Treatment of Neuromyelitis Optica With Mycophenolate Mofetil
Retrospective Analysis of 24 Patients

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Background: Neuromyelitis optica (NMO) is the first inflammatory autoimmune demyelinating disease of the central nervous system for which a specific antigenic target has been identified; the marker autoantibody NMO-IgG specifically recognizes the astrocytic water channel aquaporin 4. Current evidence strongly suggests that NMO-IgG may be pathogenic. Since disability accrues incrementally related to attacks, attack prevention with immunosuppressive therapy is the mainstay of preventing disability.

Objective: To evaluate the efficacy and safety of mycophenolate mofetil therapy in NMO spectrum disorders.

Design: Retrospective case series with prospective telephone follow-up.

Setting: Mayo Clinic Health System.

Patients: Twenty-four patients with NMO spectrum disorders (7 treatment-naive).

Intervention: Mycophenolate mofetil (median dose of 2000 mg per day).

Main Outcome Measures: Annualized relapse rates and disability (Expanded Disability Status Scale).

Results: At a median follow-up of 28 months (range, 18-89 months), 19 patients (79%) were continuing treatment. The median duration of treatment was 27 months (range, 1-89 months). The median annualized posttreatment relapse rate was lower than the pretreatment rate (0.09; range, 0-1.5; and 1.3; range, 0.23-11.8, respectively; P < .001). Disability stabilized or decreased in 22 of 24 patients (91%). One patient died of disease complications during follow-up. Six patients (25%) noted adverse effects during treatment with mycophenolate.

Conclusion: Mycophenolate is associated with reduction in relapse frequency and stable or reduced disability in patients with NMO spectrum disorders.

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NEUROMYELITIS OPTICA (NMO) is an idiopathic autoimmune inflammatory demyelinating disorder that affects the central nervous system with a predilection for the optic nerve and spinal cord. It is the first inflammatory autoimmune demyelinating disease of the central nervous system for which a specific antigenic target, the astrocytic water channel aquaporin 4, has been identified. Neurymyelitis optica-IgG is an autoantibody specific for this water channel and is a clinically validated serum biomarker that distinguishes relapsing NMO from multiple sclerosis, which has no distinguishing biomarker. Patients seropositive for NMO-IgG with either optic neuritis or longitudinally extensive transverse myelitis are considered to have limited forms of NMO, which we have called NMO spectrum disorders. Seropositivity for NMO-IgG in these disorders is predictive of further relapses.

Disability in NMO accrues incrementally in relationship to attacks. Fifty percent of patients are dependent on a wheelchair and 62% are functionally blind at 5 years. In contrast, patients with multiple sclerosis have a more favorable outcome, and disability usually occurs during the progressive rather than the relapsing phase of their disease. Because disability in NMO is attack-related, attack prevention is anticipated to be an effective strategy in prevention of cumulative disability. Immunosuppressive therapy is the mainstay of preventing attacks and thus disability. Azathioprine, corticosteroids, mitoxantrone, and more recently rituximab have been reported to be effective in small case series. No randomized controlled trials have been conducted in this disorder.
Recently, mycophenolate mofetil has been increasingly used in NMO, though to date only 1 case of NMO treated with mycophenolate mofetil has been reported. Mycophenolate mofetil (Cellcept, F. Hoffmann-La Roche, Basel, Switzerland) is a 2-morpholinoethyl ester of mycophenolic acid and a reversible inhibitor of inosine monophosphate dehydrogenase that is involved in guanosine nucleotide synthesis, on which the T and B lymphocytes are exclusively dependent for proliferation. It also exerts an inhibitory effect on antibody synthesis. It is routinely used in cardiac and renal transplant settings and is being increasingly used as a treatment option in a variety of other autoimmune conditions, including systemic lupus erythematosus–induced and other immune neuropathies, autoimmune hepatitis, psoriasis, blistering dermatopathies, and vasculitides. It is also used to treat myasthenia gravis, multifocal motor neuropathy, inflammatory myopathies, chronic inflammatory demyelinating polyradiculoneuropathy, autonomic ganglionopathy, vasculitic neuropathies, and multiple sclerosis. It is considered to have fewer adverse effects than other immunosuppressive agents and is administered orally. The optimal dose and duration and the effect size of mycophenolate mofetil for prevention of NMO attacks remain uncertain. Herein we report on our experience with mycophenolate mofetil in a cohort of adult patients with NMO.

