Neuromyelitis Optica Spectrum Disorders

It is critical to maintain a high index of suspicion for these conditions when evaluating a patient with demyelination to avoid delays in treatment.

By Michael J. Bradshaw, MD and Dorlan Kimbrough, MD

Introduction

Neuromyelitis optica (NMO) and NMO spectrum disorders (NMOSD) are clinical syndromes traditionally defined by the presence of myelitis and optic neuritis (ON). Aquaporin-4 (AQP4) is a water channel that is heavily expressed on astrocyte foot processes in the optic nerves, brainstem, and spinal cord. Antibodies to AQP4 are directly pathogenic and serve as a highly specific diagnostic biomarker for NMO, which is technically an autoimmune astrocytopathy. They are detectable in 60% to 80% of patients with NMOSD. Lesions that are positive for AQP4 antibodies (AQP4+), which have a prominent perivascular complement deposition, are pathologically distinct from lesions of multiple sclerosis (MS). Among patients with an NMOSD phenotype who are seronegative for antibodies to AQP4 (AQP4-), as many as 42% have detectable serum antibodies to myelin oligodendrocyte glycoprotein (MOG) (See Box p 78). The prevalence of NMOSD is roughly 4 to 10 per 100,000, with higher rates among those of African or Asian descent; onset occurs throughout the lifespan and 5 to 10 times more often in women than men.

Clinical Manifestations

Most patients with NMOSD have a relapsing course with attacks that have a temporal profile similar to a demyelinating episode of MS. Relapses in patients with AQP4+ NMOSD are more likely to be severe and disabling compared with MS relapses. The cardinal clinical features of NMOSD include episodes of optic neuritis, acute myelitis, and brainstem syndromes. Other core clinical features that occur less often include symptomatic narcolepsy, acute diencephalic syndrome, or acute cerebral syndromes.

Optic Neuritis

Inflammatory ON typically presents as acute to subacute monocular vision loss with impaired visual acuity that may be accompanied by color desaturation, a relative afferent pupillary defect, and/or optic disc edema. Clinical features that suggest NMOSD (or MOG antibody-associated disorder) include simultaneously bilateral ON and severe vision loss (acuity 20/200 or worse).

Brainstem Syndromes

The area postrema (AP) is an emetic reflex center located in the floor of the fourth ventricle that modulates a number of physiologic processes such as hiccups and emesis. The AP has been proposed as the initial site of entry for pathogenic AQP4 antibodies because AP capillaries lack tight junctions and AP astrocytes express an abundance of AQP4.

Area postrema syndrome (APS) occurs commonly in AQP4+ NMOSD consequent to inflammatory lesions in the AP. In contrast to ON or myelitis, AP lesions lack demyelination or necrosis, which may in part explain the nearly universal complete remission of symptoms after an attack. Proposed APS diagnostic criteria include acute or subacute nausea, vomiting, or hiccups lasting for at least 48 hours without response to treatment or evidence of other etiologies (eg, hyponatremia, CNS structural lesions, and gastrointestinal or migrainous phenomena). Dorsal medulla lesions on MRI can facilitate early diagnosis. An attack of APS may serve as warning of an impending attack of ON or myelitis as most occurrences (58%-68%) precede inflammatory involvement elsewhere. Other brainstem syndromes sometimes encountered in patients with NMOSD include oculomotor abnormalities, hearing loss, nuclear facial nerve palsy, vestibular dysfunction, and other cranial nerve abnormalities.

Myelitis

Considered a hallmark of NMOSD, longitudinally extensive transverse myelitis (LETM) is defined as myelitis spanning at least 3 spinal segments. Neurologists should be aware that short-segment myelitis is also common in NMOSD; neglecting to consider this is associated with delay in diagnosis and treatment. The anterolateral cord syndrome with prominent...
weakness and spinothalamic tract deficits is a typical but not exclusive pattern.

Pregnancy
Relapse rates in women with NMOSD do not change during pregnancy in contrast to women with MS, who have a reduced relapse rate during pregnancy. Relapse risk increases during the first 3 months postpartum in both women with NMOSD and MS, however. The placenta expresses AQP4, which may in part explain why preeclampsia, intrauterine growth restriction, and miscarriage are more common in women with NMOSD. Antibodies to AQP4 are transferred across the placenta but do not appear to be pathogenic to the fetus.

