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Review article

Saudi consensus recommendations on the management of Neuromyelitis Optica Spectrum Disorders (NMOSD)

Eslam Shosha [a,1], Salman A. Aljarallah [b,1], Norah Al Fugham [c], Ahmed H. Al-Jedai [d], Majed M. Al Luqmani [e,f], Yaser M. Al Malik [g,h], Hajer Y. Al Mudaiheem [d], Hessa S. Al Otaibi [i], Faisal Y. Al Thekair [g,h], Ibtisam A. Al Thubaiti [j], Rumaiza H. Al Yafeai [k], Nabila S. Ben Slimane [l], Reem F. Bunyan [m], Edward J. Cupler [n], Sultan M. Mubarki [o], Jameelah A. Saeedi [p], Mohammad A. Al Jumah [q,*]

[a] Division of Neurology, Department of Medicine, McMaster University, HHSC, Hamilton, ON, Canada
[b] Department of Medicine, King Saud University, Riyadh, Saudi Arabia
[c] Neurology Department, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
[d] Deputyship of Therapeutic Affairs, Ministry of Health, Riyadh, Saudi Arabia
[e] College of Medicine, Taibah University, Madinah, Saudi Arabia
[f] Division of Neurology, King Fahad Hospital, Madinah, Saudi Arabia
[g] College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[h] Division of Neurology, King Abdulaziz Medical City (National Guard Health Affairs), Riyadh, Saudi Arabia
[i] Neurology Unit, Department of Medicine, King Fahad Hospital, Jeddah, Saudi Arabia
[j] Department of Neurology, King Fahad Military Medical Complex-Dhahran, Eastern Region, Saudi Arabia
[k] Department of Psychiatry and Psychology, My Clinic International Medical Co, Jeddah, Saudi Arabia
[l] Drug Information Center, Department of Pharmaceutical Care, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia
[m] Division of Neurology, King Fahad Specialist Hospital, Dammam, Eastern Region, Saudi Arabia
[n] Department of Neurosciences, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia
[o] Pharmaceutical Care Department, King Fahd Central Hospital, Ministry of Health, Jazan, Saudi Arabia
[p] Department of Neurology, King Abdullah bin Abdulaziz University Hospital, Riyadh, Saudi Arabia
[q] Department of Neurology, King Fahad Medical City, Ministry of Health, P.O. Box: 59046, Riyadh 11525, Saudi Arabia

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ABSTRACT

This article focuses on the diagnosis and management of neuromyelitis optica spectrum disorder (NMOSD). NMOSD is an autoimmune, demyelinating condition characterized by inflammation of the optic nerve and/or the spinal cord, with symptoms that can range from mild impairment of movement to paralysis. The newly approved diagnostic criteria have improved the accuracy of NMOSD diagnosis. The management of NMOSD is under major revolution due to the many new therapeutic options. The role of the antibodies directed at aquaporin-4 (AQP4) has materialized as a biomarker for NMOSD. Several new treatments that target variable aspects in immunopathology such as IL-6, complement, or depletion of B cells are emerging. The management of AQP4-negative patients remains challenging.

1. Introduction

Neuromyelitis Optica (NMO) is an autoimmune condition of the central nervous system that is characterized by attacks of inflammation involving the optic nerve and/or the spinal cord (Kessler et al., 2022; Borisow et al., 2018). The discovery of aquaporin-4 (AQP4) antibodies, which explained the significant majority of NMO cases, has changed the understanding of this disorder and expanded the phenotype beyond the optic nerve and spinal cord to include the brainstem, diencephalon, and other cerebral regions, now termed neuromyelitis optica spectrum disorder (NMOSD) (Lennon et al., 2022). NMOSD accounts for about 1.5% of cases of demyelinating disease in Caucasian populations, with a

* Corresponding author.
E-mail address: jumahm@gmail.com (M.A. Al Jumah).
[1] These authors contributed equally to this work.

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higher proportion in non-Caucasian populations, or populations with a lower prevalence of MS. A registry involving multiple centers in Saudi Arabia, Kuwait, UAE, Oman, and Bahrain found 144 patients fulfilling the diagnosis of NMOSD, with 95 (65%) patients being AQP4 antibody-positive (Shosha et al., 2022a). NMOSD can occur at any age, with a mean age typically being in the late thirties (Shosha et al., 2022a) while the mean age of MOGAD is usually ten years less (Jurynczyk et al., 2022).

Despite the best methods of testing, about 30% of patients with clinical presentation consistent with NMOSD don't have AQP4 antibodies, i.e., seronegative NMOSD. Antibodies to myelin oligodendrocyte glycoprotein (MOG) explain a significant proportion of those cases (Kitley et al., 2022). In addition to NMOSD, patients with MOG antibodies can present with different manifestations such as acute disseminating encephalomyelitis (ADEM), and autoimmune encephalitis, among other presentations, all are included under the umbrella term anti-MOG Associated Disorder (MOGAD).

The increased recognition of this disorder in the gulf region and the availability of multiple treatment options necessitated guidance on the best practices in the diagnosis and management of this disorder. For that reason, a group of experts in Saudi Arabia from multiple disciplines, including neurologists, neuroimmunologists, and pharmacists, gathered to develop comprehensive guidance on the management of this disorder under the umbrella of the Saudi Arabian Ministry of Health.

