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The Treatment of Neuromyelitis Optica

Markus C. Kowarik, MD, John Soltys, BS, and Jeffrey L. Bennett, MD, PhD

Departments of Neurology (MCK, JLB) and Ophthalmology (JS, JLB), University of Colorado Denver, Denver, Colorado; and Neuroscience Program (MCK, JS, JLB), University of Colorado Denver, Denver, Colorado.

Abstract

Neuromyelitis optica (NMO) is an autoimmune disorder of the central nervous system directed against astrocytes. Initially diagnosed in individuals with monophasic or relapsing optic neuritis and transverse myelitis, NMO is now recognized as a demyelinating disorder with pleiotropic presentations due to the identification of a specific autoantibody response against the astrocyte water channel aquaporin-4 in the majority of individuals. As visual impairment and neurologic dysfunction in NMO are commonly severe, aggressive treatment of relapses and prophylactic immunomodulatory therapy are the focus of treatment. Although there are no approved treatments for NMO, medications and therapeutic interventions for acute and chronic treatment have been the subject of retrospective study and case reports. The goal of this review is to familiarize the reader with biologic and clinical data supporting current treatments in NMO and highlight future strategies based on advancements in our understanding of NMO pathogenesis.

NEUROMYELITIS OPTICA DIAGNOSIS

Neuromyelitis optica (NMO) is a rare inflammatory disorder of the central nervous system (CNS) that commonly presents with optic neuritis (ON) or transverse myelitis (TM) (1,2). The prevalence of NMO varies considerably across studies (3–57 per million population) (3). In North America, Australia, and Europe, NMO patients represent a small fraction (1%–2%) of Caucasians with inflammatory white matter disease; however, in Asia and the West Indies, the percentage rises to almost 50% of demyelinating disorders (1,4). Initially considered a variant of multiple sclerosis (MS), NMO is now clearly recognized to be a separate disorder with distinct clinical, radiographic, pathologic, and serologic features. Within 5 years of diagnosis, more than 50% of NMO patients develop severe visual impairment (5–7); therefore, for the neuro-ophthalmologist, early diagnosis and aggressive treatment of NMO is critical for the preservation of visual and neurologic function.

The current criteria for the diagnosis of NMO require a clinical history of ON and TM accompanied by at least 2 of 3 supportive criteria: 1) brain magnetic resonance imaging (MRI) not diagnostic of MS at disease onset, 2) spinal MRI with a contiguous lesion 3

segments, and 3) aquaporin-4 immunoglobulin G (AQP4-IgG) seropositivity (8). In NMO, the clinical presentations of ON and TM may be simultaneous or sequential, although the frequency of AQP4-IgG seropositivity is significantly lower in individuals with simultaneous ON and TM (9). The high specificity of AQP4-IgG for NMO has permitted the identification of seropositive patients with spatially limited or atypical presentations. Termed “NMO spectrum disease,” AQP4-IgG seropositive individuals with isolated ON, longitudinally extensive TM, recurrent ON or TM, protracted nausea and vomiting, narcolepsy, and encephalopathy are considered to have *formes frustes* of disease (1,10).

Certain clinical, laboratory, and MRI findings may also raise clinical suspicion for NMO. For ON, these include patients with severe vision loss (<20/200) or visual field depression, poor visual recovery, severe and diffuse peripapillary retinal nerve fiber layer loss, and MRI findings of posterior optic nerve or chiasm involvement of extensive visual pathway lesions (11–17). For TM, the presence of a longitudinally extensive spinal cord lesion or central cord involvement should raise suspicion for NMO. Cerebrospinal fluid (CSF) findings suggestive of NMO include a pleocytosis greater than 50 cells per microliter, a high percentage of polymorphonuclear cells, or the presence of eosinophils (18). In rare instances, AQP4-IgG has been reported to be restricted to the CSF (19). MRI features of brain lesions characteristic of NMO mirror the periventricular and hypothalamic localization of AQP4 and are more commonly found around the third and fourth ventricle and the aqueduct of Sylvius than the lateral ventricles and corpus callosum as in MS (20).

NEUROMYELITIS OPTICA PATHOPHYSIOLOGY

Understanding the pathophysiology of NMO is fundamental in providing a framework for the treatment and the design of new therapies. Active NMO lesions demonstrate perivascular IgG, IgM, and C9neo deposition in a “rim” or “rosette-mesh” pattern, thickened and hyalinized vessels, and heavy immune cell infiltrate, composed primarily of neutrophils, eosinophils, and macrophages (21). CD3⁺ and CD8⁺ T-cell infiltration is rare, and natural killer cells are sparse in lesions (22). Possible features of glutamate excitotoxicity and disturbed water homeostasis are also observed (23,24). All NMO lesions show a widespread and early loss of AQP4 immunoreactivity, in contrast to MS lesions where AQP4 immunoreactivity is often increased (25–27).

