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Treatment of Neuromyelitis Optica: Review and Recommendations

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Abstract

Neuromyelitis optica (NMO) is an autoimmune demyelinating disease preferentially targeting the optic nerves and spinal cord. Once regarded as a variant of multiple sclerosis (MS), NMO is now recognized to be a different disease with unique pathology and immunopathogenesis that does not respond to traditional MS immunomodulators such as interferons. Preventive therapy in NMO has focused on a range of immunosuppressive medications, none of which have been validated in a rigorous randomized trial. However, multiple retrospective and a few recent prospective studies have provided evidence for the use of six medications for the prevention of NMO exacerbations: azathioprine, rituximab, mycophenolate mofetil, prednisone, methotrexate and mitoxantrone. This review provides a comprehensive analysis of each of these medications in NMO and concludes with a set of recommended consensus practices.

Keywords

Neuromyelitis optica; aquaporin 4; drug therapy; immunosuppression

Introduction

Neuromyelitis optica (NMO), an inflammatory demyelinating disease of the central nervous system, is dominated by relapsing episodes of optic neuritis and transverse myelitis, manifestations that may also occur in multiple sclerosis (MS). The most widely accepted diagnostic criteria for NMO (Wingerchuk, Lennon et al. 2006) are based on these clinical features and additional specificity criteria that discriminate patients with NMO from those with MS, the most specific of which is an IgG autoantibody biomarker that targets the aquaporin-4 channel (NMO-IgG) (Lennon, Kryzer et al. 2005). The detection of this

biomarker, now thought to be directly pathogenic (Hinson, Pittock et al. 2007; Bennett, Lam et al. 2009; Bradl, Misu et al. 2009; Kinoshita, Nakatsuji et al. 2010; Saadoun, Waters et al. 2011), distinguishes NMO from other demyelinating disorders and is the first definitive biomarker of a CNS demyelinating disease. NMO-IgG seropositive patients with a history of optic neuritis or transverse myelitis who do not meet full clinical criteria are classified as having NMO Spectrum Disorder (NMOSD), but are treated identically to clinically definite NMO.

Disabling sequelae of NMO result from accumulating damage during acute attacks, rather than from a supervening progressive course, which is the usual case in MS (Wingerchuk, Pittock et al. 2007). Accordingly, relapse prevention is a therapeutic priority. There are no prospective randomized clinical trials offering class I evidence to direct therapy (Sato, Callegaro et al. 2012); thus, treatment decisions are largely guided by case series and expert opinions. Treatments used to date for NMO have generally been immunosuppressive drugs rather than immunomodulatory agents that are most commonly used for MS.

This review focuses on published evidence for optimal NMO management. Treatment for NMO includes management of acute attacks to promote recovery, prevention of NMO exacerbations (i.e. initiation of long-term maintenance immunosuppression), prevention and monitoring of adverse effects, and decisions regarding switching therapy due to breakthrough disease or lack of tolerability. Symptomatic treatments will not be discussed further except to mention here that paroxysmal tonic spasms occur frequently in NMO patients following myelitis and are extremely sensitive to low dose anticonvulsant and antispasmodic medication.

Treatment of acute NMO events

In the acute setting of an initial presentation or an exacerbation of NMO, treatment is focused on minimizing irreversible damage to the CNS and restoring neurologic function. Each verified clinical attack warrants treatment as soon as clinical symptoms arise. The standard of care for the treatment of an acute optic neuritis or transverse myelitis associated with NMO is high dose intravenous methylprednisolone at a daily dose of 1000 mg for at least three to five days. Although there are no published data on tapering prednisone following an exacerbation, there is consensus that a prednisone taper for 2 - 6 months may be useful when recovery is slow or incomplete. If the patient does not clinically improve with steroids alone, plasma exchange has been demonstrated to be effective including in a randomized, double-masked clinical trial in patients with severe demyelinating disease albeit not targeting specifically NMO (Weinshenker, O'Brien et al. 1999; Watanabe, Nakashima et al. 2007; Bonnan, Valentino et al. 2009). Typically, 5 cycles of plasma exchange that each remove a total of 1.0 – 1.5 volumes of circulating plasma are used for treatment of optic neuritis and transverse myelitis that did not respond to steroids alone. For resistant cases of persistent inflammation without improvement after both steroids and plasma exchange, escalation to cytoablative therapy such as intravenous cyclophosphamide has been reported as effective in a retrospective study of idiopathic transverse myelitis patients (Greenberg, Thomas et al. 2007). Intravenous immunoglobulin (IVIg) therapy has not been reliably demonstrated to be effective in the acute treatment of NMO exacerbations, though several case reports on successful relapse prevention with IVIg along with its efficacy as an alternative to plasma exchange in neurological conditions (e.g. acute inflammatory demyelinating polyneuropathy) might warrant its further investigation as an acute therapy (Bakker and Metz 2004; Okada, Tsuji et al. 2007).

