PRACTICE CURRENT: An interactive exchange on controversial topics
Luca Bartolini, MD, *Section Editor*

Practice current

How do you treat neuromyelitis optica?

Aravind Ganesh, MD

Neuromyelitis optica (NMO) is an inflammatory disorder of the CNS that preferentially affects the optic nerve and spinal cord, causing optic neuritis and transverse myelitis, the latter typically being associated with longitudinally extensive signal change on MRI. It is estimated to affect about 1–3 individuals per 100,000 in the general world population, but is overrepresented in nonwhite populations (particularly Asians and those of Afro-Caribbean descent) as a major proportion of CNS demyelinating disease.^{1–5} It follows a relapsing course in the majority of individuals, and most patients have early disability due to severe relapses; within 5 years of disease onset, over 50% of patients with relapsing NMO are blind in one eye or both eyes or require ambulatory support.^{6,7}

The discovery of aquaporin-4 immunoglobulin G (AQP4-IgG) antibodies as a specific biomarker of NMO led to revision of the diagnostic criteria for the disease that required both optic neuritis and myelitis,⁸ with AQP4-IgG seropositivity included as a supportive criterion in the 2006 NMO definition.⁹ Since then, it has been recognized that there is a wide range of phenotypes for this disease, leading to the term NMO spectrum disorders (NMOSD), defined in 2007 to include AQP4-seropositive patients with limited forms of the classic presentation (such as recurrent optic neuritis or longitudinally extensive transverse myelitis [LETM]), or with other CNS manifestations (area postrema syndrome, acute brainstem syndrome, acute diencephalic syndrome, symptomatic narcolepsy, or acute cerebral syndrome).¹⁰ The 2015 diagnostic criteria for NMOSD (including patients with typical NMO) are stratified by the presence or absence of AQP4-IgG. These criteria recognize that seropositive patients meeting the 2007 NMOSD definition all have patterns of clinical or radiologic findings that have been detected in patients meeting the 2006 NMO definition, and that about 30% of patients with a NMOSD phenotype are AQP4-IgG-seronegative but have a similar natural history and response to therapy.¹¹ Seropositive patients with more limited forms often develop typical NMO over time; however, this interval may be years or decades.^{7,12} It is unknown why some

Department of Clinical Neurosciences, University of Calgary, Canada; and Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, UK.

Correspondence to: aravind.ganesh@ndcn.ox.ac.uk

patients remain with limited forms for prolonged periods and whether this affects disability outcomes. Recent studies have demonstrated that some AQP4-IgG-negative patients with NMOSD have antibodies to myelin oligodendrocyte glycoprotein (MOG).^{13–15}

Since NMO/NMOSD carries considerable morbidity and, sometimes, mortality, the importance of prompt and accurate diagnosis, followed by swift initiation of therapy for both the acute exacerbation and prevention of future relapses, is clear.¹⁶ Untreated, around 80% of patients experience a second attack within 2 years, and disability in NMO is almost exclusively related to relapses.⁷ There is considerable evidence that immunomodulatory agents used to treat multiple sclerosis (MS)—like interferon- β , natalizumab, fingolimod, and alemtuzumab—are ineffective in NMOSD and may exacerbate relapses.^{17–24} An exception is glatiramer acetate, which has been reported to show efficacy in NMOSD in some case reports.^{25,26}

Most of the available data for NMO management comes from nonrandomized, unblinded, retrospective studies. There have been no randomized controlled treatment trials in NMO; therefore, none of the treatments being used are US Food and Drug Administration–approved for an NMO indication. Studies have been either retrospective or open-label, and relatively small: see the expanded evidence summary in appendix e-1 at Neurology.org/cp regarding acute and preventative therapies and symptomatic management strategies in NMOSD, as well as the management of MOG-IgG-positive and double-seronegative (negative for both AQP4-IgG and MOG-IgG) patients. In brief, there is broad consensus on the benefit of immunosuppression (e.g., azathioprine, methotrexate, mycophenolate, and rituximab) in these patients, and observational studies have consistently reported a marked reduction in attack frequency with immunosuppression. These studies have a number of biases introduced by their design limitations, such as an unknown natural history of changes in relapse over time, in the absence of placebo or other appropriate control groups.²⁷ Furthermore, since these studies tend to enroll at or near the time of recent exacerbation, and NMO exacerbations tend to cluster, some regression to the mean is to be expected in study observations.¹⁶ The mortality rate in NMO also appears to have decreased over time,^{7,28} perhaps related to earlier diagnosis and appropriate treatment. Overall, immunosuppressive therapies appear to reduce the severity of relapses as well as their frequency.²⁹

Several uncertainties about the choice of treatment for both acute and longer-term preventative therapy in this disease remain. The appropriate duration of chronic immunotherapy for these patients is also unknown. Given the paucity of high-quality data, expert opinion can provide valuable guidance to inform the management of this complex disease.