Early NMO lesions reveal preserved myelin despite a prominent loss of the astrocytes (28). In lesioned areas devoid of astrocytes, oligodendrocytes displayed nuclear chromatin condensation indicative of apoptosis. Additional regions of reparative gliosis are highlighted by the presence of unipolar and bipolar glial fibrillary acidic protein-positive, AQP4-negative astrocyte progenitors, indicating that demyelination in NMO is secondary to the acute destruction of perivascular astrocytes. Despite the strong evidence connecting demyelination to astrocyte loss, the link between neuronal dysfunction and astrocyte, oligodendrocyte or inflammatory pathology remains unclear. The recent identification of multiple regions of distinct histopathology within NMO lesions suggests that the disruption of glial–neuronal interactions may play an important role in NMO lesion evolution (29).

Neuromyelitis Optica Experimental Models

This identification of AQP4 as the antigenic target in the majority of NMO cases has facilitated the development of experimental laboratory models for the investigation of lesion pathogenesis and the development of highly effective, targeted therapies. In support of these models, multiple lines of evidence now support AQP4-IgG binding as an initiating pathogenic event in NMO. First, AQP4-IgG is highly specific (97%–100%) for NMO (30), and serum and CSF AQP4-IgG titers correlate with spinal cord lesion size (31). Second, current therapies designed to reduce humoral immune activity, such as plasma exchange and B-cell depletion, ameliorate both acute and chronic disease activity (32,33). And third, NMO serum and recombinant AQP4 antibodies derived from clonally expanded NMO CSF plasmablasts can reproduce NMO-specific pathology in ex vivo and in vivo NMO models of disease (34–37).

To date, an ideal animal model of NMO with spontaneous AQP4-targeted ON and TM has yet to be created. Short of this goal, a variety of in vivo, ex vivo, and in vitro experimental systems have been used. In vivo, AQP4-IgG is co-injected into murine brain with immune cells and/or human complement proteins (36,38) or transfused following the induction of experimental autoimmune encephalomyelitis (34,35). These models recapitulate major features of human lesions, including the temporal progression from astrocyte loss to demyelination with complement deposition, immune cell infiltration, and axonal injury. An ex vivo spinal cord explant model has been used to complement the in vivo injection model and characterize mechanisms and immune cell populations mediating astrocyte damage and demyelination (37). In vitro, AQP4-IgG-mediated physiologic changes, such as glutamate excitotoxicity and water transport, are studied on primary astrocyte cell lines (39,40), cell lines transfected with AQP4 (23,40), or purified reconstituted vesicles (41). Although each model has intrinsic limitations, they have proven to be extremely valuable in expanding our knowledge of the mechanisms and progression governing NMO pathogenesis.

Neuromyelitis Optica Lesion Formation and Repair

Multiple lines of evidence support a primary role for antibody effector function in inducing astrocyte damage in NMO. In vitro, ex vivo, and in vivo NMO models have independently demonstrated that AQP4-IgG can induce complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC) in the presence of complement proteins or immune cells (Fig. 1) (34,37,38,42,43). This is not unexpected, as AQP4-IgG is predominantly IgG1 (42,44) and strongly activates the classical complement cascade through binding the complement protein C1q (45,46). C1q activation produces a proteolytic cascade that ultimately results in the formation of the membrane attack complex (MAC) and cell lysis. IgG1 also binds Fc receptors (FcRs) that activate ADCC. FcRs are present on a variety of immune cells, and when co-stimulated result in the release of cytotoxic granules and enzymes that cause lysis of target cells. Both CDC and ADCC are critical for mediating the widespread astrocyte loss seen in human NMO lesions (43). At the molecular level, the structural organization of AQP4 into orthogonal array of particles (OAPs) is likely to have a profound influence in antigenicity and function of AQP4 (47,48). Significant CDC activation is only observed on AQP4 isoforms assembled into OAPs, suggesting that OAP

formation also enhances the ability for autoantibodies to bind C1q (46). The influence of OAP formation in directing ADCC remains unexplored.

Astrocyte loss is an early feature in the evolution of NMO lesions. In agreement with human lesions, experimental models demonstrate immediate and widespread astrocyte loss following co-injection of AQP4 autoantibody and human complement (36,49).

Oligodendrocyte cell body death occurs a few hours later, possibly in part by apoptosis (28,50), and is subsequently followed by demyelination and inflammatory cell infiltration (49). Several sequelae of CDC- and ADCC-mediated astrocyte insult likely contribute this temporal progression. For example, complement activation produces the anaphylatoxins and opsonins C3a and C5a (Fig. 1). These proteins serve well-established roles in immune cell recruitment into the CNS (51) and promote surface expression of FcRs (52). Indeed, in the ex vivo NMO model, ADCC is significantly enhanced by the presence of a very small percentage of human complement that produces little or no pathology on its own (37). Immune cells capable of ADCC, eosinophils, neutrophils, and macrophages can be directly linked with NMO lesion pathology (37,38,53). Neutropenic or hypoeosinophilic mice develop reduced lesion sizes in intracerebral injection models, whereas neutrophilic or hypereosinophilic mice develop larger lesions (53,54). Tissue damage is mediated through the release of toxic granules that can be influenced through the use of direct inhibitors or stabilizers (53,54). Although the role of macrophages has not been investigated in vivo, macrophage addition to NMO ex vivo models exacerbates lesion formation (37). Finally, cytokines released from local immune cell recruitment or from lysed or activated CNS cells, such as tumor necrosis factor- α , interleukin (IL)-6, IL-1 β , or interferon (INF)- γ , facilitate immune cell recruitment, mediate CNS damage, or promote the continued stimulation of AQP4 reactive plasma cells (37,55).

