Neuromyelitis Optica Treatment

Analysis of 36 Patients

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Objective: To analyze treatment response in Brazilian patients with neuromyelitis optica.

Design: Retrospective review.

Setting: Neuroimmunology Clinic of the Federal University of São Paulo, São Paulo, Brazil.

Patients: Thirty-six patients with relapsing-remitting optic-spinal disease; long, extending spinal cord lesions; and brain magnetic resonance images not meeting Barkhof criteria for multiple sclerosis, thus fulfilling the 1999 and 2006 criteria for neuromyelitis optica. Patients were followed up from 1994 to 2007.

Main Outcome Measures: Relapses and accumulation of disability.

Results: Mean follow-up time was 47.2 months and mean age at onset was 32.3 years. Sixty-four treatments were implemented in 36 patients, which included interferon beta, methotrexate, cyclophosphamide, prednisone, and azathioprine solely or plus prednisone. Patients who were treated with azathioprine or azathioprine with prednisone had a reduction in the occurrence of relapses and Expanded Disability Severity Scale score stabilization, as opposed to patients who received other treatments. Of the 4 patients who died, only 1 had received azathioprine treatment.

Conclusion: Azathioprine as monotherapy or with prednisone seems to have reduced the relapse frequency and halted disability progression in the majority of patients treated, with minor and manageable adverse effects.

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N EUROMYELITIS OPTICA (NMO) (Devic disease) is an inflammatory autoimmune disease of the central nervous system that affects preferentially the optic nerve and spinal cord,[1] distinct from multiple sclerosis (MS). Pathological study results obtained from patients with NMO have shown inflammation with macrophage predominance, perivascular granulocytes, eosinophils, immunoglobulin deposition, extensive axonal loss within the spinal cord, and optic nerve lesions.[2] The recent identification of a specific antibody targeted to the blood-brain barrier water channel aquaporin 4 in patients with NMO (NMO-IgG) has turned it into a central nervous system autoimmune chanellopathy.[3,4]

Treatment of patients with NMO is based on small case series using azathioprine, corticosteroids, and other immunosuppressive treatments, such as mitoxantrone, mycophenolate, rituximab, and intravenous immunoglobulin[5-12]; it differs from MS treatment because interferon beta and glatiramer acetate are not able to control relapses and disability progression.

As with MS, most reports on NMO are from the northern hemisphere,[13,14] leaving its prevalence and characteristics in South America not clearly identified. We recently published the clinical characteristics of 41 Brazilian patients with NMO followed up from 1994 to 2007 and found that the most important prognostic factor in this group of patients was incomplete resolution from relapses.[15] To evaluate the effect of treatment in Brazilian patients with NMO, we performed a retrospective study of all drug regimens implemented in this cohort, focusing on the influence of treatments on relapses and accumulation of disability.

METHODS

We retrospectively reviewed, from the Neuroimmunology Clinic of the Federal University of São Paulo, the files of all 63 patients followed up for NMO from 1994 to July 2007. Patients were selected for analysis if they had a follow-up longer than 6 months, predominant optic-spinal clinical course, recurrent disease (nonmonophasic NMO), brain magnetic resonance imaging not meeting criteria for MS,[16] and spinal cord magnetic resonance imaging with at

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Table. Clinical, Demographic, and Laboratory Data of 36 Patients With NMO Selected for Treatment Analysis[15]

Feature	No. (%) (N=36)
Age at onset, y, mean (SD)	32.3 (11.0)
Sex	
M	1
F	3.5
Follow-up, mo, mean	47.2 (23.3)
First relapse	
Myelitis	15 (42)
Optic neuritis	14 (39)
Optic neuritis plus myelitis	7 (19)
Disease duration, y, mean (SD)	7.3 (4.2)
EDSS score at first appointment, mean (SD)	4.0 (1.5)
EDSS score at last appointment, mean (SD)	5.3 (2.5)
Total relapses for all patients	218 (100)
Myelitis	120 (55)
Optic neuritis	65 (30)
Optic neuritis plus myelitis	33 (15)
Relapse rate[a]	1.1 (0.8)
Progression index[b]	0.9 (0.7)
Positive NMO-IgG test results (17 patients tested)	7 (41)

Abbreviations: EDSS, Expanded Disability Status Scale; NMO, neuromyelitis optica.
[a] Total number of relapses divided by disease duration.
[b] The EDSS score at last appointment divided by disease duration.

least 1 lesion longer than 3 vertebral segments (long, extending cord lesion), thus meeting the 1999 and 2006 criteria for NMO.[13,17] All patients admitted for treatment and follow-up in 2007 were tested for the NMO-IgG antibody[4] by indirect immunofluorescence. We did not have the test available before that date. All patients were evaluated for rheumatologic diseases, hepatitis B and C, syphilis, human T-lymphotropic virus 1 and 2, and human immunodeficiency virus as part of our standard investigation for demyelinating disease.