Preventative Therapy: General Principles

Guidelines for preventive therapy in NMO have been crafted to balance effectiveness with short- and long-term side effects, but clinicians must also consider age, associated medical conditions, functional status, access to medications and response to previous preventative therapies. Several series have reported findings suggesting poor efficacy or harmful effects from immunomodulating agents used for MS, including beta-interferons (Papeix, Vidal et al. 2007; Shimizu, Palace, Leite et al. 2010; Hatanaka et al. 2010; Uzawa, Mori et al. 2010), natalizumab (Barnett, Prineas et al. 2012; Kleiter, Hellwig et al. 2012) and fingolimod (Min, Kim et al. 2012). Therefore, we strongly recommend avoiding these medications for NMO patients. We recommend preventive therapy with one of the six immunosuppressive regimens that have multiple studies reporting efficacy in NMO - azathioprine, rituximab, mycophenolate mofetil, methotrexate, prednisone and mitoxantrone. No randomized controlled trials of preventive agents for NMO have been published, in part due to the relative rarity of the disease. As a result, we have developed treatment algorithms largely based on small prospective or retrospective series of off-label use of various agents. A concise list of the off-label studies that provide evidence of a therapeutic effect in preventing NMO exacerbations is provided in Table 1.

The duration of preventive treatment in NMO that is needed has not been adequately studied. Indeed for many autoimmune diseases including MS, duration of treatment is not adequately addressed in the literature. Furthermore, it has only been in the past 5-10 years that NMO has been adequately defined as a disease entity and treatment studies have clarified the drugs that are and are not effective. The natural history of NMO is relatively unpredictable, with relapses tending to occur in clusters after periods of remission that can last years even without treatment. Absence of new clinical relapses during an extended period of preventive therapy (e.g., more than 2 years) is viewed as probable treatment success. The absence of a valid therapeutic biomarker results in Weinshenker and colleagues suggested that NMO-IgG seropositive patients who present with a first ever attack of longitudinally extensive transverse myelitis should be treated with immunosuppression for five years. This time period is arbitrary but attempts to balance the potential benefits of therapy during a period of higher relapse risk (the first 2-3 years after presentation) against the risks of long term toxicity, especially treatment related malignancy. For NMO or NMOSD patients with established relapsing disease, long term immunosuppression with the medications discussed below are recommended, and any decision to stop treatment must be based on a careful discussion between the patient and treating physician, taking into account past relapse history (frequency, severity, recovery), treatment toxicity (actual or potential), treatment duration, and external motivating factors (e.g., a woman’s desire to become pregnant). Whether NMO-IgG serology status influences the chance of successful treatment discontinuation after long remission is unclear, however, there are case reports of seropositive individuals experiencing relapses more than a decade apart without treatment, suggesting that such individuals may always face risk of relapse.

Azathioprine

The pro-drug azathioprine is effective in a variety of applications for immunosuppressive therapy, with Food and Drug Administration (FDA)-approved indications including renal transplantation and rheumatoid arthritis. Metabolically downstream of azathioprine, activated 6-mercaptopurine is converted to nucleotide anti-metabolites that inhibit de novo purine synthesis and preferentially hinder B and T lymphocyte proliferation.

In 1998, Mandler and colleagues reported the first prospective study of NMO treatment with azathioprine and prednisone in seven patients (Mandler, Ahmed et al. 1998). Each patient

had disease duration of two years or less and most began treatment within 3 – 6 months of onset. At presentation with attacks of transverse myelitis or optic neuritis and after reaching a diagnosis of NMO, patients were treated with five days of intravenous steroids followed by oral steroids and azathioprine. Prior to treatment, patients were severely disabled (EDSS scores 6.0 - 9.0). Oral prednisone, 1 mg/kg/day, was administered for two months and azathioprine 2 mg/kg/day was added after three weeks. After two months, prednisone was tapered to a maintenance dose of 10 mg per day. By 18 months of treatment, patients were receiving approximately 75-100 mg of azathioprine and 10 mg of prednisone daily. Each patient improved clinically and there were no new neurologic symptoms, exacerbations, or serious adverse events in that short 18-month follow up time period. The mean EDSS score declined from 8.2 to 4.0, indicating marked recovery of ambulation (Mandler, Ahmed et al. 1998). However, as with many of the other trials in this review, baseline EDSS scores were assessed at the time of acute relapse and would be anticipated to decline regardless of treatment. Regression towards the mean may have influenced the results of this study in which patients were treated at the time of active disease, although the disease state of patients is not specified in most of the studies included in this review.