Children
Although median age of onset is 30 to 40 years, 3% to 5% of patients with NMOSD present as children, which can be clinically challenging. The most common presenting features of NMOSD in children include visual, motor, and constitutional symptoms (ie, vomiting, fever, seizures). A single study reported a mean annualized relapse rate (ARR) of 0.6 in pediatric-onset NMOSD compared with 1.0 in adult-onset NMOSD; time to disability is longer in patients with pediatric-onset, largely explained by the severity of a first episode of myelitis in adults. Time to first treatment was significantly longer in children compared with adults (13.1 vs 3.4 years). Children with acute disseminated encephalomyelitis (ADEM) frequently have LETM, which also occurs in a substantial minority of children with MS and monophasic myelitis. As in adults, antibodies to AQP4 are a critical diagnostic biomarker.

Coexisting Autoimmunity
Systemic autoimmune disorders such as systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome, and Sjögren’s syndrome often coexist with NMOSD. Clinical episodes concerning for APS, myelitis, or ON in patients with systemic autoimmunity should prompt testing for serum AQP4 antibodies. Conversely, patients with NMOSD, especially if seronegative, should be asked about systemic symptoms and have a rheumatologic workup commensurate with the degree of clinical suspicion for Sjögren’s syndrome, SLE, and related conditions.

Diagnosis
The International Panel for NMO Diagnosis (IPND) updated diagnostic criteria for NMOSD are shown in the Table.

Laboratory Studies
Serum samples rather than cerebrospinal fluid (CSF) should be used to test for AQP4 antibodies and cell-based assays (eg, fluorescence-activated cell sorting or direct immunofluores-

<table>
<thead>
<tr>
<th>TABLE. DIAGNOSTIC CRITERIA FOR NMOSD IN ADULTS</th>
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<tr>
<td><strong>AQP4+ NMOSD</strong></td>
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<tr>
<td>Positive test for AQP4-IgG³</td>
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<tr>
<td>Exclusion of alternate diagnoses</td>
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<tr>
<td>At least 1 of the following:</td>
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<tr>
<td>Optic neuritis</td>
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<tr>
<td>Acute myelitis</td>
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<tr>
<td>Area postrema syndrome</td>
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<tr>
<td>Acute brainstem syndrome</td>
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<tr>
<td>Symptomatic cerebral syndrome w/ NMOSD-typical brain lesion</td>
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<tr>
<td>Symptomatic narcolepsy OR acute diencephalic clinical syndrome with NMOSD-typical diencephalic lesions.</td>
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<tr>
<td><strong>AQP4- or AQP4 status unknown NMOSD</strong></td>
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<tr>
<td>Negative or inconclusive test for AQP4-IgG³</td>
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<tr>
<td>Exclusion of alternative diagnoses</td>
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<tr>
<td>At least 1 of the following:</td>
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<tr>
<td>Optic neuritis</td>
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<tr>
<td>Acute myelitis with LETM</td>
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<tr>
<td>Area postrema syndrome</td>
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<td>If only 1 of above present, then also 1 of following:</td>
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<tr>
<td>Acute brainstem syndrome</td>
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<tr>
<td>Symptomatic narcolepsy OR acute diencephalic clinical syndrome with NMOSD-typical diencephalic lesions.</td>
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<tr>
<td>PLUS THE FOLLOWING MRI FINDINGS</td>
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<tr>
<td><strong>Acute optic neuritis</strong></td>
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<tr>
<td>Brain MRI normal or with nonspecific white matter lesions OR optic nerve hyperintense lesion or T1 Gd⁺ lesion extending over more than half the optic nerve or involving optic chiasm</td>
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<tr>
<td><strong>Acute myelitis</strong></td>
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<tr>
<td>Associated intramedullary lesion extending over 3 or more contiguous segments (LETM) OR focal spinal cord atrophy over 3 or more contiguous segments and compatible history</td>
</tr>
<tr>
<td><strong>Area postrema syndrome</strong></td>
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<tr>
<td>Dorsal medulla/area postrema lesions</td>
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<tr>
<td><strong>Acute brainstem lesion</strong></td>
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<td>Periependymal brainstem lesions</td>
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<td><strong>Abbreviations:</strong> AQP4, aquaporin-4; Gd⁺, gadolinium positive; IgG, immunoglobulin G; LETM, longitudinally extensive transverse myelitis; NMOSD, neuromyelitis optica spectrum disorders. ^ a cell-based assay preferred for AQP4 antibody testing</td>
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</table>
**Introduction**