Patients were treated with 1 or a combination of immunomodulatory and immunosuppressive drugs. The choice of each patient's drug was based on clinical presentation and availability in the Brazilian public health system. Treatment efficacy was evaluated by analysis of relapse frequency and disability progression measured by the Expanded Disability Severity Scale (EDSS)[18] at the moment a single treatment was implemented (pretreatment) and at the end of treatment course or last evaluation, if the patient was still receiving active treatment at the time this study was performed (posttreatment). A single treatment course had to last at least 6 months to be included in this efficacy evaluation and patients who were treated only at relapses were not selected for the analysis. Annualized relapse rate (ARR) was calculated as the number of relapses divided by time in years.

Statistical analysis was performed using GraphPad Prism version 5.0 (GraphPad Software, La Jolla, California). An unpaired *t* test or Mann-Whitney test was used when comparing different groups and a paired *t* test was used when accessing relapse frequency and EDSS score variation for each patient. Data are presented as mean (SD) and significance was set at $P<.05$. Approval by the Internal Review Board of the Federal University of São Paulo was obtained prior to study onset.

RESULTS

Thirty-six patients met the inclusion criteria and were selected for analysis, with a mean follow-up of 47.2 months (range, 11-92 months). One patient was excluded be-

cause of monophasic disease; 2, because of diagnostic uncertainty; 5 never received treatment apart from pulse steroids during relapses; and the other 19 had a follow-up time of less than 6 months. Clinical and demographic data at last follow-up are shown in the **Table**. Sixteen (44%) of the 36 patients evaluated were white; 10, Brazilian multiracial (28%); 9, African (28%); and 1, Asian (3%).

Sixty-four treatments were implemented in 36 patients, which included interferon beta, 7.5 mg of oral methotrexate once a week, cyclophosphamide (monthly intravenous administration of 500-750 mg/m^2 per dose), intravenous immunoglobulin (2 g/kg over a 5-day period), prednisone, and azathioprine solely or with prednisone. At the last appointment, 25 patients were taking azathioprine solely or with prednisone, 2 were taking azathioprine with interferon beta, 2 were taking interferon beta only, 2 had received cyclophosphamide, 1 was taking oral methotrexate (7.5 mg/wk), 1 was taking prednisone only, and 1 was receiving intermittent intravenous immunoglobulin. The mean azathioprine dose was 2 mg/kg and prednisone use ranged from 5 to 60 mg/d, with doses at the last appointment as follows: azathioprine, mean 125 mg/d (range, 50-150 mg/d); prednisone, mean 23 mg/d (range, 5-40 mg/d) when used with azathioprine and 33 mg/d (range, 20-40 mg/d) when used solely. Patients were divided in 2 groups according to treatments that were implemented along follow-up: patients treated with azathioprine solely or with prednisone (azathioprine group, 29 treatments) and those who received other treatments ("other treatment" group, 20 treatments). Because some patients in the "other treatment" group received multiple drug regimens at different points, it was not possible to evaluate each individual treatment; thus, the EDSS score variation and relapse rate were evaluated pooled together. Therefore, the totality of treatments implemented along follow-up (N=64) was larger than the sum of treatments analyzed (n=49). Both patients who received interferon beta with azathioprine were included in the azathioprine group and some patients took part in both groups at different points because treatments changed along follow-up. Acute relapses were treated with intravenous methylprednisolone (total of 3-5 g) in most patients and intravenous immunoglobulin (2 g/kg over a 5-day period) in 3. By the time this cohort was closed for analysis, patients had been taking azathioprine or azathioprine plus prednisone for a mean (SD) of 28 (14) months and those in the "other treatment" group had received the other drugs for a mean (SD) of 19 (17) months.