Larger subsequent studies also support the efficacy of azathioprine. Among 58 pediatric NMO patients reviewed by McKeon et al (2008), ten were treated with azathioprine for median follow-up of 42 months, four of whom took prednisone as well; five did not have a new relapse and two others had reduced relapse frequency (McKeon, Lennon et al. 2008). A retrospective review of 25 Brazilian NMO patients on azathioprine by Bichuetti et al (2010) found that azathioprine plus prednisone led to stable disability scores and a meaningful decrease in the annualized relapse rate from 2.1 to 0.6 (Bichuetti, Lobato de Oliveira et al. 2010). The mean azathioprine dose was 2 mg/kg/day (125 mg/day; range 50 – 150 mg/day), and the mean prednisone dose was 23 mg/day (range 5 – 40 mg/day). A similar retrospective study in an Iranian population by Sahraian et al (2010) studied 28 NMO patients who received azathioprine 200 mg/day (approximately 3 mg/kg/day) and noted that the annual relapse rate over a median period of 9 months dropped from 0.99 to 0.4 in the azathioprine group; 57.1% remained relapse free over an average of 18.8 months (Sahraian, Moinfar et al. 2010). A longitudinal evaluation of disability scores was not reported in this study.

The largest experience with azathioprine in NMO to date was reported by Costanzi et al (2011), who retrospectively reviewed 99 NMO/NMO spectrum cases treated with azathioprine over a fifteen year period from 1994-2009 (Costanzi, Matiello et al. 2011). Eighty-six fulfilled 2006 Wingerchuk NMO criteria (Wingerchuk, Lennon et al. 2006) while the remaining cases were AQP4 autoantibody seropositive cases with limited forms of NMO (“NMO spectrum disorders”). Among the 70 patients who had been followed for at least one year, the annualized relapse rate (ARR) decreased when treated with azathioprine either with or without prednisone from 2.20 to 0.52 relapses/year over a median treatment duration of 22 months. The reduction in ARR was less robust in those taking less than 2 mg/kg/day, (pre-treatment ARR 2.09 versus on-treatment ARR 0.82 relapses/year). The mean EDSS and mean visual outcome scores (3.5 and 2, respectively) were stable during treatment. Azathioprine was prescribed alone in 18 patients whose diagnosis occurred during quiescent periods, while concurrent prednisone was initiated to maintain remission in 52 patients who had attacks at treatment initiation. The median prednisone dose was 60 mg/day with a 12-month median taper duration. Prednisone was discontinued in 80% of patients within one year while the remainder had extended courses due to relapses that occurred while attempting to wean prednisone. At the time of these relapses, the median dose was 30 mg (range 1-60 mg/day). Azathioprine was discontinued in 38 patients for reasons including apparent lack of efficacy (13 patients), side effects (22 patients), or lymphoma (3 patients; 2 non-Hodgkin’s and 1 Hodgkin’s). Efficacy was associated with an increase of the mean

corpuscular volume (MCV) by at least 5 points from baseline, although further studies are needed to determine the correlation between rise in MCV and efficacy of azathioprine.

The most frequent side effects of azathioprine in the NMO population included nausea, elevated transaminases, leukopenia, and diarrhea (Costanzi, Matiello et al. 2011). Potential additional adverse effects described in other patients include bone marrow suppression, fatigue, hair loss, and hepatotoxicity (Drugdex Database). Up to 11% of the population in the United States has reduced thiopurine methyltransferase (TPMT) activity leading to azathioprine toxicity (Weinshilboum and Sladek 1980). Therefore, optimally, new patients starting azathioprine should be tested for TPMT activity. Those with mutations affecting TPMT activity may be very sensitive to azathioprine-induced gastrointestinal adverse effects and excessive immunosuppression (Priest, Begg et al. 2006). One should consider an alternative treatment option for heterozygotes with low-normal TPMT activity; if azathioprine is used, these patients require more frequent blood count monitoring and a lower dosage for effective immunosuppression. Homozygotes with low TPMT activity should avoid azathioprine in favor of one of the other treatments discussed below. Long-term use of azathioprine has been associated with myelotoxicity in up to 10% of patients (Gisbert and Gomollon 2008). An increased risk of lymphoma has also been observed in patients with inflammatory gastrointestinal disease on azathioprine (Kandiel, Fraser et al. 2005).