Myelin oligodendrocyte glycoprotein (MOG) is expressed on the outermost surface of the myelin sheath and may function in cell adhesion, microtubule stability, and interactions with the immune system. Antibodies targeting MOG have been implicated in the rodent model of multiple sclerosis (MS), experimental autoimmune encephalitis (EAE); identified in a small percentage of patients with MS; and reported in patients with neuromyelitis optica spectrum disorder (NMOSD). Early studies were limited by the use of older techniques that did not use the MOG antigen in its human conformational, or native, state but with the use of cell-based assays in which cells express native-state MOG, presence of antibodies to MOG are a specific biomarker of a central nervous system (CNS) immune-mediated disease that is distinct from MS and AQP4 antibody seropositive (AQP4+) NMOSD. Pathologically, lesions in anti-MOG disease are indistinguishable from type II MS lesions and antibodies to MOG isolated from patients are pathogenic when infused into the cerebrospinal fluid (CSF) of rodents, suggesting a pathogenic role of the antibody in at least some cases, although this remains uncertain.

There are few population-based epidemiologic studies of MOG antibody-associated disease. In contrast to MS and NMOSD, the increased incidence in women vs men seems lower.

**Clinical Features**

The major clinical features of MOG antibody-associated disease are optic neuritis (ON), myelitis, acute disseminating encephalomyelitis (ADEM), and brainstem encephalitis with a course typical of other inflammatory demyelinating diseases. Patients can have either a monophasic or relapsing course; higher titers of MOG antibodies as well as persistent seropositivity over time predict a relapsing course.

Often bilateral with disc edema and inflammation involving more than half the length of the optic nerve, ON is associated with better outcomes than in AQP4+ NMOSD as is myelitis, which occurs in approximately 50% of patients with MOG antibody-associated disease.

**Neuroimaging**

Relapses of longitudinally extensive transverse myelitis (LETM) are rare in MOG antibody-associated disease whereas AQP4+ NMOSD accounts for 90% of relapsing LETM. Pontine and thalamic lesions of the brainstem are more likely in MOG antibody-associated disease than AQP4+ NMOSD, which more often manifests with area postrema syndrome or medullary lesions. In a small study of patients with an ADEM-like presentation, 88% of both adults (7/8) and children (8/9) with persistent seropositivity had a relapsing course, compared with no children (0/4) and 25% of adults (1/4) with transient seropositivity.

**Laboratory Studies**

Approximately 40% of children with ADEM have at least transient MOG antibodies and MOG-antibody seropositivity was associated with fewer emotional and behavioral problems, higher CSF pleocytosis, more frequent LETM, and higher relapse risk compared with patients with ADEM who were seronegative for MOG antibodies. Diagnostic recommendations published in 2018 recommended against testing for MOG antibodies in all patients with MS. The overall specificity of MOG antibody detection using a cell-based assay is 98.5%, although the sensitivity is lower. Testing should be done on serum and not CSF. Analysis of CSF reveals lymphocytic pleocytosis in approximately half of patients with MOG antibody-associated disease and only rarely oligoclonal bands or an elevated IgG index (5.7 and 7.3% respectively in one large study), in contrast to CSF findings typical of MS.

**Treatment**

Treatment of MOG antibody-associated disease consists of managing acute relapses and reducing risk of further relapses. Acute relapses are treated with intravenous methylprednisolone (IVMP), plasmapheresis (PLEX), and intravenous immunoglobulins (IVIG), and most patients respond well, although early relapses tend to occur after treatment. We generally use IVMP as a first-line treatment, with PLEX promptly for patients who do not respond well to IVMP or who have responded best to PLEX in the past. Either treatment can be followed by IVIG with or without a prolonged oral prednisone taper to minimize the risk of early relapse.