EXPERT OPINIONS

The subsequent sections summarize the approach to immunotherapy in NMOSD followed by 3 experts in the field. The questions posed to the experts focused on the acute management of NMOSD, the prevention of relapses, and the suggested duration of immunosuppressive treatments. The interviews were recorded and are available online, as are the complete interview transcripts, which include additional questions posed to the experts in follow-up correspondence. In addition to immunotherapy, all 3 experts emphasized that the clinical approach to NMOSD is multidisciplinary, and that symptomatic management must be high in the priorities and tasks of the multidisciplinary team (see appendix e-2 for their detailed commentary on symptomatic management).

Michael Levy, MD, PhD (United States)

Acute treatment On the acute management side for NMO, there is less controversy as most neurologists still adopt the 1,000 mg IV methylprednisolone (IVMP) course for 5 days that we use for MS, acute disseminated encephalomyelitis, and other CNS autoimmune diseases. Only about a third of our patients with NMO are put on steroids alone; about two-thirds escalate and require something else. Most people in the field use plasma exchange (PLEX) as that next step. We do 1–1.5 volumes of blood for 5 cycles, and this removes 90%–95% of circulating

Supplemental Data

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antibodies and other inflammatory plasma components. This leads to remission and improvement in about two-thirds of cases. For those who do not improve, there are some thoughts about using cyclophosphamide or other chemotherapies or acute B-cell-depleting drugs, but nothing else has caught on as standard of care. IV immunoglobulin (IVIg) has been brought up as a potential alternative option. I applaud my colleagues who have launched a trial of IVIg vs standard therapy for transverse myelitis (A Multicentre Randomised Controlled Trial of Intravenous Immunoglobulin versus Standard Therapy for Transverse Myelitis [STRIVE], NCT02398994).³⁰ This trial includes treatment of transverse myelitis in NMO.

Immunotherapy for relapse prevention On the preventative side, there are many published studies of immunosuppressant drugs. The studies are all biased, either retrospective or prospective open-label, so we do not have the good hard data that we have in the case of MS or other diseases. But out of the approximately 25 studies that have looked at some form of immunosuppression, all of them have shown some sort of benefit, so they are all going in the same direction. It is the relative efficacy that is in question. The vast majority of the NMO world is on 1 of 4 drugs—azathioprine, mycophenolate, rituximab, or prednisone. They are all doing well, at least in the eyes of the patients and the physicians treating them. But even within each treatment option, there are uncertainties; for example, the dosage and monitoring required with rituximab, and the cancer risk with mycophenolate and azathioprine. There are unknowns specifically with respect to NMO: Are these patients more at risk of opportunistic infections? There is still the question of progressive multifocal leukoencephalopathy (PML); we are waiting for more cases of PML in NMO. We do not know with which drug it will occur, but it is likely to be in a chronically immunosuppressed patient. While there are unknowns, there are 3 phase III worldwide trials of different strategies in NMO that will shed light on appropriate treatments of NMO, including second-line immunotherapy options. This includes the following: (1) an anti-CD19 monoclonal antibody, MEDI-551 (N-Momentum study, NCT02200770)³¹; (2) eculizumab, a complement inhibitor approved for hemolytic anemias (Prevention of Recurrent Venous Thromboembolism [PREVENT] study, NCT01892345)³²; and (3) an anti-IL6 monoclonal antibody, SA237 (NCT02073279),³³ a long-acting form of tocilizumab.

Duration of immunotherapy What we know about NMO is that the disease will return if treatment is ever stopped. The disease persists lifelong, so treatment must be provided indefinitely. We always weigh the risks and benefits of any long-term immunosuppression, favoring those that have the safest profiles, like rituximab.

Management of MOG-IgG-positive and double-seronegative patients As for managing patients with differing antibody profiles, if their disease is relapsing, then regardless of the antibody profile, I treat them all equally aggressively. If the disease is monophasic, but AQP4-IgG-positive, I treat aggressively. Monophasic disease in the absence of AQP4 IgG is an unknown. I observe some patients, while I treat others.