Animal models and human histopathology reveal features suggestive of a dynamic interplay between lesion formation, astrocyte recovery, and remyelination. As noted previously, acute NMO lesions in affected individuals and animal models show unique unipolar astrocytes that repopulate regions of astrocyte destruction (28,49). In some CNS locations, NMO lesions may demonstrate a relative preservation of myelin with no neuronal or axonal pathology (29,56), suggesting that noninflammatory mechanisms such as AQP4 internalization and altered water transport may contribute to lesion propagation. These mechanisms, however, remain controversial (24,41,57). In addition, AQP4-IgG may play a role in the repair of NMO lesions by interfering with AQP4-facilitated astrocyte migration. AQP4 expression on tumor cells increases metastatic potential and invasiveness (58), and AQP4-null astrocytes demonstrate impaired cellular migration (59). In migrating cells, AQP4 localizes to the leading edge of migrating cells potentially assisting in the formation of lamellipodia (60). In NMO lesions, AQP4-IgG may hamper the migration of relevant glial populations that promote lesion recovery or injure those cells through CDC or ADCC. A better understanding of the role of AQP4 in lesion repair may lead to therapies that reduce neuronal injury and preserve myelin.

NEUROMYELITIS OPTICA THERAPY

Treatment of NMO includes both the management of acute attacks and the prevention of future exacerbations. The goal of acute therapy is to minimize irreversible damage and accelerate recovery. Preventative therapy should lower the frequency and severity of future exacerbations. In contrast to MS, disease progression is uncommon outside of clinical relapse in NMO; therefore, the prevention of future exacerbations should also minimize the progression of disability in affected individuals (61). Table 1 gives an overview of current acute and preventive therapies discussed below.

Treatment of Acute Attacks

In the setting of an acute initial presentation or exacerbation of NMO, the typical treatment is the administration of intravenous methylprednisolone therapy (IVMP; 1,000 mg daily for 3–5 days). Although the role of steroid taper (prednisone, methylprednisolone, or dexamethasone) has not been investigated, many practitioners taper steroid treatment slowly over several months when recovery is incomplete or to bridge the interval between acute exacerbation and the initiation of preventive therapy. These strategies are adopted from the treatment of MS and idiopathic ON; there has been no therapeutic trial for the acute treatment of NMO. If there is no significant clinical improvement on steroids, plasma exchange (PLEX) has been shown to be effective for both ON and TM associated with NMO. Typically, 5 cycles are administered daily or every other day. An early, randomized controlled trial of plasma exchange in steroid refractory CNS demyelinating diseases included 2 patients with NMO, of which 1 patient responded to PLEX (62). Subsequent studies and case series reported significant improvement in around 44%–75% of the NMO patients treated with PLEX (33,63–65). Male gender, preserved reflexes and early initiation of treatment were associated with moderate or marked improvement. Patients who were treated successfully improved rapidly following PLEX and improvement was sustained (65). The efficiency of plasma exchange was independent of NMO-IgG seropositivity (64). Since published series have failed to define clinical or temporal criteria for response to IVMP, the institution of PLEX is left to the clinician's judgment and experience.

A recent study comparing IVMP monotherapy with IVMP in combination with PLEX treatment for cases of ON associated with NMO demonstrated IVMP and PLEX in combination being more efficient than IVMP alone. High-contrast visual acuity, visual fields, and temporal retinal nerve fiber layer thickness improved significantly with PLEX treatment (66). Interestingly, low-contrast letter scores (Sloan 0.25%) and color vision (Farnsworth-Munsell 100 Hue) did not improve. These results suggest that the lack of rapid visual improvement following IVMP therapy for NMO acute ON should prompt consideration for the rapid initiation of PLEX.

Intravenous immunoglobulin (IVIg) and cyclophosphamide have also been used to treat acute NMO exacerbations and prevent relapses. IVIg frequently is substituted for PLEX in other neurologic disorders, including myasthenia gravis and Guillain-Barré syndrome. In idiopathic ON, however, IVIg has failed to improve the outcome of steroid resistant cases (67,68), suggesting that caution should be exercised before automatically substituting IVIg for PLEX in NMO. Recently, 2 small case series have reported benefit in NMO patients

receiving either acute or short-term prophylactic IVIg therapy (69,70), indicating that IVIg therapy may warrant further investigation in NMO (71). For acute exacerbations resistant to IVMP and PLEX, some patients with acute TM have benefited from cyclophosphamide infusion (72). Interestingly, a recent case series has reported lack of efficacy for the use of cyclophosphamide in NMO relapse prevention (73), indicating that distinct immunologic mediators may drive NMO lesion onset and propagation.