Identifying which patients to treat with long-term immunotherapy is not straightforward because approximately half of patients with MOG antibodies may have a monophasic course. In a large cohort, 36% of patients relapsed after a median of 16 months. At 48 months, 47% of patients had permanent neurologic disability. With repeat testing, most patients remain seropositive for MOG antibodies but those who seroconvert to negative status appear to be at low risk for relapse; patients with simultaneous ON or myelitis or ADEM-like illness appear to be less likely to remain seropositive over time. Repeat testing after 6 months is valuable for prognostication.

Most clinicians use similar management strategies for patients with MOG antibody-associated disease as for those...
with NMOSDs, favoring azathioprine (AZA), mycophenolate mofetil (MMF) and rituximab (RTX) (not necessarily in this order) over disease-modifying treatments (DMTs) used for patients with MS. A multinational study of 102 children with MOG antibody-associated disease found that treatment with interferon β and glatiramer acetate did not improve the annualized relapse rate (ARR), whereas a significant reduction in ARR was seen with AZA (ARR: 1.84 to 1.0), MMF (ARR: 1.79 to 0.52) and RTX (ARR: 2.16 to 0.51). We favor MMF or RTX, and research is needed to determine if either is more efficacious. When using MMF, it is important to provide additional immunotherapy (eg, oral prednisone or IVIG) for 3 to 6 months while titrating MMF and awaiting full efficacy. Further studies are needed to help guide prognostication and therapeutic decision-making in MOG antibody-associated disease.


Neuroimaging

Neuroimaging features are useful for distinguishing among NMOSD, MS and MOG antibody-associated diseases (Figure 1).

MRI. Inflammation involving more than half the length of the optic nerve, simultaneous bilateral ON, or involvement of the optic chiasm suggest NMOSD, and lesion length correlates with visual prognosis. Myelitis in NMOSD tends to involve central gray matter nonexclusively. Although LETM is a hallmark manifestation of NMOSD, it has a broad differential diagnosis including but not limited to infection, neurosarcoidosis, and SLE. Neurosarcoidosis, for example, can produce LETM distinguishable from NMOSD by the presence of constitutional symptoms, pulmonary or hilar adenopathy, hypoglycorrachia, elevated angiotensin converting enzyme levels, and persistent subpial contrast enhancement.

Corpus callosum lesions occur in 12% to 40% of patients with NMOSD and typically follow the ependymal lining: acute lesions are often edematous and heterogeneous, creating a marbled pattern. The complete thickness of the splenium may be involved, termed the arch bridge pattern. Extensive hemispheric white matter lesions may have a tumefactive appearance resembling Baló’s concentric sclerosis, ADEM or posterior reversible encephalopathy syndrome (PRES). Such large or confluent lesions are more common in children. Lesions surrounding the third ventricle and cerebral aqueduct (including the hypothalamus, ventral midbrain and near the circumventricular organs in the dorsal medulla) are typical of NMOSD. With gadolinium, lesions may appear poorly marginated, subtle, and patchy, терmed a cloud-like enhancement pattern. Pencil-
thin enhancement of lateral ventricle ependymal surface has been described, as have well-marginated nodular or meningeal areas of enhancement.  

Most lesions seen on MRI in patients with NMOSD are not typical of MS, and only 10% to 20% of patients who have brain lesions will meet Barkhof criteria for MS. In common practice across multiple centers, classic MS brain lesions (eg, Dawson’s fingers or subcortical u-fiber lesions) appear useful in distinguishing MS from NMOSD and MOG antibody-associated disease. The sensitivity and specificity of lesions for distinguishing between MS and NMOSD at disease onset was 79.8% and 87.5%, respectively in a study.

Optical Coherence Tomography. Widely used to characterize structural injury to the retina in demyelinating diseases (particularly MS), optical coherence tomography (OCT) has shown that ON episodes in patients with NMOSD cause a greater degree of retinal damage than in patients with MS (Figure 2). Studies with OCT have also demonstrated that retinal damage in NMOSD can occur independently of ON attacks, raising the possibility that neurodegeneration may contribute to disability, in addition to the relapse-driven disability most commonly attributed to AQP4+ NMOSD.