Mycophenolate Mofetil

Mycophenolic acid, the active metabolite of its pro-drug mycophenolate mofetil, is a reversible inhibitor of inosine monophosphate dehydrogenase and thereby hinders *de novo* synthesis of guanosine nucleotides. Unlike most other cells that can recycle purines through a salvage pathway, T- and B-lymphocytes predominantly depend on *de novo* guanosine synthesis and are thus sensitive to mycophenolate. Antibody formation by B-lymphocytes is also suppressed. Though developed for transplant rejection (cardiac, liver, renal), mycophenolate is used in a variety of autoimmune conditions.

In 2006, Falcini and colleagues reported a case of a nine-year-old girl with NMO who sustained clinical remission during two years of treatment with mycophenolate mofetil (Falcini, Trapani et al. 2006). Jacob et al (2009) reported a retrospective case series of 24 patients treated with mycophenolate, including 15 patients meeting NMO diagnostic criteria and 9 patients with seropositive NMO spectrum disease (Jacob, Matiello et al. 2009). Seven were treatment-naive, while the remainder had used various other immunosuppressive or immunomodulatory therapies. The median dose of mycophenolate was 2000 mg/day, ranging from 750 – 3000 mg/day. Patients were contacted at a median of 27 months after beginning mycophenolate treatment. At last follow-up, 19 patients continued treatment; two had discontinued mycophenolate: one received rituximab (personal preference), and the other died (“cardiopulmonary failure; respiratory drive failure and Devic’s disease,” 54 months after starting mycophenolate). In those patients who continued treatment, the ARR declined from 1.28 to 0.09 relapses/year. Further analysis excluding patients with abbreviated treatment durations and the single deceased patient still showed statistical ARR reductions. The EDSS score, however, was unchanged (6.0 pre treatment vs. 5.5 post treatment; $p = 0.17$).

Six patients experienced adverse effects including headache, constipation, bruising, anxiety, hair loss, diarrhea, and leukopenia. Progressive multifocal leukoencephalopathy (PML) was not observed in this study, although it is a potential complication of mycophenolate therapy. Fourteen cases of PML were reported among over 32,000 renal transplant patients who had been taking mycophenolate mofetil (Neff, Hurst et al. 2008) and in four non-transplant lupus

patients on mycophenolate (Molloy 2011). Other rarely occurring safety concerns with mycophenolate in transplant patients include lymphoprolilferative disease, skin malignancies, and severe neutropenia .

Rituximab

Rituximab is a chimeric mouse/human monoclonal antibody directed against the CD20 antigen, an epitope that is expressed on the B-cell lineage from pre B through mature B-cells but absent on plasma cells. Its FDA-approved indications include B-cell lymphomas, chronic lymphocytic leukemia, refractory rheumatoid arthritis, microscopic polyarteritis nodosa, and Wegener's granulomatosis. Although the rationale for rituximab treatment of NMO is based on putative pathogenic antibodies (Lucchinetti, Mandler et al. 2002), rituximab does not target mature plasma cells directly and in MS trials the rapid effect of this drug suggests it mostly affects antibody-independent pathways (Hauser, Waubant et al. 2008). Yet, patients who respond well to rituximab can demonstrate lower titers of NMO-IgG (Jarius, Aboul-Enein et al. 2008).

Cree et al (2005) reported results of a prospective open label rituximab study of eight patients with severe NMO refractory to a variety of immunosuppressive and immunomodulatory therapies (Cree, Lamb et al. 2005). Rituximab was administered in four weekly 375 mg/m^2 infusions, later followed by two weekly 1,000 mg infusions as retreatment upon detecting the return of CD19+ B-cells to the peripheral circulation. Six of the eight patients remained relapse free during an average follow-up of 12 months. The median attack rate declined from 2.6 attacks/patients/year to zero on rituximab. The median EDSS and functional system scores improved, although most patients were treated acutely during an attack and the improvement represents, at least partially, the recovery from acute attacks. This study encouraged further investigations of rituximab in NMO.