Prevention of Attacks

Immunosuppressive therapy typically is instituted after the initial attack given the risk of severe disability associated with a single exacerbation. The decision for preventive treatment strategies is often challenging given the absence of prospective clinical trials and the risk of serious side effects. Due to the low incidence and prevalence of NMO, interventional studies with level I or II evidence are not currently available; therefore, treatment strategies are mostly based on small case series and case reports (74). Besides balancing the best available data on clinical efficacy with established short- and long-term side effects, risk factors such as age, gender, comorbid conditions, functional status, and response to previous therapies have to be taken into consideration. Predictors of high risk of disability in NMO patients include male gender, Afro-Caribbean and Asian ethnicity, and young age at onset (75).

Corticosteroids and Plasma Exchange—Watanabe et al (76) performed a retrospective study of 25 Japanese NMO patients treated with low-dose prednisone monotherapy (doses ranged from 2.5 to 20 mg/d) over a median observation period of 19.3 months. The median annual relapse rate (ARR) decreased from 1.48 pretreatment to 0.49 during treatment. Treatment with more than 10 mg/d of prednisone was significantly more effective than therapy with 10 mg/d or less. Another case series analyzed the efficacy of concurrent PLEX treatment in NMO relapse prevention (77). Four patients treated with oral prednisolone in combination with azathioprine or cyclophosphamide received regular PLEX for residual disease activity. Two of 4 patients stabilized with the additional therapy.

Azathioprine—The pro-drug azathioprine is converted to nucleotide antimetabolites that inhibit the purine synthesis and interfere with the proliferation of cells, especially B and T lymphocytes. Costanzi et al (78) reported the largest experience of azathioprine in NMO/NMO spectrum diseases. In their retrospective study of 99 patients, 86 patients fulfilled the 2006 Wingerchuk criteria (8) while the remaining 13 patients were diagnosed with AQP4 seropositive NMO spectrum disorders. In 70 patients who had been followed up for at least 1 year, the ARR decreased from 2.20 to 0.52 relapse per year over a median treatment interval of 22 months. The improvement was not as robust in patients taking less than 2 mg/kg/day but seemed to improve with an increase in the mean corpuscular volume. Azathioprine was discontinued in 38 patients because of apparent lack of efficacy (13 patients), severe side effects (22), and lymphoma (3). A reduced level of thiopurine methyltransferase (TPMT) leads to azathioprine toxicity, so TPMT activity should be tested before administration. Additional studies of azathioprine have reported similar results. Bichuetti et al (79) noted a decrease in the ARR from 2.1 to 0.6 during therapy (2 mg/kg/day with or without steroids) in their retrospective analysis, and Sahraian et al (80) reported a reduction in the ARR from 1.13 to 0.4 (3 mg/kg/day) in their small prospective cohort.

Mycophenolate Mofetil—Mycophenolate mofetil is a pro-drug that is converted to the active metabolite mycophenolic acid. By reversibly inhibiting the inosine monophosphate dehydrogenase, de novo synthesis of guanosine nucleotides is hindered and proliferation of T and B lymphocytes is inhibited. Treatment of NMO with mycophenolate mofetil (median dose 2,000 mg/d) was analyzed in a retrospective study of 24 patients (81). At a median follow-up of 28 months, 19 patients were still on treatment and the median posttreatment relapse rate was 0.09 compared with a pretreatment rate of 1.28. The expanded disability scale score (EDSS) remained relatively unchanged (6.0 pretreatment vs 5.5. posttreatment). Six patients had adverse effects during therapy, and 1 patient died of disease complications during the follow-up.

Methotrexate—Methotrexate is an inhibitor of the dihydrofolate reductase and other folate-dependent enzymes necessary for purine and thymidylate synthesis. Recently, Kitley et al (82) reported a retrospective observational case series of 14 AQP4 positive NMO and NMO spectrum disorder patients treated with methotrexate (median maintenance dose 17.5 mg/wk). The median duration of treatment was 21.5 months and the median ARR decreased significantly following therapy (0.18 during treatment vs 1.39 pretreatment). Forty-three percentage of the patients were relapse free, and none of the patients discontinued due to adverse effects. In an earlier case series, Minagar (83) treated 7 NMO patients with methotrexate (50 mg) weekly and oral prednisolone (1 mg/kg daily) and observed stabilization in disease activity as evidenced by unchanged or reduced EDSS.