Patients in the azathioprine group had a statistically significant reduction in the total number of relapses after treatment implementation, from a mean (SD) of 5 (2.9) relapses pretreatment (including relapses while receiving prior treatment) to 1 (1.8) after azathioprine or azathioprine plus prednisone treatment ($P<.001$) (**Figure 1**); moreover, their mean (SD) EDSS score remained unchanged after treatment (4.7 [2.2]; $P=.76$) (**Figure 2**). Patients in the "other treatment" group, despite also having a reduction of relapses from a mean (SD) of 4.2 (1.9) pretreatment to 1.7 (1.3) during treatment ($P<.001$), had an increase in EDSS score from 4.2 (1.7) pretreatment to 6.5 (2.7) posttreatment ($P=.003$) (**Figure 3**). The evaluation of ARR was as follows: mean (SD), pretreatment, 2.1 (1.9); "other treatment" group, 1.5 (1.9); and azathioprine group, 0.6 (0.8).
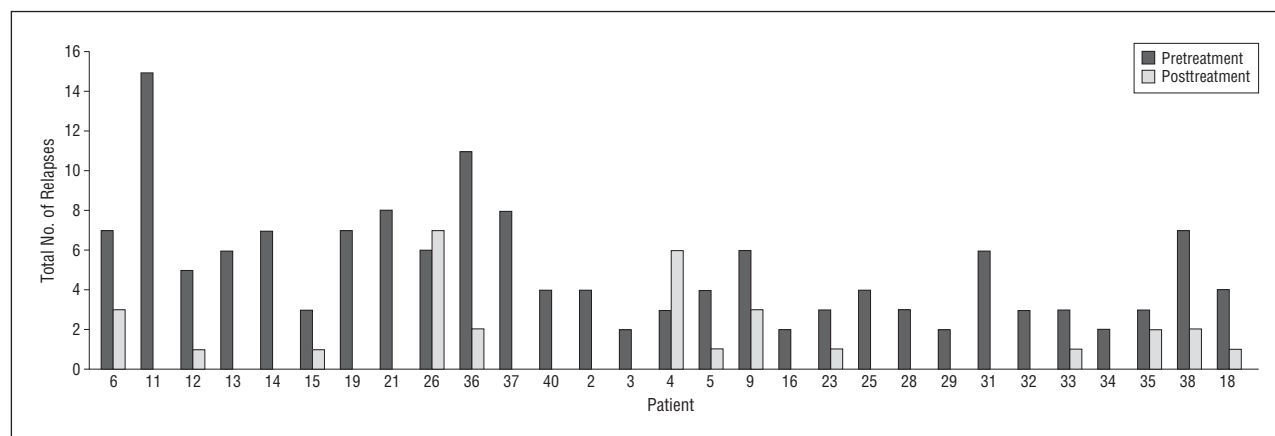
Figure 1. Relapses pretreatment and posttreatment in the azathioprine group (patients treated with azathioprine solely or plus prednisone). Each number on the x-axis refers to 1 patient in treatment. Patients 6, 11, 12, 13, 14, 15, 19, 21, 26, 36, 37, and 40 received other treatments prior to azathioprine.
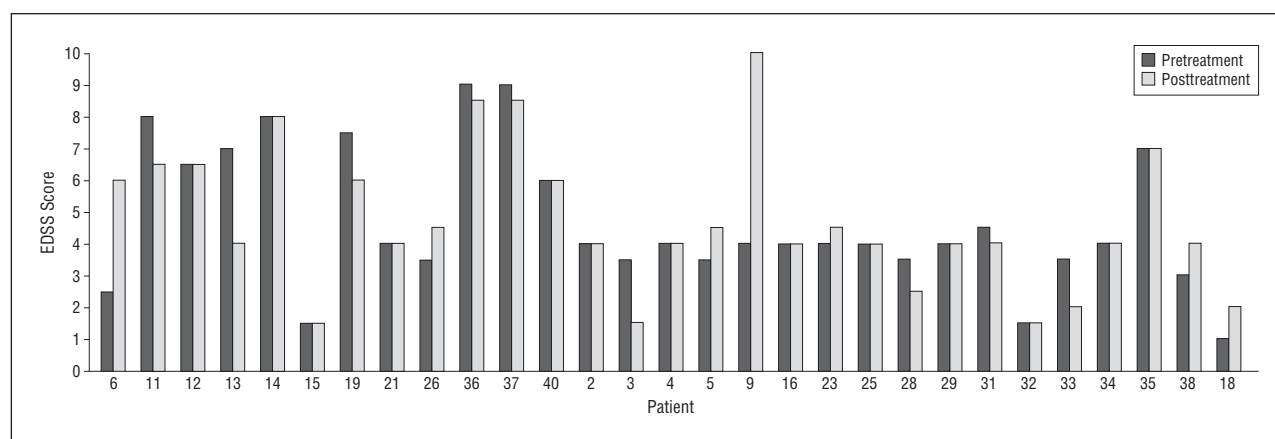

Figure 2. Expanded Disability Severity Scale (EDSS) score pretreatment and posttreatment in the azathioprine group (patients treated with azathioprine solely or plus prednisone). Each number on the x-axis refers to 1 patient in treatment. Patients 6, 11, 12, 13, 14, 15, 19, 21, 26, 36, 37, and 40 received other treatments prior to azathioprine.