METHODS

We performed a retrospective medical record review of all Mayo Clinic patients with NMO (per 2006 diagnostic criteria) or an NMO spectrum disorder (NMO-IgG–seropositive patients with optic neuritis or longitudinally extensive transverse myelitis) who were treated with mycophenolate mofetil anytime from June 1999 until June 2006. Patients were identified by searching the centralized medical records of all the 3 Mayo Clinic sites (Rochester, Minnesota; Scottsdale, Arizona; and Jacksonville, Florida) using the search terms neuromyelitis optica, Devic’s disease, optic neuritis, or myelitis and mycophenolate or Cellcept.

Local institutional review board approval was secured and informed consent obtained from patients or next of kin. Telephone follow-up was performed by one of us (A.J., M.M., or S.J.P.) in 2008. Data analysis was performed at the Mayo Clinic, Rochester, using JMP, version 6.0 (SAS Institute Inc, Cary, North Carolina). Wilcoxon signed-rank test was used to compare pretreatment and posttreatment relapse rates and Expanded Disability Status Scale (EDSS) scores. Relapses and disability were assessed by medical record review and telephone interview. A relapse was defined as objective worsening of neurologic function lasting more than 24 hours.

RESULTS

PATIENT CHARACTERISTICS

Twenty-four patients (19 women) were identified. The median age of the patients at onset of treatment with mycophenolate mofetil was 56 years (range, 34-77 years). The median duration of NMO to onset of treatment with mycophenolate mofetil was 4.2 years (range, 0.1-39 years).

The diagnosis was NMO in 15 patients (63%); 13 of 14 tested were NMO-IgG–seropositive and all fulfilled 2006 NMO diagnostic criteria; relapsing longitudinally extensive transverse myelitis in 7 patients (29%); relapsing optic neuritis in 1 patient (4%); and a single episode of longitudinally extensive transverse myelitis in 1 patient (4%). The patients with relapsing or single episodes of longitudinally extensive transverse myelitis or relapsing optic neuritis were all NMO-IgG–seropositive.

TREATMENT WITH MYCOPHENOLATE MOFETIL

Seven patients (29%) were treatment-naïve. The remaining 17 patients (71%) had previously used other immunosuppressive (n=6), immunomodulatory (n=2), or combination (n=9) therapy. Twelve (50%) received azathioprine (Table). Reasons for switching to mycophenolate mofetil included medication adverse effects (n=7 [29%]), continued relapses (n=8 [33%]), and contraindication to azathioprine owing to low thiopurine methyltransferase levels (n=2 [8%]). The median dose of mycophenolate mofetil used was 2000 mg per day (range, 750-3000 mg per day). The clinical and demographic profiles of the patients are summarized in the Table.

FOLLOW-UP

After identification of the initial cohort in June 2007, telephone follow-up and medical record review were again performed in 20 patients in late 2008 at a median of 27 months after starting treatment (range, 18-89 months). Telephone contact was not possible for 4 patients (1 died); medical record review in these patients provided posttreatment follow-up data for a median of 46 months (range, 21-54 months). The median follow-up of all patients (irrespective of whether they continued treatment) was 28 months (range, 18-89 months).

The median duration of treatment with mycophenolate mofetil was also 27.4 months (range, 1-89 months). At last review, 19 patients (79%) continued treatment with mycophenolate mofetil, with a median duration of 29.4 months (range, 20-89 months). Five patients (21%) discontinued the drug after a median interval of 16 months (range, 1-54 months). The reasons for discontinuation were death in 1 (patient 21), relapses in 2 (patient 3 switched to rituximab at 3 months, patient 14 to azathioprine at 25 months), and adverse effects in 1 (patient 24 had low white blood cell counts and switched to azathioprine at 1 month). Patient 1 had neither relapses nor adverse effects but chose to switch to rituximab after 1 month of mycophenolate mofetil.

TREATMENT EFFICACY

Relapse Rates

The Figure depicts the timing of relapses before and after treatment. All relapses after initiation of mycophenolate mofetil until its discontinuation or until the last date of follow-up were included in the analysis. Nine pa-
tients were undergoing additional treatments (oral \([n=8]\) and intravenous \([n=1]\) corticosteroids) for variable periods after starting treatment with mycophenolate mofetil (Table).

The median annualized posttreatment relapse rate was 0.09 (range, 0-1.56), and the pretreatment rate was 1.28 (range, 0.23-11.78; \(P < .001\), Wilcoxon signed-rank test). Nineteen of the 24 patients (79%) had an improvement in annualized relapse rate. Because analyses of the total group were confounded by short duration of treatment, death, and concomitant treatments, we performed the following 3 subgroup analyses.