Treatment

Treatment of Acute Relapses

Because most disability in NMOSD accumulates as a direct consequence of relapses that typically leave substantial residual disability, a relapse can be considered an emergency, calling for prompt neurologic examination and evaluation for occult infection to identify pseudorelapses. Vision loss may be the only early predictor of true relapse. Emergent spinal MRI may be necessary for patients with new or changing symptoms and a prior episode of myelitis, particularly when signs and symptoms are not clearly localizable to a new lesion. High clinical
suspicion, aggressive acute treatment, and prompt initiation of preventative immunotherapy are critical.

Given our understanding of the pathophysiology of NMOSD, our practice is to administer intravenous methylprednisolone (IVMP) and plasma exchange (PLEX) as first-line acute therapy as quickly as possible for most patients with NMOSD when the clinical presentation is consistent with an exacerbation, especially those with AQP4+ NMOSD.

Corticosteroids. Acute exacerbations of NMOSD are initially treated with IVMP, typically 1 g daily for 3 to 5 days. Some clinicians include an oral prednisone taper starting at up to 1 mg per kg per day (usually 15-30 mg/day) and decreasing gradually over several weeks depending on individual factors such as timing of disease modifying therapy, patient comorbidities, and tolerance of oral glucocorticoids. Long-term oral glucocorticoids are associated with significant toxicity and are often avoided in favor of steroid-sparing immunotherapy.

Apheresis therapy (plasma exchange or immunoadsorption). Because antibodies to AQP4 activate the complement cascade leading to demyelination and necrosis with loss of astrocytes, axons, and oligodendrocytes, many clinicians, including the authors, advocate for early PLEX rather than using it only as a rescue therapy for patients who are not improving with IVMP. A retrospective study demonstrated improved outcomes when patients were treated with PLEX early in the course of an exacerbation.28 Probability of complete recovery decreased from 50% with PLEX immediately (day 0), to 1% to 5% after day 20, emphasizing the importance of early treatment. In another study, 51% of patients treated with IVMP and PLEX at day 5 after presentation recovered to prerelapse Expanded Disability Status Scale (EDSS) baseline compared with only 16.6% of patients who received IVMP only.29 Retrospective analysis of 871 patients having NMOSD attacks found the addition of PLEX to IVMP improved responder rates and that first-line PLEX was superior to IVMP for myelitis.30 Immediate initiation of apheresis (within 2 days of symptom onset) was associated with a 40% rate of complete response compared with 3.2% when started at 6 days after symptom onset, again emphasizing the importance of early PLEX.31 Strong predictors of a complete response were the use of apheresis as first-line therapy, time from onset of attack to start of therapy in days, presence of antibodies to AQP4, and monofocal attack. There was no significant difference between PLEX and immunoadsorption.

Intravenous Immunoglobulins. Data on the use of intravenous immunoglobulin (IVIG) in patients with NMO relapses remain limited, although small studies suggest that IVIG may be effective in preventing relapses.32,33

Relapse Prevention

We recommend prompt initiation of long-term immunosuppression once a diagnosis of NMOSD is made.34 No randomized clinical trial investigating preventative therapy in NMOSD has had final results published to date, therefore treatment is based on open-label prospective and retrospective studies. Given the available data, we prefer rituximab (RTX) for most patients with NMOSD. If there are contraindications to RTX, we typically use mycophenolate mofetil (MMF).