Comparing ARR in the "other treatment" group with pretreatment was marginally significant (P=.049), whereas comparing ARR in the azathioprine group with pretreatment (pretreatment and "other treatment" group ARR pooled together) was strongly statistically significant (P<.001) (**Figure 4**).

We further compared mean EDSS score change after treatment was implemented for each group (Figure 4). Patients in the "other treatment" group had a mean (SD) increase of 2.3 (2.8) in EDSS score after each treatment, whereas patients in the azathioprine group had a mean (SD) increase of 0.04 (1.6) in EDSS measures after azathioprine or azathioprine plus prednisone treatment, a statistically significant difference (P=.002) (**Figure 5**) favoring EDSS score stability in the azathioprine group as opposed to patients in the "other treatment" group.

A subgroup evaluation was performed in 12 patients who had initially been treated with other therapies (evaluated as part of the "other treatment" group) and later were given azathioprine with or without prednisone, ie, migrated to the azathioprine group. They remained in the "other treatment" group for a mean (SD) of 22 (15) months and had a mean (SD) EDSS score increase of 1.8 (2.8) during that period (75% worsened, 17% were stable, and only 8% im-

proved) before changing treatment regimen. After a mean (SD) of 31 (13) months receiving azathioprine or azathioprine plus prednisone treatment, these 12 patients had a mean (SD) EDSS score change of −0.2 (1.6), due to improvement in 50% and clinical stabilization in 33%. Two patients kept having relapses even after treatment change: 1 died and the other improved after immunoglobulin pulses every 2 months for 10 months. There was a statistically significant difference between EDSS score changes after implementation of azathioprine treatment in these 12 patients (P=.02). Six patients in the azathioprine group started with azathioprine treatment solely, but relapses were only halted when prednisone was added.

We did not observe any severe adverse events in patients receiving azathioprine. A few patients had minor and manageable adverse effects, such as weight gain, lymphopenia, hepatic enzyme elevations 3 times more than normal values, gastric discomfort, and minor infections.

