levy.
Drafting of the manuscript: Mealy, Levy.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Mealy, Greenberg, Levy.
Study supervision: Palace, Levy.

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