Mitoxantrone—Mitoxantrone, an anthracenedione antineoplastic drug, inhibits topoisomerase II and suppresses development of both lymphocytes and macrophages. The drug also induces differential inhibitory effects on subgroups of leukocytes, preferentially targeting CD19⁺ B cells. Kim et al (84) reported on the use of mitoxantrone in 20 NMO and NMO spectrum disorder patients (maximum cumulative doses of 120 mg/m², 3–6 monthly cycles of 12 mg/m² followed by 6–12 mg/m² maintenance doses). During the average treatment duration of 17 months, the ARR declined from 2.8 pretreatment to 0.7 posttreatment, and the mean EDSS decreased from 5.6 to 4.4. In another case series of 5 NMO patients, improvement was noted in 4 individuals, although 2 patients still had relapses during treatment (85). Serious adverse events included decline of left ventricular ejection fraction in one patient that caused discontinuation after a cumulative dose of 72 mg/m². Therapy-related leukemia, a consequence of mitoxantrone treatment in other disorders, was not observed in either study.

Rituximab—Rituximab is a chimeric mouse/human anti-CD20 monoclonal antibody that depletes naive and memory B cells. Different dosing regimens have been reported for the treatment of NMO, especially in the maintenance stage. In most studies, 375 mg/m² was administered weekly for 4 weeks followed by 1,000 mg infused twice within 2 weeks every 6 months (32,86–89); however, some patients received infusions (usually 1,000 mg) every 2–12 months (88) or depending on circulating B cell numbers (32,86,87). Recently, Greenberg et al (90) suggested a monthly monitoring of CD19 B-cell counts in the blood and the rapid redosing of patients when B cells rise above 2%.

In 2 retrospective studies, NMO patients treated with rituximab over a median interval of 19–32.5 months demonstrated a significant reduction in ARR and stabilization of EDSS. Bedi et al (88) reported decreases in the ARR from 1.87 to 0.0 relapse/patient per year, and Jacob et al (86) recorded a decline in ARR from 1.7 to 0. EDSS scores stabilized or improved in most patients in both studies. Two patients died during the follow-up, one due to severe brainstem relapse and the other due to septicemia (86). Kim et al (89) reported the results of a 5-year study of 30 NMO patients treated with rituximab. The ARR lowered in 26 of 30 patients (2.4 pretreatment vs 0.3 posttreatment), 18 patients became relapse free, and in 28 patients, the disability was either improved or stabilized. Pellkofer et al (91) recorded a reduction in ARR from 2.35 to 0.93 (decline in 80% of the patients) and stabilization of EDSS scores in a cohort of 10 NMO patients. In their study, NMO disease activity correlated with B-cell depletion but not with AQP4-IgG titer or B-cell cytokine levels. One patient died because of cardiovascular failure, but no significant infections were reported.

Eculizumab—Eculizumab is a humanized monoclonal antibody against complement C5 that inhibits its cleavage by C5 convertase. In NMO, eculizumab blocks AQP4-IgG-mediated CDCC. In an open-label phase II study of 14 NMO patients with refractory disease, eculizumab therapy significantly reduced attack frequency and stabilized or improved neurological disability (92). After 12 months of treatment, 12 of 14 patients were relapse free; however, 1 patient developed meningococcal sepsis and sterile meningitis but fully recovered after treatment.

Questionable Therapies

Although effective in MS, INF- β , natalizumab, and fingolimod have been reported to be inefficacious or even harmful when used for the treatment of NMO. Kim et al (93) reported a study on 40 patients with NMO spectrum disorders who had been treated with INF- β for more than 5 months. In 95% of the patients, the treatment was not effective and even worsened the disease course. The mean ARR increased from 1.49 to 2.38 and the mean EDSS scores increased from 2.72 to 4.78 points during therapy. Additional case reports have highlighted severe exacerbations following the initiation of INF- β -1b therapy in NMO patients (94–96). The biologic mechanisms by which INF-beta exerts its effects in NMO spectrum disorders are unclear but may involve the upregulation of B-cell activating factor or IL-17 levels with INF-beta therapy (97).

In a case series of 5 NMO patients who tested positive for AQP4 autoantibodies, natalizumab treatment (median duration of 8 infusions, range, 2–11 infusions) failed to control disease or worsened disease activity (98). In all patients, a total of 9 relapses occurred (median duration to relapses 120 days) and the mean EDSS increased from 4.0 to 7.0 after natalizumab therapy. In addition, a severe NMO attack in a natalizumab treated patient was described with florid active demyelination, the presence of neutrophils and eosinophils, and the massive fragmentation of glial fibrillary acidic protein-positive astrocytes (99). It has been hypothesized that the peripheral sequestration of proinflammatory T cells during natalizumab treatment may stimulate pro-inflammatory B cell populations critical to NMO disease activity. Alternatively, the increased number of

peripheral eosinophils associated with natalizumab treatment (100) may exacerbate lesion formation (21,53) and facilitate the generation of new peripheral plasma cell niches (101).

Two cases of NMO exacerbations associated with oral fingolimod have recently been reported. Min et al (102) described a patient with NMO spectrum disorder who developed extensive brain lesions 2 weeks after initiation of fingolimod treatment. The patient suffered residual encephalomalacia but had no further exacerbations with steroid treatment over 3 years following the withdrawal of fingolimod. In another case, a patient with NMO spectrum disorder developed a fulminant course with multiple white matter lesions ten days after initiation of fingolimod therapy (103). The mechanisms by which fingolimod might cause these severe exacerbations remain speculative. Similar to natalizumab, fingolimod may exacerbate NMO lesion formation by promoting bone marrow egress of eosinophils (104). Alternatively, fingolimod may alter CNS B cell trafficking and enhance the production of intrathecal autoantibodies (105).