Three patients were treated with intermittent intravenous immunoglobulin (2 g/kg over a 5-day period) every 2 months, from 6 months to 2 years. One had persistent relapses even taking azathioprine with prednisone, 1 had allergic reactions to azathioprine and cyclosporine and had the drugs discontinued, and the other received 3 courses of immunoglobulin at disease onset. All
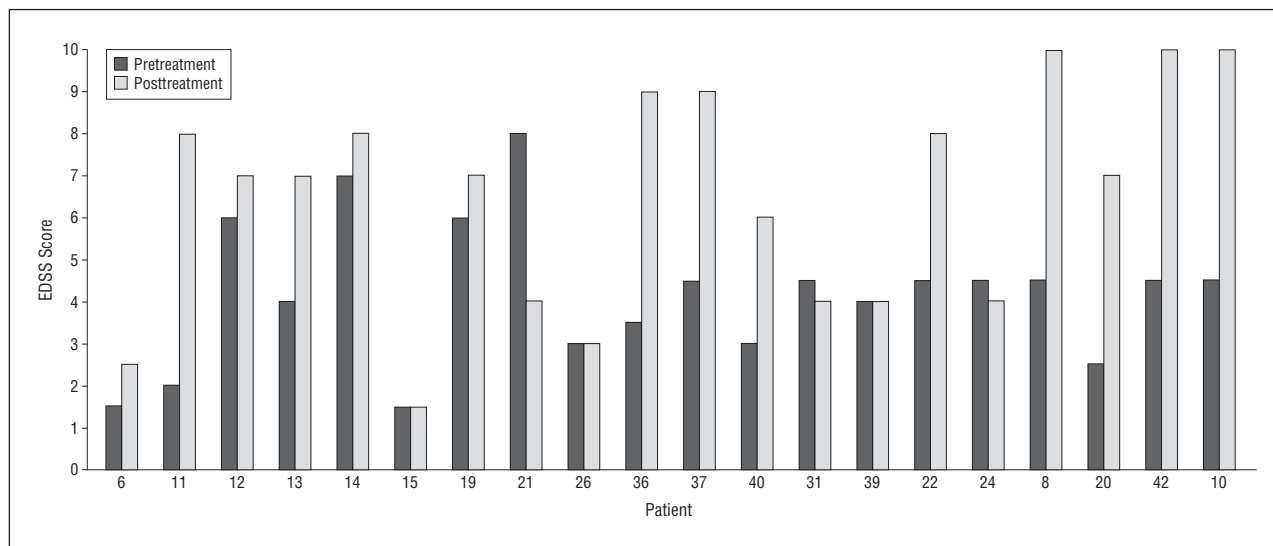
Figure 3. Expanded Disability Severity Scale (EDSS) score pretreatment and posttreatment in the "other treatment" group (patients who received treatment other than azathioprine). Each number on the x-axis refers to 1 patient in treatment. Patients 6, 11, 12, 13, 14, 15, 19, 21, 26, 36, 37, and 40 received other treatments prior to azathioprine.
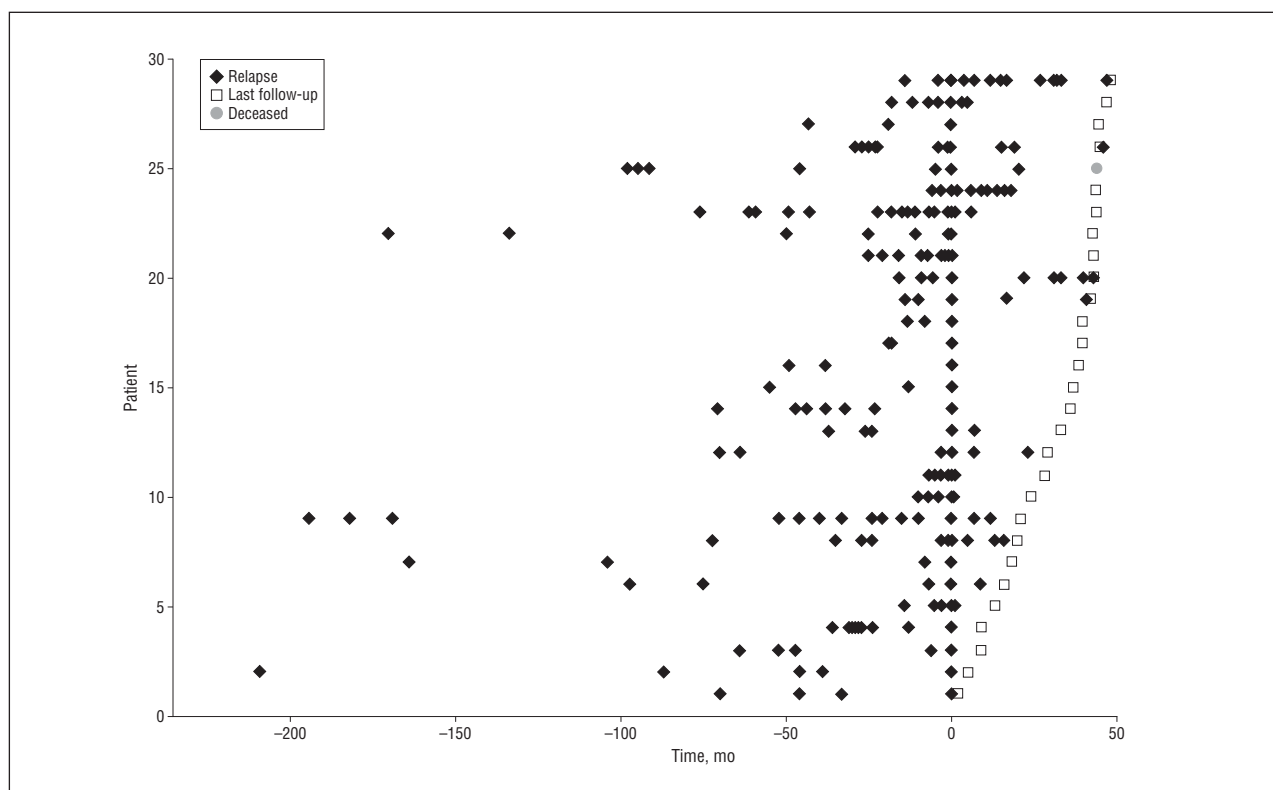

Figure 4. Neuromyelitis optica relapses before and after treatment with azathioprine. Zero on the x-axis indicates the start date of azathioprine treatment. Numbers on the x-axis do not correspond to the same numbers in other Figures. Patients 3, 9, 13, 14, 19, 21, 22, 23, 25, 26, 28, and 29 received other treatments prior to azathioprine. Patient 20 was last seen during a relapse when data were closed for analysis, so his date of last follow-up coincides with a relapse.

3 had relapse reduction and clinical improvement evaluated by the EDSS after intravenous immunoglobulin, independent of prior therapy.