Maria Isabel Leite, MD, DPhil (United Kingdom)

Acute treatment We approach acute attacks comprehensively with one or more treatments according to the patient's characteristics—age, severity of neurologic deficits, general health, and medical features like hemodynamic stability. We generally use high-dose IVMP (1g/d for 3–5 days) right away, with virtually all patients receiving a prolonged and slow taper of oral steroid afterwards. If the attack causes moderate to severe deficits, and patients have no contraindication for PLEX, this is started as soon as possible, sometimes overlapping with IVMP, ideally before day 10–15 post symptom onset. In patients with a quick and significant response to steroids, milder neurologic features, or significant comorbidities (e.g., hemodynamic instability or systemic infections), PLEX is not done. If there is no response to PLEX within 1 to 2 weeks of completion, another course of PLEX or an IVIg course may be used. Overall, acute treatment for attacks is similar in all forms of the disease, regardless of the antibody status. However, if the manifestations are not severe or there are potential relevant risks for using PLEX or IVIg, these treatments are not used in AQP4-IgG-negative patients because the risk/benefit ratio may be too high.

Immunotherapy for relapse prevention We use a small number of agents, mostly centered on those used in other autoimmune antibody-mediated diseases. In our experience, the use of low-dose oral steroid helps to maintain patients free of relapse. If patients agree and tolerate, we suggest taking prednisolone daily (5–15 mg) in addition to another immunosuppressive agent. Azathioprine and mycophenolate mofetil are the ones we use more frequently as first-line. The former is known to be safe in pregnancy; hence we tend to recommend this agent to younger women of childbearing age. We have been using mycophenolate mofetil more often now than in the past, mainly because it has been shown to be more effective than azathioprine in a retrospective study.³⁴ In older patients, especially, if weekly treatment suits them best, we use methotrexate, which we find equally effective and well-tolerated in many patients. Exceptionally we use new agents, such as rituximab, as first-line; never very soon after the attack because of the risk of increasing the autoimmune activity as a compensatory response to the CD20+ B-cell depletion.³⁵ The main reasons for leaving rituximab for second-line are the characteristics of the other agents, e.g., prednisolone, azathioprine, mycophenolate mofetil, and methotrexate: they are well-known by other health care providers, relatively well-tolerated, easily accessible and affordable, and offer good preventive response in the majority of our patients. Around 80% of our patients respond well to first-line treatments. As for second-line choices, because further attacks can leave irreversible and severe deficits, we almost always offer a new treatment regimen. This may be one of the other first-line agents. The first step in this process is, however, to understand why the disease became more active (new NMOSD attack)—is there an infection triggering the attack? Did the attack happen close to the time when the maintenance treatment had started (e.g., less than 3–4 months)? Was the patient taking a lower dose of the agents than recommended, and why? We rarely change from mycophenolate to azathioprine, unless the patient wants it and there is some clear rationale (e.g., pregnancy). In a small number of patients, we use rituximab as second-line, usually combined with low-dose steroids. We rarely treat with 2 agents (immunosuppressive and biological/monoclonal) as we have identified <1% of patients requiring such an aggressive approach, and because of the fear of serious complications like opportunistic infections.

Duration of immunotherapy Because patients with AQP4 antibodies have high risk of relapse, and the attacks often cause irreversible neurologic deficits, even many years after disease onset, regardless of their antibody level, we recommend long-term immunosuppression. AQP4-IgG-positive patients may need to be on treatment for many years, probably decades or for life. In our practice, if patients tolerate immunosuppression that provides effective relapse prevention, we keep them on that medication for as long as possible. Opportunistic or severe infections in patients with NMOSD on immunosuppression are relatively rare. We identified such problems in approximately 10% of our AQP4-IgG-positive patients with NMOSD, nearly all over the age of 60 at the time of infection and on treatment for more than 3 or 4 years.

Management of MOG-IgG-positive and double-seronegative patients For preventive chronic immunotherapy, we treat all AQP4-IgG-positive patients, as long as they are not contraindicated. Double-seronegative patients are offered immunosuppression only if they have a clearly recurrent illness that is not MS. If disease is inactive for more than 5 years of treatment, we may consider weaning off the immunosuppression. We rely on our clinical experience, over 3 years, to treat MOG-IgG-positive patients. In contrast to our first impressions, the disease is not always monophasic with good outcome; nearly 50% of patients have at least one relapse and do not always have complete recovery of deficits. To avoid early relapses, we tend to treat these patients with a reducing dose regimen of oral steroid for 6–12 months to prevent recurrent attacks, although we are still learning about the risk and severity of relapses among those patients, and their response to prompt treatment of acute attacks. If patients relapse on steroids, we may consider starting immunosuppressive medication.