Therapeutic Recommendations

Although no therapy has been evaluated in a prospective clinical trial, the previously noted retrospective and prospective case series provide a framework for guiding treatment decisions for NMO patients. For NMO patients with acute ON, TM, or CNS syndrome, IVMP should be administered rapidly and continued for 3–5 days. If clinical improvement is not noted in this time period, then plasma exchange should be initiated and repeated for a total of 5 cycles. For patients with idiopathic ON or TM and a high suspicion of NMO, an identical treatment program should be strongly considered. Currently there is no evidence to support the immediate and simultaneous administration of IVMP and PLEX for NMO or other acute demyelinating relapses. For refractory demyelinating events that are not responsive to IVMP and PLEX, treatment with cyclophosphamide or IVIg may be considered. Following relapse, a prolonged taper of prednisone (from 60 to 100 mg/d to off over 4–8 weeks) is generally advised.

Azathioprine, mycophenolate mofetil, and rituximab are the most extensively studied preventative treatments and are generally considered the first-line therapies for NMO prophylaxis. While prednisone and mitoxantrone remain alternatives for monotherapy, the lower efficacy of prednisone and the potential toxicity of mitoxantrone should limit them to add-on use for refractory cases. We recommend starting NMO patients or seropositive NMO spectrum patients with azathioprine, mycophenolate, or rituximab using the doses and schedules noted in Table 1. The ultimate choice of therapy will be dependent on drug availability, patient preference, mode of administration, cost, and potential side effects. Disease relapse on therapy should prompt a re-evaluation of the treatment regimen. Before considering a change in therapeutics, careful consideration should be given to critical factors that may influence therapeutic response: drug dosage, treatment duration, adherence, and treatment resistance (anti-chimeric antibodies or B cell repletion with rituximab). For patients failing azathioprine or mycophenolate, a switch to rituximab is advised. If rituximab is not available, the addition of oral prednisone remains an alternative. For NMO patients failing rituximab therapy, combination therapy with azathioprine or mycophenolate or the off-label use of tocilizumab, are two potential approaches.

Emerging Neuromyelitis Optica Therapeutics

Improved understanding of NMO pathophysiology has facilitated the development of novel approaches to the treatment of disease (Fig. 2). Although many strategies remain focused on immunosuppression and immunomodulation, some potential therapies are engineered to interfere with the targeted immune response against AQP4.

B Cell and Plasma Cell Targeted Therapies: Anti-CD20 and Anti-CD19—As noted previously, multiple clinical studies have shown that depletion of CD20⁺ naive and memory B cells reduces relapse frequency in NMO patients. CD20, however, is not expressed on plasmablasts and plasma cells; B cell populations considered to be critical for the production of AQP4-IgG. CD19 is a B cell marker that is, expressed later in the B cell lineage and is retained on the surface of plasmablasts and some plasma cells (106). A CD19-depleting antibody may offer a promising avenue to directly deplete AQP4-IgG-producing B cells and reduce pro-inflammatory lymphocyte populations in NMO. Although there are no clinical trials initiated to date, CD19 depleting therapies are currently under active investigation (107).

Cytokine Modulation: Interleukin-6 and Interleukin-17—The cytokines IL-6 and IL-17 have both been implicated in NMO pathology. IL-6 signaling prolongs long-term plasma cell survival in vitro (108) and promotes anti-AQP4 antibody production by circulating plasmablasts (109). Since IL-6 is elevated in the CSF of NMO patients (110), IL-6 signaling may enhance the survival of CNS B cells and increase intrathecal autoantibody production. In addition, IL-6 may polarize T cells toward a pro-inflammatory TH17 phenotype (111). Tocilizumab is a monoclonal antibody that binds to the IL-6 receptor and blocks binding of IL-6 signaling. Two case reports have suggested that tocilizumab may be beneficial for the treatment of NMO. Araki et al (112) and Kieseier et al (113) reported on clinical and radiographic improvement in treatment-resistant NMO patients following IL-6 receptor blockade.

Based on the histopathology and cytokine signature of NMO, several groups have posited a central role for the TH17 pathway in NMO pathogenesis (114,115). Acute NMO lesions demonstrate prominent granulocytic infiltration (21), IL-17 levels are elevated in the serum of NMO patients (115), and AQP-4 specific T cells recovered from the peripheral blood of NMO patients demonstrate a TH17 bias (111). Blockade of IL-17 signaling offers a novel approach to NMO therapy by hindering the development of Th17 T cells and reducing the infiltration of polymorphonuclear cells into active lesions.