By the time this cohort was closed for analysis, 4 of the 36 patients had died of complications of cervical myelitis (respiratory failure) or sepsis within 8 years from disease onset. Only 1 of the 4 deceased patients received azathioprine plus prednisone during follow-up.

COMMENT

We retrospectively evaluated treatment efficacy for NMO in 36 Brazilian patients and demonstrated that the use of azathioprine solely or with prednisone was able to reduce relapse frequency and disability accumulation in comparison with pretreatment and other treatments
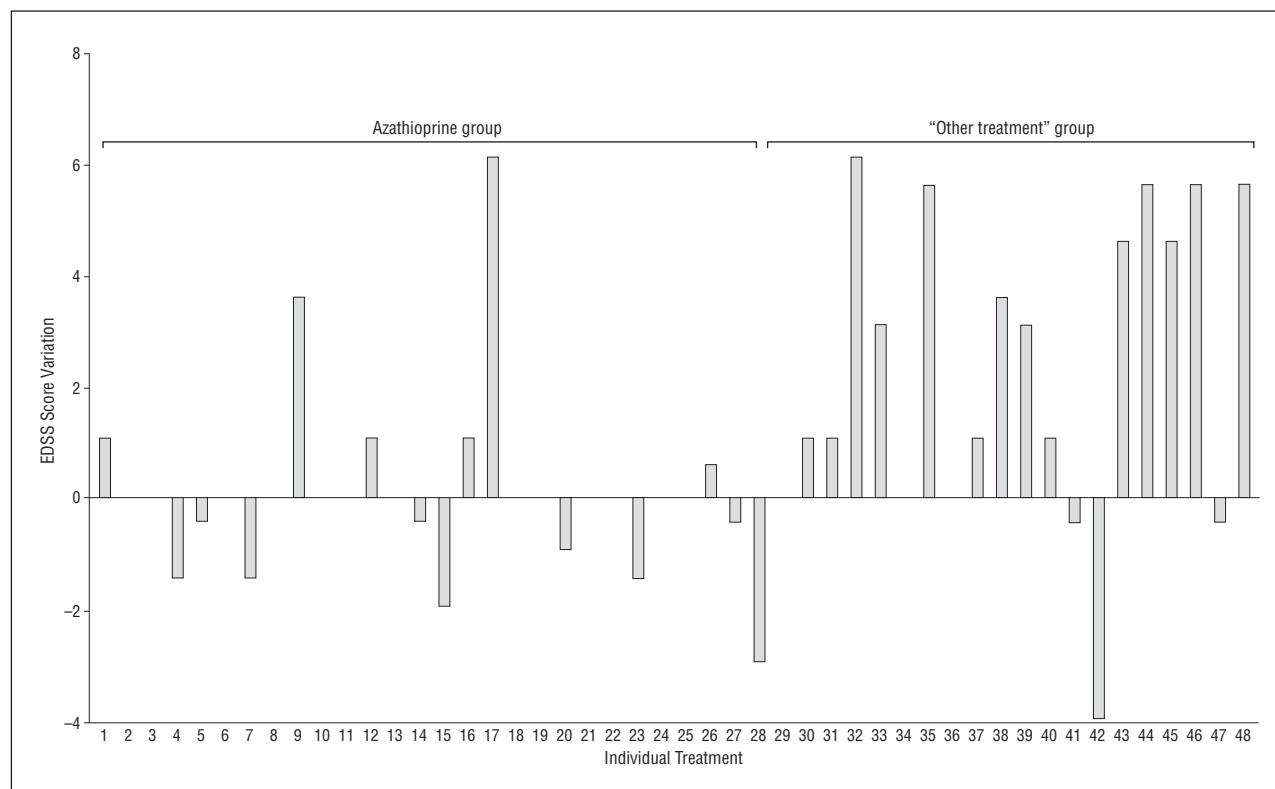
Figure 5. Expanded Disability Severity Scale (EDSS) score variation during treatment. The azathioprine group is patients treated with azathioprine solely or plus prednisone. The "other treatment" group is patients who received treatment other than azathioprine. Treatments 1 to 28 refer to the azathioprine group. Treatments 29 to 48 refer to the "other treatment" group. Numbers on the x-axis do not correspond to the same numbers in other Figures. Bars on the y-axis refer to EDSS score variation while receiving active treatment.

implemented (interferon beta, methotrexate, cyclophosphamide, and prednisone as monotherapy).