Several additional case series also suggest that rituximab reduces relapse rate in NMO. A review of 8 pediatric NMO patients by McKeon et al (2008) found that seven who were treated with rituximab were relapse free during a median follow-up period of twelve months (McKeon, Lennon et al. 2008). A retrospective review of 25 rituximab-treated NMO patients from seven tertiary referral centers reported experience with two regimens that were typically employed: 375 mg/m^2 weekly for four weeks, as recommended for lymphoma treatment (18 patients), and 1000 mg infused twice with two weeks between doses (4 patients; dosing schedule was unreported in 3 patients) as used for treatment of autoimmune diseases (Vose, Link et al. 2001; Emery, Fleischmann et al. 2006; Jacob, Weinshenker et al. 2008). Retreatment doses were initiated either at scheduled 6 to 12 month intervals or upon return of detectable CD19+ B-cell counts, depending on local practice. The median annualized pretreatment relapse rate declined from 1.7 to zero at a median post treatment follow-up of 19 months. EDSS scores stabilized or improved in 80% of the patients. Safety concerns included new or reactivated infections (n=5) and transient infusion related adverse events that were not dose limiting (n=7). Two patients died, one with an active brainstem lesion nine months after the last rituximab infusion and a second from presumed sepsis six months following the last rituximab dose.

Bedi et al. (2011) reported favorable results in a retrospective review of 23 NMO patients treated with rituximab, induced in the first four participants with four weekly intravenous doses of 375 mg/m2 followed by two more infusions of the same dose biweekly every 12 months (Bedi, Brown et al. 2011). The remaining 19 participants were dosed with 1000 mg biweekly every 6 months. In this retrospective review of rituximab in NMO, the median relapse rate declined from 1.87 relapses/patient/year to zero during median follow-up 32.5 months. The median EDSS declined from 7.0 before treatment to 5.5 after treatment.

Seventeen of the patients remained relapse free during the observation period and the remaining six patients each had only one relapse. When relapses occurred, they appeared to be attributable to unplanned prolongation of the interval between rituximab infusions. Adverse events occurred in 7 of 23 patients and included recurrent herpes zoster, a urinary tract infection, two mild respiratory infections, fatigue, transient leukopenia and transient transaminase elevation.

Further experience continues to support rituximab as an effective treatment option for long-term treatment of NMO. Pellkofer et al (2011) followed ten patients treated with up to five cycles of rituximab 1000 mg infused twice, separated by two weeks, with the first subsequent dose following reappearance of peripheral B cells and later doses every 6-9 months (Pellkofer, Krumbholz et al. 2011). Relapse rates declined in eight patients by 80% while EDSS scores were stable. One patient died of cardiovascular failure, which did not appear related to treatment. Other adverse events included infections, including recurrent zoster and pneumonia for two patients who also had mild decreases in immunoglobulin levels. Otherwise, rituximab was generally well tolerated.

In a two-year prospective open label rituximab study, Kim et al (2011) treated 30 patients with rituximab, 24 of whom failed to respond to other therapies, with either 375 mg/m^2 per week for 4 weeks or 1000 mg biweekly infusions and then re-dosed upon reconstitution of CD27+ memory B cells (Kim, Kim et al. 2011). Twenty-eight of the 30 patients had reduction in relapse rate; the mean ARR declined from 2.4 to 0.3 over 24 months; 70% were relapse-free on treatment. The EDSS score declined for all but a single patient. Aquaporin-4 antibody levels also declined. In contrast to previous studies, maintenance rituximab therapy was provided upon the reappearance of peripheral CD27+ memory B cells rather than CD19 cells. CD27+ B cells are markers of antigen-specific memory B cells that differentiate into antibody producing cells upon re-exposure of the antigen (Wingerchuk and Weinshenker 2011). Although a few patients continued to relapse despite depletion of CD27+ B cells below the accepted threshold, the role of CD27+ B cells in NMO pathogenesis warrants further study as a biomarker of response to rituximab therapy. The most common adverse events in this study occurring during the initial infusion were transient hypotension and transient flu-like symptoms; approximately 40% of patients developed at least one mild infection during the course of treatment.