Analysis Excluding Patients With Less Than 6 Months of Mycophenolate Mofetil Therapy. Two of the 24 patients took mycophenolate mofetil for a very short duration (patients 1 and 2 for 1 month each) and discontinued taking the drug early owing to adverse effects. With these patients excluded from the analysis, the median treatment duration was 28 months (range, 16-89 months). The median posttreatment annualized relapse rate on treatment for the remaining 22 patients was 0.2 (range, 0-1.5), a significant reduction compared with the pretreatment rate of 1.37 (range, 0.23-11.78; \(P < .001\)). Seventeen of 22 patients (77%) had an improvement in relapse rate.

Analysis Excluding Those in First Analysis and 1 Patient Death. After exclusion of the patient who died (patient 21) and those excluded in the first subgroup analysis, the median duration of treatment for the 21 patients was 27.4 months (range, 16-89 months). The median posttreat-

<table>
<thead>
<tr>
<th>Patient No./</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Disease Duration at First Mycophenolate Mofetil Treatment, y</th>
<th>NMO-IgG Status</th>
<th>LETM on MRI</th>
<th>Drugs Used Prior to Mycophenolate Mofetil</th>
<th>Concomitant Immunotherapy</th>
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<td>1/M</td>
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<td>Prednisone on alternate days</td>
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<td>Pulsed intravenous methylprednisone monthly</td>
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<td>+</td>
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<td></td>
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<td>10.83</td>
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<td>-</td>
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<td>+</td>
<td>+</td>
<td>Glatiramer acetate, azathiopine, interferons, prednisone</td>
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<td>+</td>
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<td>NMO</td>
<td>6.5</td>
<td>+</td>
<td>+</td>
<td>Azathiopine, interferon</td>
<td></td>
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</tbody>
</table>

Abbreviations: LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; U, unknown; +, present; -, absent.
ment annualized relapse rate with treatment for this subset was 0.18 (range, 0-1.5), and the pretreatment rate was 1.15 (range, 0.23-11.78; \( P < .001 \)).

Analysis Excluding Those in Second Analysis and Patients Receiving Concomitant Therapies. After exclusion of patients who received concomitant immunosuppressive treatment (patients 3, 5, 6, 9, 12, 13, 15, 21, and 22) and those in the second subgroup analysis, the median duration of treatment in months was 31 (range, 21-89 months) for the remaining 12 patients. The median posttreatment annualized relapse rate on treatment for this subset was 0.24 (range, 0-1.22), and the pretreatment rate was 1.15 (range, 0.23-7.6; \( P < .001 \)).

Disability

The median EDSS score was 6 (range, 0-8) at the start of treatment with mycophenolate mofetil (n=24) and 5.5 (range, 0-10) at last follow-up (at a median of 28 months; \( P = .17 \)). Exclusion of 2 patients who underwent treatment for a very short period did not alter the median scores.

The EDSS scores were unchanged in 15 and improved in 7 (22 of 24 [91%]). The median reduction in EDSS score was 1 point (range, 0-5-2.5). Four of these patients no longer needed a cane. The EDSS score worsened in 2 patients (patient 3 worsened from 6 to 8, and patient 21 died after being bed bound for 54 months).

ADVERSE EVENTS

Patient 21 died. He was a 45-year-old Hispanic man who presented with optic neuritis and myelitis in 1999 and had 3 additional relapses in the same year. He began treatment with mycophenolate mofetil and prednisone in 2000, after developing liver dysfunction with azathioprine. No adverse effects were noted in the first year of treatment. He was subsequently lost to follow-up. Telephone interviews with his family following his death indicate that the patient continued to relapse approximately every 6 months and died 54 months after onset of treatment with mycophenolate mofetil. The death certificate documents the cause of death as “cardiopulmonary failure; respiratory drive failure and Devic’s disease.”

Six patients (25%) reported adverse effects: headache (n=1), constipation (n=1), easy bruising (n=1), anxiety (n=1), hair loss (n=1), diarrhea and abdominal pain (n=1), and low white blood cell counts that required discontinuation (n=1).

COMMENT

The single previous case report of mycophenolate mofetil in NMO described a 9-year-old girl with NMO who had 5 relapses within a 2-year period despite azathioprine. Corticosteroid therapy was followed by a vertebral fracture. Mycophenolate mofetil introduced 16 months after onset of NMO was followed by sustained remission at 2 years.\(^7\)

The mainstay of treatment for most patients with NMO is prednisone, alone or combined with azathioprine. This approach is largely based on a series of 7 patients with NMO who were treated with long-term prednisone and azathioprine and were followed up every 2 months for at least 18 months. Their EDSS scores improved significantly and no relapses occurred for more than 18 months.\(^12\)

A series of 5 patients treated with mitoxantrone during 2 years also showed improvement.\(^14\) However, 2 patients relapsed once within the initial 5 months of treatment and 1 patient had a reversible decrease in cardiac ejection fraction. Cardiotoxicity is a concern with mitoxantrone, and the duration of treatment is limited to about 2 years because of restricted cumulative lifetime dosing.