The combination of azathioprine and prednisone has been used for preventing relapses and disability progression in patients with NMO since Mandler et al[5] published their report on 7 patients in 1998. Immunosuppressants, such as mitoxantrone,[6] intravenous immunoglobulin,[7] mycophenolate,[12] and plasmapheresis,[19,20] have also been shown to stabilize disability or halt relapses in small series. Recently, efficacy has been demonstrated with the use of rituximab,[10,11,21] a monoclonal antibody that binds to CD20 on B lymphocytes, but the long-term safety of this drug has not been evaluated. Reports on patients with neoplastic diseases and inflammatory disorders who were treated with rituximab and further developed progressive multifocal leukoencephalopathy warrant caution on unrestrictive use of this drug for patients with NMO.[22-24]

Twenty-six of our 29 patients treated in the azathioprine group had their relapse frequency reduced or became relapse free after treatment and most had stable or slightly reduced disability measured by the EDSS. Six patients still had relapses even with continuous azathioprine use and became relapse free after the addition of prednisone, an effect previously described.[8] In a series of 25 patients, Watanabe et al[8] demonstrated that there was a tendency for relapsing when the corticosteroid dose was reduced lower than 10 mg/d, reinforcing the importance of steroid maintenance therapy in conjunction with other drugs in some patients with NMO. We have treated 3 patients with intravenous immunoglobulin, 1 at disease onset, 1 whose treatment with azathioprine plus prednisone failed, and the other who discontinued azathioprine and later cyclosporine treatment because of allergic reactions. All 3 had their disease stabilized with intravenous immunoglobulin.

Patients in the "other treatment" group had a slight ARR reduction, but their EDSS score progressed while receiving treatment, suggesting that relapses while receiving azathioprine treatment were either less severe or patients had a better response to pulse methylprednisolone, favoring neurological recovery. Indeed, NMO relapses are known to be more severe when compared with MS and seem to be the predominant factor of disability progression,[15] since a degenerative process invariably found in MS appears not to occur in patients with NMO.[25,26] Therefore, relapse control should be the crucial goal in the management of patients with NMO.

Neuromyelitis optica is a rare disease; thus, prospective randomized controlled trials evaluating drug regimens for NMO are difficult to perform. Maintenance treatment remains based on small retrospective series,[5-9] such as this one, and expert opinions.[27] The recommended therapy for relapses is pulse intravenous methylprednisolone and intravenous immunoglobulin or plasmapheresis for selected patients.[27] Neuromyelitis optica IgG has been shown to predict future relapses in patients with a single attack of long, extending cord lesions or recurrent optic neuritis,[28,29] and 3 series suggest that its positivity or titer are related to acute episodes,[30-32] but its serial use for monitoring disease status and treatment

response is under research and validation. Because of the retrospective nature of this study and the fact that all of our NMO-IgG test samples came from patients seen in 2007, when treatment with azathioprine had already been implemented in most of our patients, the relationship between NMO-IgG status and disease severity could not be established in this analysis.

Although we evaluated a relatively large number of patients and treatments compared with other series, a retrospective study is subject to some bias. First, some relapses might have been missed if patients did not recall them during appointments; second, assessment of individual therapies in the "other treatment" group could not be done since they were grouped together in the analysis; and third, 2 patients in the azathioprine group and 1 in the "other treatment" group received intravenous immunoglobulin for severe relapses. Nonetheless, the latter 3 patients count for less than 5% of all treatments evaluated and hence had little influence on the overall results. A prospectively designed study should be performed to minimize these biases.

In summary, our study demonstrates a therapeutic benefit of azathioprine and prednisone as a maintenance therapy for patients with NMO. In this series, azathioprine as monotherapy or with prednisone was able to reduce relapse frequency and halt disability progression in the majority of patients treated, with minor and manageable adverse effects. Prospective studies focusing on prognostic factors and treatment responses to different and new agents, such as rituximab, other monoclonal antibodies, and intravenous immunoglobulin, should be performed to identify patients who should receive azathioprine with prednisone only or a more aggressive therapy.