Rituximab induces B-cell activating factor (BAFF), a potential concern and explanation for occasional reports of transient exacerbation of NMO following initial treatment (Nakashima, Takahashi et al. 2011). BAFF levels rose within 2 weeks of the first rituximab infusion in 7 NMO patients treated with rituximab (Nakashima, Takahashi et al. 2011); in 3 of those patients, anti-AQP4 titers concomitantly increased. However, in 4 of those patients, there was a decline in anti-AQP4 titer or no change. Further study is needed to understand the importance of BAFF levels in NMO pathogenesis.

Efficacy and tolerability were generally demonstrated in all studies of rituximab in patients with NMO. The most common infusion related adverse effect is an allergic response that can be mitigated with pre-treatment with a combination of methylprednisolone (125 mg intravenously 30 minutes prior to rituximab), diphenhydramine (25 – 50 mg oral dose) and/or acetaminophen (650 mg oral dose). The most common non-infusion related adverse events among all patients treated with rituximab have been infections (Genentech Product Information). Among patients treated for autoimmune conditions (e.g., systemic lupus erythematosus) or malignancies (e.g., lymphoma) and in association with other immunosuppressive agents, there have been rare reports of progressive multifocal leukoencephalopathy (Carson, Focosi et al. 2009) in patients receiving either concomitant or sequential immunosuppressive drugs. The estimated risk of PML in all patients is now

estimated at 1:25,000; there has not been a PML case reported in association with rituximab use for NMO or MS.

Methotrexate

Methotrexate, an inhibitor of dihydrofolate reductase and folate-dependent enzymes necessary for purine and thymidylate synthesis, is indicated for hematologic malignancies, juvenile rheumatoid arthritis, and severe cases of psoriasis and rheumatoid arthritis. It has been used as therapy for NMO patients although the number of reported cases is fewer than 10 (McKeon, Lennon et al. 2008; Bichuetti, Lobato de Oliveira et al. 2010; Sahraian, Moinfar et al. 2010).

Minagar and colleagues (2000) treated 8 NMO patients with methotrexate in conjunction with prednisone. Four were treated weekly with combined 50 mg of methotrexate intravenously and oral prednisone 1 mg/kg/day (Minagar A 2000). Four others were treated with intravenous methylprednisolone (1 g/day for 10 days) and cyclophosphamide (8 mg/kg/day for 10 days as a loading dose followed by a 700 mg/m^2 maintenance dose q4weeks), three of whom were later switched to methotrexate plus prednisone after treatment failure. Each of the seven methotrexate patients subsequently stabilized, as evidenced by unchanged or reduced EDSS scores.

Oral Corticosteroids

Corticosteroids are the mainstay of acute anti-inflammatory treatment, most typically being administered intravenously in high doses (e.g. 1 gram of methylprednisolone for 3-5 days) for acute exacerbations of NMO. While non-steroidal immunosuppressive agents are the most commonly used as long-term treatment, low-dose corticosteroids have been used as monotherapy for long-term remission-maintenance, as an adjunctive bridge while another initiated immunosuppressive agent escalates to full efficacy, or as adjunctive therapy if another immunosuppressive agent alone is ineffective. Corticosteroids bind to the glucocorticoid receptor in all cells and inducing a wide range of gene expression changes to lead to immunosuppression (Luhder and Reichardt 2009).

Watanabe et al (2007) retrospectively investigated a series of 25 Japanese patients treated with low-dose prednisone monotherapy (Watanabe, Misu et al. 2007). Within-patient efficacy was evaluated during treatment versus a period of no steroid therapy. Maintenance doses ranged from 2.5 mg/day (5 mg on alternate days) to 20 mg daily. Annualized relapse rates, maintenance doses necessary for sustained remission, and autoantibody status were assessed. The median observation period of corticosteroid treatment was 19 months while the median observation period without prednisone use was 45 months. The median ARR during dropped from 1.48 relapses/year pre-treatment to 0.49 during treatment with low-dose prednisone. Relapses were more frequent at prednisone doses at or below 10 mg/day. While no adverse events were noted in this study, long-term steroid use is associated with hyperglycemia, hypertension, insomnia, mood disturbances, truncal weight gain, osteoporosis and glaucoma, and possibly impaired growth in children.