Rituximab, a monoclonal antibody against CD20\(^+\) B cells,\(^16\) has been used to prevent attacks of NMO. Following up on an initial report on 8 patients, a recent retrospective multicenter experience in 25 patients (23 of whom were refractory to other medications, including 1 patient treated with mycophenolate mofetil) showed that rituximab treatment was associated with reduction in relapse rates and stabilized disability scores in 80% of treated patients.\(^13,16\) However, 28% of patients had infusion-related adverse events and 20% had infections that could have been related, at least in part, to immunosuppression. Two patients died, one likely because of septicemia. Rituximab, therefore, was potentially beneficial but (1) required intravenous infusion (which may necessitate admission), (2) was associated with infection risk, and (3) some patients remained refractory to treatment. These factors and the risks of significant infections from
immunosuppression may limit its use, especially as a first-line agent in the treatment of NMO spectrum disorders. Mycophenolate mofetil may also produce serious toxicity. Progressive multifocal leukoencephalopathy has been reported in kidney, heart, and lung transplant patients and in systemic lupus erythematosus when mycophenolate mofetil was used in conjunction with or after the use of other immunosuppressants. A retrospective cohort study of 32,757 renal transplant recipients using the United States Renal Data System kidney transplant files identified 9 cases. The incidence of progressive multifocal leukoencephalopathy in those taking mycophenolate mofetil was 14.4 cases per 100,000 person-years at risk vs 0 for those not taking mycophenolate mofetil. However, because 75% of patients in the cohort were taking mycophenolate mofetil, the putative association was not statistically significant. No cases of progressive multifocal leukoencephalopathy were found in patients undergoing mycophenolate mofetil monotherapy. Although an increased risk of lymphoma was initially reported in patients who underwent transplants and occasionally in autoimmune disorders, an international prospective registry of 6751 patients receiving mycophenolate mofetil and an equal number of matched controls receiving other immunosuppressive treatments did not find an association with lymphoma in renal transplant patients with lupus nephritis. The adverse effects observed in the present study were dose limiting in 1 patient and necessitated change to azathioprine in another.

The efficacy of mycophenolate mofetil remains uncertain. Despite anecdotal evidence supporting its effectiveness in myasthenia gravis, 2 recent large randomized trials reported no benefit. It has not been established whether mycophenolate mofetil is superior to azathioprine in preventing acute rejections in recipients of cadaver kidney transplants. Mycophenolate mofetil is considerably more expensive than azathioprine, but less expensive than rituximab. The estimated drug cost for 1 year of treatment, exclusive of cost of administration, is $846.80 for 150 mg of azathioprine per day, $11,373.40 for 2000 mg of mycophenolate mofetil per day, and $23,287.60 for 4000 mg of infusions of rituximab per year.

The uncontrolled design of the study, the small sample, and confounding comitant treatments preclude definitive evaluation of the efficacy of mycophenolate mofetil for NMO relapse prevention. The reduction in the posttreatment relapse rate could be explained by regression to the mean. The effects of EDSS score could have been confounded by recent attacks at the time of initiation of mycophenolate mofetil treatment and effects on attack suppression. There was no washout period to eliminate effect of prior therapies. Follow-up was incomplete, and the cause of death in 1 patient had to be ascertained by contact with his family and review of the death certificate.

This is a cumulative experience of all patients with NMO treated by 10 neurologists at 3 different Mayo Clinic sites. Despite the aforementioned limitations, this case series provides some justification for the use of mycophenolate mofetil to prevent attacks of NMO. There have been no placebo- or active comparator–controlled trials in NMO. Azathioprine with or without oral prednisone, rituximab, mycophenolate mofetil, and other immunosuppressants all seem effective; therefore, adverse effects and cost along with the urgency to achieve immediate immunosuppression influence the choice of treatment. Controlled trials are necessary.

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Financial Disclosure: Drs Lucchinetti and Weinshenker are named inventors on a patent relating to the NMO-IgG marker for diagnosis of NMO and related disorders. To date, they have received less than $10,000 in royalties. Drs Pittock and Lucchinetti are named inventors on a filed patent application relating to the functional effects of NMO-IgG.

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REFERENCES