Neutrophil and Eosinophil Inhibitors—Neutrophils and eosinophils are a significant component of the inflammatory infiltrate in NMO lesions and contribute to local CNS injury through ADCC and phagocytosis. Sivelestat, a potent neutrophil elastase inhibitor, reduces lesion formation in both animal and ex vivo slice models of NMO (54). Currently, sivelestat is only approved in Japan for the treatment acute respiratory distress syndrome. It may be useful as a corticosteroid-sparing agent in the treatment of acute NMO exacerbations by inhibiting both CNS neutrophil migration and tissue damage. Recently, the eosinophil stabilizers cetirizine and ketotifen were shown to reduce NMO lesion formation in the

intracerebral injection model (53). Improved understanding of the therapeutic window for delivery for these drugs would aid in determining how these agents may be used individually or in combination to treat acute NMO exacerbations or lessen the severity of future attacks.

Competitive Inhibitors of NMO IgG: Aquaporumab and Small Molecules—

Disrupting the binding of pathogenic AQP4 autoantibodies to target astrocytes is an attractive nonimmunosuppressive therapeutic strategy for AQP4-IgG-seropositive NMO patients. To date, both blocking antibodies and small molecule inhibitors have been investigated in in vitro, ex vivo, and in vivo assays. An engineered, monoclonal AQP4 antibody that exhibits tight AQP4 binding and slow dissociation kinetics was mutated to make the Fc domains nonpathogenic by eliminating both CDC and ADCC effector activity (116). This mutated competitive blocking antibody, termed “aquaporumab,” was observed to outcompete pathogenic AQP4 serum autoantibodies and inhibit NMO lesion formation in vivo and ex vivo. High-throughput screening has been used to identify small molecule blockers that prevent NMO IgG binding to the extracellular surface of AQP4 (117,118). Both small molecule and antibody blocking therapies may be used for disease prevention or during disease exacerbations. To date, no blocking therapy or engineered AQP4 antibody has been shown to disrupt AQP4 water channel function (41,119). Therefore, it is less likely that blocking therapies will disrupt the normal function of AQP4 and produce undesirable toxicity.

Antibody Modulation: Deglycosylation of NMO IgG and Fc Cleavage—IgG

effector functions are dependent on the presence of an intact and glycosylated Fc region. Endoglycosidase S (EndoS) and IgG-degrading enzyme (IdeS) from *Streptococcus pyogenes* are 2 distinct enzymes that may be used to modify endogenous AQP4 autoantibody pathogenicity. EndoS is an enzyme that selectively cleaves asparagine-linked glycans (120). Tradtrantip et al (121) showed that treatment of patient sera with EndoS neutralizes NMO sera pathogenicity and prevents lesion formation in ex vivo and in vivo NMO models. IdeS is an enzyme that cleaves the Fc domain of immunoglobulin to produce a nonpathogenic Fab (122,123). IdeS co-injection with human complement into a murine brain 15 minutes after AQP4 autoantibody injection interrupts the lesion development (121). During acute relapses, antibody modulatory therapies may enhance the efficacy of apheresis to combat the pathogenicity of AQP4-IgG. The potential immunogenicity of these enzymes, however, may limit their chronic applications in humans.

Modulation of AQP4 OAP Formation—

CDC activation is critical for the development of lesions in NMO animal models (43,49). As CDC activation is dependent on OAP formation (46), disrupting OAP formation may limit CDC activation and represents a novel approach to decrease further immune activation in the presence of NMO IgG. The utility of this approach remains uncertain, as the endogenous roles of OAP formation in the CNS remain unclear. Likewise, disrupting OAP formation in other tissues where AQP4 is highly expressed may produce undesirable toxicity. The utility of such agents for both acute and chronic therapy will require careful investigation.

CONCLUSIONS

Current NMO therapeutics are centered on immunosuppression. Improved understanding of NMO pathogenesis has led to the development of novel therapeutic strategies designed to limit AQP4-IgG-mediated inflammatory injury, pro-inflammatory B-cell development, and cell-mediated injury. A variety of novel approaches are either in development, beginning early phase clinical testing, or beginning drug registration trials. They include targeted nonimmunosuppressive AQP4-IgG blocking therapies, complement inhibitors, cytokine modulators, and agents that minimize granulocyte or eosinophil toxicity. The expanding armamentarium of potential NMO therapeutics provides a promising environment for the initiation of formal treatment trials and the development of evidence-based approaches that minimize visual and neurologic morbidity in disease.

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FIG. 1.

Mechanisms of neuromyelitis optica (NMO) pathogenesis. Tissue or bone marrow resident plasma cells produce aquaporin-4 (AQP4) autoantibodies that bind to AQP4 orthogonal array of particles (OAPs) on the astrocyte foot processes. AQP4-IgG binding recruits complement C1q, which initiates the classical complement cascade and produces the anaphylatoxins C3a and C5a. Complement activation leads to membrane attack complex (MAC) deposition and astrocyte destruction, promotes the recruitment of immune cells into the central nervous system, and locally stimulates immune cells in the lesion to enhance immune cell effector activity. Astrocyte damage occurs from the combined effects of MAC deposition and AQP4-IgG-mediated antibody-dependent cell-mediated cytotoxicity, and polymorphonuclear degranulation and phagocytosis. Secondary demyelination may occur due to the withdrawal of astrocyte-mediated homeostatic functions, complement activation, or immune cell degranulation. EAAT, excitatory amino-acid transfer.