To date, the best-studied immunotherapies for NMOSD include RTX, MMF, and azathioprine (AZA). Treatment with RTX or MMF, and to a lesser degree, AZA, is associated with a decrease in relapse rates in patients with NMOSD; retrospective studies suggest that relapse risk is significantly higher with AZA compared with MMF or RTX.35,36 Treatment with RTX decreased relapse rate by up to 88%, with 2 of 3 patients achieving complete remission during a 10-year study period, whereas MMF reduced relapse rates by 87.4% with 36% failure rate and AZA reduced relapse rates by 72% with a 53% failure rate even when used concurrently with prednisone.35 A retrospective review of 116 patients found predictors of poor response to AZA or MMF included pretreatment history of severe attack and younger age. Among 40 patients with a poor
response to oral agents, 29 were changed to RTX, and among those, only 10% had a poor response to RTX.37

Adequate RTX dose is important in order to maintain remission. Although the optimal dosing regimen has yet to be determined, we agree with dosing protocols tailored to an individual’s rate of immune reconstitution. A target B-cell (CD19+ and CD20+) count less than 0.05% of total lymphocytes in the first 2 years and less than 0.1% thereafter can be considered.38 Some practices are monitoring the number of CD27+ cells in isolation as there is evidence that these are a marker for the return of disease activity.39 Because RTX can produce hypogammaglobulinemia which may be associated with significant infections, we monitor immunoglobulin levels prior to initiation and maintenance doses of RTX.40 Patients must also be counseled regarding the risk of infusion reactions and infections. No studies of ocrelizumab (an anti-CD20 monoclonal antibody approved for treating relapsing and primary progressive MS) for NMOSD have been reported.

Breakthrough Disease

If a relapse is confirmed while on immunotherapy, it is important to determine if the medication is being optimally dosed. For RTX, B-cell reconstitution should be investigated and dosing adjusted to optimize suppression of memory B cells. Based on clinical experience, we consider PLEX just prior to RTX infusions for patients with appropriately suppressed memory B cells who have a breakthrough relapse. Ongoing clinical trials will likely provide additional options for such patients. For patients on MMF, the lymphocyte count can be targeted to less than 1,500 per μL and dose increased up to the maximum dose of 3 g per day if necessary.

Treatment During Pregnancy

Risks of withholding acute treatment, including irreversible paralysis and blindness for the mother must be weighed carefully against risks of treating relapses during pregnancy. Lower infant head circumference and birth weight have been reported with corticosteroid exposure during pregnancy. Although historical data suggested corticosteroid exposure increased risks of cleft lip or palate, more recent studies have not reproduced this and suggest that the risk, if any, is very small.51 Plasma exchange has been administered safely for pregnant women with NMOSD relapse at various gestational stages.52

For preventative therapy, methotrexate and cyclophosphamide are contraindicated during pregnancy, whereas AZA and RTX appear to have better safety profiles.53 Although listed by the Food and Drug Administration (FDA) as pregnancy class D, in 3,124 women exposed to AZA during pregnancy, there was no increased risk of preterm birth, low birth weight, miscarriage, birth defects, major congenital malformations or neoplasia compared with that seen in unexposed mothers.54 Although RTX crosses the placenta after gestational weeks 16 to 20 and depletes fetal B cells, miscarriage and congenital malformation rates in children exposed prenatally are similar to that seen in the general population and B-cell depletion was associated with serious infection in only 1 of 153 offspring in a study.42 Given the relative safety of RTX, patients can be treated with RTX well before planned conception (e.g., a few months) and again in the early postpartum period. Monthly IVIG has also been used, although there is less data regarding efficacy.32 33

Treatment in Children

Treatment of pediatric NMOSD is largely similar to treatment in adults,43 although pediatric patients treated with RTX often require more frequent dosing as their B cells tend to reconstitute more rapidly than in adults.

Medications to Avoid in NMOSD

Several studies have suggested inefficacy or worsening of NMOSD associated with the use of some disease modifying agents used to treat MS, including interferon β,44 natalizumab,45 and fingolimod.46 Therefore, we avoid these agents for NMOSD.

Future Directions

Since 2014, clinical trials for several agents with potential to treat patients with NMOSD have been launched, including tocilizumab, satralizumab, eculizumab, and inebilizumab.47

Tocilizumab

Two open-label trials of tocilizumab, an interleukin-6 (IL-6) receptor antagonist, demonstrated a reduction in relapse rates in patients with AQP4+ NMOSD as adjunctive treatment or monotherapy.48 49 In one of these, 7 patients had an ARR reduction from 2.9 (despite background immunotherapy, including AZA or corticosteroids) to 0.4 with the addition of tocilizumab.49 In the other, 8 patients who were refractory to RTX treatment had an ARR reduction from 4.0 to 0.4 after treatment with tocilizumab.48 There was significant reduction in neuropathic pain for patients who received tocilizumab in both studies.