Tarso Adoni, MD, PhD (Brazil)

Acute treatment For acute management of NMOSD attacks, we always prescribe methylprednisolone for 5 consecutive days. If there is no improvement of at least 50% in muscle

strength or visual acuity after 1 week, we start PLEX. We have not seen good results with IVIg at our center. We also have had trouble with the price. Our public system does not allow us to prescribe IVIg for indications other than Guillain-Barré syndrome.

Immunotherapy for relapse prevention For first-line maintenance immunotherapy, in terms of both cost and availability, we prefer to use azathioprine $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, plus prednisone tapered for 6 months. We use rituximab for patients who have failed on azathioprine. If it is impossible to obtain rituximab, then mycophenolate is the third option. Rituximab is more expensive than mycophenolate, but it appears to be more effective and we need to repeat rituximab dosing less frequently than mycophenolate (rituximab is given IV every 6 months whereas mycophenolate requires daily oral dosing).

Duration of immunotherapy The relatively recent understanding of the pathophysiology of NMO, coupled with the rarity of the disease, make it difficult to decide on the duration of immunosuppressive treatment as well as on the safety of discontinuing the medication after a certain period of disease inactivity. Given its severity and the potential for incomplete recovery, our approach is not to discontinue treatment in patients with NMO, maintaining close clinical and laboratory monitoring for possible infectious or neoplastic complications.

Management of MOG-IgG-positive and double-seronegative patients After the first clinical event in double-seronegative patients, I take into account the severity of the episode, whether there was good recovery, and whether there are other markers of autoimmunity, and I discuss the risks vs benefits of introducing immunosuppressive medication with the patient. If a second episode occurs, even in those seronegative patients, we always prescribe azathioprine. For those patients who are MOG-positive, whose clinical course is usually monophasic, we do not recommend immunosuppressive drugs unless there is a recurrence.

Lower/middle-income country (LMIC) challenges As for issues with NMOSD management in LMIC settings, one of the main challenges for Brazil as a whole is the difficulty of immediate access to MRI and CSF evaluation to exclude differential diagnoses. Our major concern when evaluating patients with potential NMOSD for the first time is the possibility of an infectious etiology. The northeast region of Brazil, which is the poorest area of the country, has the highest rates of schistosomiasis—this can pose a diagnostic challenge, particularly in those cases with LETM. Another issue is the highly unequal distribution of physicians and consequently of neurologists in the country, which leads to a long delay in the diagnosis of NMO and in turn a worse prognosis. We should also point out that only a quarter of the population has private health insurance, with most of them relying on the public health care system, which is not able to properly absorb this contingent. Testing for NMO-IgG is not available for everyone, so it can be difficult to establish the diagnosis. There is also the problem of high cost of proper investigation and treatment of patients with NMO, taking into account not only the cost of medications but also the long hospitalization in most cases. Other problems include the difficulty of getting rituximab or mycophenolate when recommended, owing to the price. There are known public centers of excellence in the treatment of patients with immune-mediated neurologic disease, but most of these centers are located in the southern and southeastern regions. My own region in São Paulo has at least 20 centers for the treatment of demyelinating disease. We try to send patients to these centers to avoid delay in diagnosis and treatment. There is a national effort for patients with suspected NMO/NMOSD to be cared for in such centers, and the Brazilian Academy of Neurology is working closely with the National Health System to facilitate access to drugs like rituximab for patients with NMO.

Preliminary survey results (February 9, 2017): Section Editor Luca Bartolini, MD

We collected 217 complete responses since January 26, 2017. The majority of survey takers ($n = 169$, 78%) treat adults only, in a hospital-based setting ($n = 172$, 79%) outside of the United States ($n = 141$, 65%). We observed equal distribution of responses between

Figure Interactive world map with survey results

A) Snapshot of the interactive world map centered on the United States with pie charts representing medications of choice for escalation of therapy of an acute neuromyelitis optica spectrum disorder attack in case of lack of response to a first-line agent after a week. Fifty-four percent of responders escalate to plasma exchange (red slice) and 23% to IV immunoglobulin (blue slice). (B) Snapshot of first choice for chronic preventative immunotherapy, highlighting lack of consensus across the globe, with 37% of responders who choose rituximab (blue slice), 32% who choose azathioprine (teal slice), and 14% oral steroids (deep pink slice). The size of all pie charts is proportional to the number of responses from each country or state.

trainees ($n = 96$, 44%) and faculty ($n = 114$, 52%), which confirms a strong interest of residents and fellows in offering a contribution to this initiative.