Mitoxantrone

Mitoxantrone, an anthracenedione antineoplastic drug that intercalates DNA and inhibits topoisomerase II, is indicated for acute myeloid leukemia (among other malignancies) and used in aggressive relapsing and sometimes secondary progressive MS. Mitoxantrone was first studied in five patients with NMO by Weinstock-Guttman et al (2006). Infusions of 12 mg/m^2 monthly for six months were followed by three subsequent treatments at three-month intervals. During a two-year follow-up period, two patients experienced relapses. One

initially improved after the induction protocol but subsequently had a relapse and later died due to pulmonary embolism that was thought to be unrelated to treatment. The second patient developed a relapse shortly after induction treatment. These two patients had only three months of induction therapy; the remaining patients received a modi ed induction course for six months. Their EDSS scores improved and no patient experienced a relapse. The small sample size precluded meaningful statistical analysis of relapse rate or EDSS changes. Adverse events included one patient with reduced cardiac ejection fraction after a cumulative dose of 86 mg/m^2 and other instances of transient leukopenia and a recurrent urinary tract infection (Weinstock-Guttman, Ramanathan et al. 2006).

Kim et al (2011) have recently reported efficacy of mitoxantrone for a series of 20 NMO spectrum patients (Kim, Kim et al. 2011). They treated seven patients with three monthly cycles of 12 mg/m^2 of IV mitoxantrone infusions followed by maintenance doses of 6-12 mg/m^2 every three months. After three patients continued to experience relapses, the regimen was modified for the subsequent 13 patients: induction consisted of six monthly cycles of 12 mg/m^2 infusions followed by 6-12 mg/m^2 every three months up to a maximum dose of 120 mg/m^2. The median pretreatment ARR declined from 2.8 to 0.7 and the mean EDSS score declined from 5.6 to 4.4. Nausea was the most common adverse event; elevated liver function tests, amenorrhea, leukopenia, leukemia and minor infections were also noted. One patient discontinued mitoxantrone due to an asymptomatic decline in the left ventricular ejection fraction after a cumulative dose of 72 mg/m^2, but no other concerning cardiac or life-threatening events were noted. Because of the risk of major side effects including irreversible cardiotoxicity and leukemia, mitoxantrone is generally not considered an initial treatment option.

Summary and Current Recommendations

Based on relatively small retrospective and prospective case series, several treatments appear to be likely effective in preventing attacks and stabilizing disability in NMO patients. Such studies provide a limited but helpful insight on treatment effect and tolerability. They are limited by lack of randomization and lack of adjustments for potentially important covariates of ARR or disability. Given the rarity of NMO, randomized studies will likely require participation of many centers. Prospective trials in treatment-naive patients are still required to corroborate the efficacy suggested from nonrandomized studies, compare the effectiveness of various regimens to each other, and to determine optimal first-line treatment. Azathioprine, mycophenolate mofetil, prednisone, rituximab, and mitoxantrone are the most extensively studied treatments thus far. Despite the inherent limitations of studies comparing pre and post-treatment attack rates, the treatments appear moderately or highly effective. We recommend starting with one of four options for first-line monotherapy treatments for NMO: azathioprine, mycophenolate, rituximab, or prednisone, in doses and schedules according to Table 2. Cost, availability, patient choice, route of administration, side effects, and the prescribing physician’s familiarity with the specific agent will also influence the treatment decision.

Depending on the severity of a breakthrough attack and the duration of the previous remission, every exacerbation should prompt a re-evaluation of the current treatment regimen. Potential reasons for treatment failure in NMO include suboptimal dosage, inadequate duration of treatment, or, in the case of rituximab, possible anti-chimeric antibodies to the drug. Breakthrough disease should also prompt evaluation of patient adherence, which may be influenced by tolerability and side effects. Resolution of these issues may allow one to continue the current therapy or may ultimately lead to a decision to switch to a different immunosuppressive medication. For each treatment, we propose criteria for “treatment failure” that would warrant consideration of changing to an alternative

treatment. Several other first-line options detailed in the text above exist for therapy in NMO if one agent fails to control disease.

Future therapy for the treatment of NMO is aimed at several pathways involved in disease pathogenesis. A potentially exciting antigen-specific treatment has been developed. Aquaporumab is a human monoclonal antibody against AQP4 that has been engineered to abrogate toxic Fc effector functions and to avidly bind to endogenous AQP4 so as to prevent NMO-IgG from binding to its target antigen (Tradtrantip, Zhang, et al. 2012). New or re-purposed drugs that target B cells and T cells may be useful in treating acute NMO attacks and suppressing ongoing disease (Van Herle, Behne, et al. 2012). Neutrophils and eosinophils are being targeted as downstream effector cells to potentially prevent the CNS damage caused by recruited granulocytes (Herges, de Jong, et al. 2012). For those patients with previous, debilitating spinal cord or optic nerve damage, neural and glial stem cells could provide some hope for regeneration in the future.