Satralizumab

Based on the success of tocilizumab, which requires dosing every 1-2 weeks, satralizumab (SA237) was developed. It is a humanized recycling monoclonal antibody targeting the IL-6 receptor with extended dosing frequency of once per month or longer. Preliminary results from a randomized, international, double blind phase 3 trial of satralizumab as adjunctive therapy showed satralizumab reduced the risk of relapse by 62% in patients with NMOSD (n = 83); those who
were AQP4* (n = 53) had a 79% risk reduction and who were AQP4* (n = 30) had a 34% risk reduction.\textsuperscript{50}

**Eculizumab**

Eculizumab is a monoclonal antibody that inhibits activation of C5 complement protein, thereby disrupting the complement cascade. In an open-label pilot study, 12 of 14 patients with AQP4* NMOSD (6 who had failed prior immunotherapy) had no attacks and 2 had possible minor single attacks while being treated with eculizumab for 48 weeks. After the trial, when returned to alternative immunotherapy (AZA, RTX, MMF, or prednisone), 5 had a relapse in the subsequent year. Hemolytic complement activity dropped from a mean of 88.5% to 0.4% after 6 weeks of treatment and remained suppressed during the study.\textsuperscript{51}

An open-label phase 3 double-blind placebo-controlled randomized trial of eculizumab in patients with AQP4+ NMOSD that permits patients to remain on certain background immunosuppressants to attenuate the placebo risk is ongoing. Eculizumab shows great promise, including in treatment-resistant NMOSD. However, use is associated with increased risk of infection by encapsulated bacteria that includes more than a 1,000-fold increased risk of meningococcal disease.\textsuperscript{52}

**Inebilizumab**

Inebilizumab (MEDI551) is a humanized monoclonal antibody against CD19 that targets B cells, B-cell precursors, and plasmablasts. The rationale for the considering inebilizumab is based on observations with RTX. Inebilizumab is currently being studied in a phase 3 clinical trial during which patients are randomized in a 3:1 ratio (inebilizumab to placebo) and those assigned placebo are transitioned to an open-label phase after 6.5 months. In results from the N-MOmentum\textsuperscript{a} trial announced via press release, inebilizumab treatment of patients with NMOSD reduced the risk of relapse by 77% compared with treatment with placebo. Primary and secondary endpoints of the trial were reportedly achieved.

**Other Investigational Drugs**

An open-label phase 1b trial of a C1-esterase inhibitor added to IVMP for patients with NMO/NMOSD relapses demonstrated safety and preliminary evidence for improved outcomes.\textsuperscript{53} Bortezomib is a proteasome inhibitor that depletes plasma cells and was given as adjunctive therapy to 5 patients with AQP4+ NMOSD who were not responsive to standard therapy. Clinical stability was seen in 5 of 5 patients and 80% of patients achieve relapse-free status.\textsuperscript{54}

In an open-label prospective pilot study of 16 patients with AQP4+ NMOSD, oral cetirizine (10 mg) daily added to current immunotherapy was well-tolerated and associated with a marginal but significant reduction in ARR.\textsuperscript{55}

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\textsuperscript{a} A double-masked, placebo-controlled study with open label period to evaluate MEDI-551 in neuromyelitis optica and neuromyelitis optica spectrum disorders (NCT02200770).

**Conclusions**

The diagnostic criteria for NMOSD were updated in 2015 and account for both patients who are AQP4 seropositive and seronegative. Treatment recommendations have been largely based on retrospective studies and expert clinical experience with data supporting RTX, MMF, or AZA. Ongoing clinical trials may offer more evidence for using new therapies in the near future. It is critical that neurologists encountering patients with suspected demyelinating disorders consider NMOSD in the differential diagnosis, thereby avoiding delays in recognition and treatment.


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**Disclosures**

MB serves on the editorial board of *Continuum: Lifelong Learning in Neurology*. The authors have no financial relationships relevant to this content to disclose.