There is agreement on the choice of therapy for an acute NMOSD attack, with the majority choosing IV methylprednisolone ($n = 160$, 74%) and escalating to plasma exchange ($n = 116$, 54%) in case of lack of response after a week (figure, A). Interestingly, 23% of responders escalate to IVIg, which is the intervention currently being investigated by the STRIVE trial for transverse myelitis. We look forward to seeing the results of this study, which are expected in summer 2018, with potentially a subanalysis of patients with NMO. There is no consensus on first-line chronic preventative immunotherapy: a third of responders ($n = 81$) chose rituximab, a third ($n = 70$) azathioprine, and 14% ($n = 30$) oral steroids (figure, B); in case of relapse 6 months later, second choice for maintenance was rituximab ($n = 88$, 41%), azathioprine ($n = 24$, 11%), or mycophenolate ($n = 20$, 9%). In terms of duration of preventative treatment, the majority 60% ($n = 131$) recommended lifelong immunotherapy, as long as the patient remains relapse-free (31%) or free of opportunistic infections, neoplasms, and intolerable side effects (30%).

CONCLUSION

Treatment options for acute exacerbations in NMOSD include corticosteroids, PLEX, and less commonly, IVIg. There are few high-quality data but our experts agree that preventative treatment with immunosuppressive agents is indicated to mitigate debilitating relapses. Although

they disagree on the specific immunotherapeutic regimen, they tend to use monotherapy or some combination of prednisone, azathioprine, mycophenolate mofetil, or methotrexate as first-line agents, with rituximab mentioned as generally a second-line or more rarely a first-line agent. Management of patients with rarer forms of the disease—such as those who are MOG-IgG-positive or double-seronegative—is more controversial. Ongoing clinical trials will furnish higher-quality evidence to shed light on some of these questions.

Michael Levy, MD, PhD, is an Associate Professor of Neurology at the Johns Hopkins University and Director of the Neuromyelitis Optica Clinic. He completed the MD/PhD program at Baylor College of Medicine (Houston, Texas) with a focus on neuroscience. Dr. Levy came to Johns Hopkins in 2004 for a 1-year internship in the Osler Medicine program, then a 3-year residency in the Hopkins neurology program and a 2-year fellowship in neuroimmunology. In 2009, he was appointed to the faculty as Assistant Professor. Clinically, he specializes in taking care of patients with rare neuroimmunologic diseases including neuromyelitis optica, transverse myelitis, and recurrent optic neuritis. In addition to 4 monthly clinics, Dr. Levy is the principal investigator on several clinical studies and drug trials for these conditions. In the laboratory, his research focus is on the development of animal models of neuromyelitis optica with the goal of identifying new targets for therapies.

Maria Isabel Leite, MD, DPhil, is an Honorary Consultant Neurologist and Senior Clinical Research Fellow at the Nuffield Department of Clinical Neurosciences at the University of Oxford. Dr. Leite has clinical and laboratory experience in the field of autoimmune neurology. In particular, her clinical and research work are focused on patients with autoantibody-mediated diseases of the nervous system such as neuromyelitis optica spectrum disorders, autoimmune encephalitis, glycine receptor antibody-mediated syndromes, and myasthenia gravis. Dr. Leite has specific interests in understanding autoimmunization and the biological relationship between autoimmune diseases. In addition, she is studying the interaction between antibody-mediated diseases and pregnancy and autoimmune neurology in older adults to improve clinical care. She serves on the editorial board of *Neuromuscular Disorders* and has published in leading journals including *Neurology*[®], *JAMA Neurology*, *Neurology Neuroimmunology & Neuroinflammation*, *Annals of Neurology*, and *Brain*.

Tarso Adoni, MD, PhD, is the Director of the Multiple Sclerosis and Neuromyelitis Optica Treatment Center at Hospital Sírio-Libanês, São Paulo, Brazil, and member of the Executive Board of the Academia Brasileira de Neurologia. He obtained his medical degree from São Paulo State University, Brazil, and completed his neurology residency and a fellowship in demyelinating diseases at São Paulo University, where he also obtained his PhD working with neuromyelitis optica.

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