FIG. 2.

Current and emerging therapeutic strategies for NMO. Therapeutics (red) that are current (bold) and novel are listed individually next to the process that they inhibit.

Immunosuppressant medications are designed to decrease the activity of antibody-producing B cells and pro-inflammatory T cells. Aquaporin-4 immunoglobulin G (AQP4-IgG) modulation may block the pathogenic action of autoantibodies. Blocking therapies are designed to prevent the binding of pathogenic autoantibodies to their astrocytic target. Reducing orthogonal array of particle (OAP) formation is intended to modify the assembly of AQP4 target to decrease antibody binding. Neutrophil and eosinophil inhibitors are intended to limit Fc receptor-mediated destructive mechanisms. Complement inhibition is designed to limit complement-dependent cytotoxicity (CDC) and membrane attack complex formation. Definitive therapies to promote remyelination in lesioned tissue remain to be developed. ADCC, antibody-dependent cell-mediated toxicity; APP, amyloid precursor protein; LFB, luxol fast blue.

TABLE 1

Current therapies for neuromyelitis optica

	Mechanism	Side Effects	Efficacy	Literature
Corticosteroids	Bind to glucocorticoid receptor	Insomnia, mood changes, weight gain, glaucoma, osteoporosis, diabetes, hypertension, growth impairment, insomnia	Prophylaxis: reduced ARR from 1.48 to 0.49 relapses per year	76
Dosage for acute attack: methylprednisolone 1,000 mg, 3–5 days For prophylaxis: prednisone 2.5–20 mg/d	Induce gene expression and modulates immune function			
Plasma exchange	Immunoglobulins are separated from the patient's blood	Hypotension, hypocalcaemia, transfusion reactions, transfusion transmitted diseases, bleeding		33, 62–66, 77
Acute attack: 1–1.5 plasma volumes per exchange, 5×	Removes pathologic NMO-IgG from Circulation			
Azathioprine	Imidazolyl derivate of 6-mercaptopurine	Bone marrow suppression, leukopenia, nausea, hepatotoxicity, diarrhea, hair loss, fatigue	Reduced ARR from 2.20–1.13 to 0.40–0.60	78–80
Usual maintenance dosage: 2 mg·kg ⁻¹ ·d ⁻¹	Acts as an immunosuppressive antimetabolite by interfering with proliferation of T and B lymphocytes and alterations in antibody production Metabolism of azathioprine requires TPMT	Check TPMT activity to avoid drug toxicity!	EDSS was stable/unchanged	
Mycophenolate	Converted to active metabolite mycophenolic acids	Leukopenia, skin malignancy, lymphoma, PML, headache, hair loss, diarrhea, constipation, bruising, anxiety	Reduced ARR from 1.28 to 0.09	81
Median maintenance dosage: 2,000 mg/d, range 750–3,000 mg	Reversible inhibitor of inosine monophosphate dehydrogenase that is involved in guanosine nucleotide synthesis Proliferation of T and B lymphocytes is impaired by interruption of guanosine synthesis		EDSS was stable/unchanged	
Methotrexate	Inhibitor of dihydrofolate reductase and purine	Leukopenia, pancytopenia,	Reduced ARR from 1.39 to 0.18	82,83

	Mechanism	Side Effects	Efficacy	Literature
	and thymidine synthesis	infections, hepatotoxicity, joint pain, stomatitis, nausea, diarrhea		
Median maintenance dosage: 17.5–50 mg/wk	Inhibits proliferation of T and B lymphocytes		EDSS was stable	
Mitoxantrone	Intercalates with DNA and inhibits topoisomerase II	Cardiotoxicity, leukemia, hepatotoxicity, leukopenia, nausea, stomatitis, diarrhea	Reduced ARR from 2.8 to 0.7	84,85
Dosage: max. cumulative doses 120 mg/m ² 3–6 monthly cycles of 12 mg/m ² followed by 6–12 mg/m ² maintenance doses	Suppresses development of T and B lymphocytes and macrophages		Reduced EDSS from 5.6 to 4.4	
Rituximab	Chimeric anti-CD20 monoclonal antibody	Infusion reactions, infections, (e.g. recurrent herpes zoster, respiratory infections, urinary tract infections), fatigue, transient leukopenia and transaminase elevation, PML	Reduced ARR from 1.7–2.6 to 0.0–0.93	23,86–91
Usual dosage: initiation with 375 mg/m ² weekly for 4 wk, 1,000 mg twice biweekly, maintenance (1,000 mg) either fixed or upon recurrence of B cells	Depletes B cells from pre-B cells through memory lineages		EDSS stabilized or improved	

ARR, annualized relapse rate; EDSS, expanded disability scale score; PLEX, plasma exchange; PML, progressive multifocal leukoencephalopathy; TPMT, thiopurine methyltransferase.