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Highlights

1. This review discusses the evidence supporting treatment of neuromyelitis optica.
2. Acute and preventive therapies are addressed.
3. Consensus recommendations for use of various immunosuppressive agents is provided.

Table 1

Trials supporting the use of immunosuppressive drugs in the treatment of NMO.

Drug	Date	Lead Author	Location	Population size
Azathioprine	1998	Mandler	United States	7
	2008	McKeon	United States	10
	2010	Bichuetti	Brazil	25
	2010	Sarhaian	Iran	28
	2011	Constanzi	United States	99
Mycophenolate	2009	Jacob	United States	24
Rituximab	2005	Cree	United States	8
	2008	McKeon	United States	8
	2008	Jacob	United States	25
	2011	Bedi	United States	23
	2011	Pellkofer	Germany	10
	2011	Kim	Korea	30
Methotrexate	2000	Minagar	United States	8
Oral corticosteroids	2007	Watanabe	Japan	11
Mitoxantrone	2006	Weinstock-Guttman	United States	5
	2011	Kim	Korea	20

Table 2

Primary treatment options for NMO

Medication	Dose	Route	Schedule	Monitoring	Treatment Change Considerations
*Azathioprine (+ prednisone)	2 - 3 mg/kg/ day (+ 30 mg/ day)	Oral	1-2 daily doses (prednisone taper after 6 – 9 months)	Initial: TPMT activity assay. Periodic: Mean corpuscular volume (MCV) increase of at least 5 points from baseline; monthly liver function tests for first 6 months, then twice yearly; maintain absolute neutrophil counts > 1000 cells/μL.	If MCV did not rise on initial dose, consider increase by 0.5 – 1 mg/kg/day. Or consider increasing dose or duration of prednisone. *Switch to:* Rituximab or mycophenolate mofetil.
*Mycophenolate mofetil (+ prednisone)	1000 – 3000 mg/day (+ 30 mg/ day)	Oral	Two daily doses (prednisone taper after 6 months)	Absolute lymphocyte count (ALC) target of 1.0 – 1.5 k/μL; monthly liver function tests for first 6 months, then twice yearly	If ALC goal cannot be reached at maximum dose of 3000 mg/day, observe closely for relapse. *Switch to:* Rituximab
*Rituximab	1000 mg for adults; 375 mg/m^2 for children	IV	Two doses of 1000 mg 14 days apart or 4 weekly doses of 375 mg/m^2 for children; each pair can be given routinely q6 months without monitoring of CD19 counts, or by following CD19+ cell counts and dosing as soon as it exceeds 1%.	Monthly CD19+ B cells starting immediately post-infusion; if CD19+ count exceeds 1% of total lymphocytes, re-dose with rituximab. If suppression of CD19+ count does not occur, consider switching to alternative. Monitor immunoglobulins yearly.	Relapses during first 3 weeks of initial dosing are not failures. Relapses when CD19+ count is greater than 1% are failures due to undertreatment. *Switch to:* Azathioprine or mycophenolate mofetil.
*Prednisone	15-30 mg	Oral	Daily dose; taper after 1 year	Blood sugar to avoid hyperglycemia, blood pressure; DEXA scans as appropriate for osteoporosis; vitamin D and calcium supplementation as needed; consider proton pump inhibitors for gastric protection	Prednisone monotherapy not recommended for long-term use beyond 1.5 years. *Switch to:* Azathioprine, mycophenolate or rituximab.
Methotrexate	15 – 25 mg	Oral	Weekly	Check for liver toxicity every 3 months; recommend folate 1 mg supplementation; avoid non-steroidal anti-inflammatory drugs.	*Switch to:* Azathioprine, mycophenolate mofetil or rituximab
Mitoxantrone	12 mg/m^2	IV	Monthly ×6, followed by monthly maintenance dose of 6 mg/m^2. Total cumulative dose no greaterthan 120 mg/m^2.	Baseline and monthly echocardiogram to exclude patients and discontinue drug if left ventricular ejection fraction < 50%.	Only recommended as second line agent. The maximum cumulative dose is 140 mg/m^2. *Switch to:* Azathioprine, mycophenolate mofetil or rituximab

*Recommended first-line agent