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REFERENCES

1. Jacob A, Matiello M, Wingerchuk DM, Lucchinetti CF, Pittock SJ, Weinshenker BG. Neuromyelitis optica: changing concepts. *J Neuroimmunol.* 2007;187(1-2):126-138.
2. Lucchinetti CF, Mandler RN, McGavern D, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain.* 2002;125(pt 7):1450-1461.
3. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med.* 2005;202(4):473-477.
4. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet.* 2004;364(9451):2106-2112.
5. Mandler RN, Ahmed W, Dencoff JE. Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. *Neurology.* 1998;51(4):1219-1220.
6. Weinstock-Guttman B, Ramanathan M, Lincoff N, et al. Study of mitoxantrone for the treatment of recurrent neuromyelitis optica (Devic disease). *Arch Neurol.* 2006;63(7):957-963.
7. Bakker J, Metz L. Devic's neuromyelitis optica treated with intravenous gamma globulin (IVIG). *Can J Neurol Sci.* 2004;31(2):265-267.
8. Watanabe S, Misu T, Miyazawa I, et al. Low-dose corticosteroids reduce relapses in neuromyelitis optica: a retrospective analysis. *Mult Scler.* 2007;13(8):968-974.
9. Papeix C, Vidal JS, de Seze J, et al. Immunosuppressive therapy is more effective than interferon in neuromyelitis optica. *Mult Scler.* 2007;13(2):256-259.
10. Cree BA, Lamb S, Morgan K, Chen A, Waubant E, Genain C. An open label study of the effects of rituximab in neuromyelitis optica. *Neurology.* 2005;64(7):1270-1272.
11. Capobianco M, Malucchi S, di Sapio A, et al. Variable responses to rituximab treatment in neuromyelitis optica (Devic's disease). *Neurol Sci.* 2007;28(4):209-211.
12. Jacob A, Matiello M, Weinshenker BG, et al. Treatment of neuromyelitis optica with mycophenolate mofetil: retrospective analysis of 24 patients. *Arch Neurol.* 2009;66(9):1128-1133.
13. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology.* 1999;53(5):1107-1114.
14. Ghezzi A, Bergamaschi R, Martinelli V, et al; Italian Devic's Study Group (IDESG). Clinical characteristics, course and prognosis of relapsing Devic's neuromyelitis optica. *J Neurol.* 2004;251(1):47-52.
15. Bichuetti DB, Oliveira EM, Souza NA, Rivero RL, Gabbai AA. Neuromyelitis optica in Brazil: a study on clinical and prognostic factors. *Mult Scler.* 2009;15(5):613-619.
16. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol.* 2005;58(6):840-846.
17. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology.* 2006;66(10):1485-1489.
18. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* 1983;33(11):1444-1452.
19. Watanabe S, Nakashima I, Misu T, et al. Therapeutic efficacy of plasma exchange in NMO-IgG-positive patients with neuromyelitis optica. *Mult Scler.* 2007;13(1):128-132.
20. Weinshenker BG. Plasma exchange for severe attacks of inflammatory demyelinating diseases of the central nervous system. *J Clin Apher.* 2001;16(1):39-42.
21. Jacob A, Weinshenker BG, Violich I, et al. Treatment of neuromyelitis optica with rituximab: retrospective analysis of 25 patients. *Arch Neurol.* 2008;65(11):1443-1448.
22. Bonavita S, Conforti R, Russo A, et al. Infratentorial progressive multifocal leukoencephalopathy in a patient treated with fludarabine and rituximab. *Neurol Sci.* 2008;29(1):37-39.
23. Harris HE. Progressive multifocal leucoencephalopathy in a patient with systemic lupus erythematosus treated with rituximab. *Rheumatology (Oxford).* 2008;47(2):224-225.
24. Kranick SM, Mowry EM, Rosenfeld MR. Progressive multifocal leukoencephalopathy after rituximab in a case of non-Hodgkin lymphoma. *Neurology.* 2007;69(7):704-706.
25. Bichuetti DB, Rivero RL, de Oliveira EM, et al. White matter spectroscopy in neuromyelitis optica: a case control study. *J Neurol.* 2008;255(12):1895-1899.
26. Wingerchuk DM, Pittock SJ, Lucchinetti CF, Lennon VA, Weinshenker BG. A secondary progressive clinical course is uncommon in neuromyelitis optica. *Neurology.* 2007;68(8):603-605.
27. Wingerchuk DM. Diagnosis and treatment of neuromyelitis optica. *Neurologist.* 2007;13(1):2-11.
28. Weinshenker BG, Wingerchuk DM, Vukusic S, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. *Ann Neurol.* 2006;59(3):566-569.
29. Matiello M, Lennon VA, Jacob A, et al. NMO-IgG predicts the outcome of recurrent optic neuritis. *Neurology.* 2008;70(23):2197-2200.
30. Takahashi T, Fujihara K, Nakashima I, et al. Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titre. *Brain.* 2007;130(pt 5):1235-1243.
31. Weinstock-Guttman B, Miller C, Yeh E, et al. Neuromyelitis optica immunoglobulins as a marker of disease activity and response to therapy in patients with neuromyelitis optica. *Mult Scler.* 2008;14(8):1061-1067.
32. Jarius S, Paul F, Franciotta D, et al. Mechanisms of disease: aquaporin-4 antibodies in neuromyelitis optica. *Nat Clin Pract Neurol.* 2008;4(4):202-214.