2. Diagnosis

The first criteria for the diagnosis of NMO were published in 1999 then later revised in 2006 (Wingerchuk et al., 2022a, 2022b). In 2015, the International Panel for NMO Diagnosis (IPND) met and proposed new criteria which introduced the nomenclature of NMOSD and expanded the spectrum to include cerebral, brain stem, and dicephalic syndromes (Wingerchuk et al., 2022c). This new iteration increased the sensitivity of the criteria and significantly lead to an increase in the number of patients diagnosed with NMOSD without reducing the specificity (Papeix et al., 2022; Hamid et al., 2022).

The key diagnostic criteria are summarized in Box 1.

Box 1. Key diagnostic criteria for NMOSD[9].

- Presence of any neurological manifestation, or a CNS lesion with a corresponding non-neurological manifestation, along with positive AQP4-IgG ***or***
- NMOSD symptoms alongside radiologic changes fulfilling the MRI criteria according to IPND, in addition to:
  - *Absence of AQP4-IgG and anti-MOG antibodies in the serum and in CSF using cell-based assay (CBA)*
  - *Supportive criteria from CSF (neutrophilic or eosinophilic pleocytosis and absence of oligoclonal bands)*
  - *Testing for antibodies is performed during the attack and off immunotherapies*
  - *Exclusion of other demyelinating diseases*
- Asymptomatic positivity for AQP4-IgG does not qualify for diagnosis
- Double seropositive (for AQP-4 IgG4 and anti-MOG antibodies) patients is uncommon (0.7%)
- The presentation of NMOSD may overlap with a number of other conditions, including systemic lupus erythematosus (SLE), Sjögren's syndrome, Behçet's disease, neurosarcoidosis, vascular pathologies, chronic infections, lymphoma, genetic conditions, autoimmune diseases/autoantibodies, compressive disorders, CNS or other malignancy, and neurodegenerative conditions.

IPND: International Panel for NMO Diagnosis.

Several additional points should be considered within the differential diagnosis for NMOSD. Care has to be taken in making or excluding the diagnosis of NMOSD based on imaging alone. For example, area postrema syndrome (APS) causes symptoms of unexplained nausea, vomiting, or hiccups that occur with or without identifiable imaging abnormality, which is highly suggestive for NMOSD. However, a lesion within the area postrema is not specific for NMOSD and can be seen in a variety of other disorders affecting the brainstem (Shosha et al., 2022). Longitudinally extensive transverse myelitis is a core feature in NMOSD. However, short segment myelitis can occur in NMOSD, and failure to consider it leads to a delay in the diagnosis (Flanagan et al., 2022). Also, seronegative NMOSD could potentially encompass a multitude of conditions with variable aetiologies and pathophysiologies. Therefore, other immune or non-immune causes must be carefully considered. The management for NMOSD is based on the administration of corticosteroids (see below), but the presence of symptoms that respond to steroids is not specific to this condition. NMOSD can arise in rare cases through an autoimmune reaction to neoplastic disease (paraneoplastic NMOSD) (Sepúlveda et al., 2022; Yuan et al., 2022).

3. Managing acute NMOSD relapses

Managing acute NMOSD attack involves various modalities; high dose of steroids, plasma exchange, and IVIG. Previous finding in a retrospective study where a 7-day delay in methyl prednisone treatment was detrimental to recovery from optic neuritis (Stiebel-Kalish et al., 2022), early initiation of treatment as it is crucial to optimize recovery. In addition, tapering the course of steroids until effective steroid-sparing immunosuppression is achieved. Studies have shown that the duration of taper varies depending on the steroid-sparing medication, usually between 3 and 9 and up to12 months (Watanabe et al., 2022; Kleiter et al., 2022).

Retrospective studies show that early plasma exchange (PLEX) therapy for patients with NMOSD has clinical benefits (Kleiter et al., 2022; Bonnan et al., 2022). Evidence of IVIg efficacy in NMOSD relapses is limited based on available data (Li et al., 2022).

Based on the above findings and our expertise, we recommend the following:

1 Initiating early treatment with a short (3–5 day) course of pulse IV methylprednisolone (1000 mg), followed by tapering the course of steroids and maintenance dose (10–20 mg), until effective steroid-sparing immunosuppression is achieved.
2 PLEX to be given as 5 to 7 exchanges of 1–1.5 plasma volume per session as an effective management option for NMOSD relapses. PLEX should be considered for NMOSD in the following scenarios:

- Failure to improve by more than or equal to 25–50% of deficit 7 days after steroids. A second course of corticosteroid can be considered if plasma exchange is contraindicated or unavailable.
- PLEX should be used as a first-line or additive to steroids in the following scenarios:

lowerRoman%1 Patients with prior history of poor response to steroids.
lowerRoman%1 Patients with severe relapses. Early use of plasma exchange is highly recommended for any patient with disabling relapse.
lowerRoman%1 The panel agreed on the following definitions of severe relapses:
a Severe overall disability (EDSS ≥4) or,
b Ambulatory functional systems scale (FS) ≥5 or,
c A relapse causing pyramidal FS ≥4 or
d Severe optic neuritis (visual FS ≥4) or bilateral involvement
lowerRoman%1 .
1 IVIG can be considered as an alternative to steroids or plasma exchange if they are contraindicated or not available and the patient cannot be transferred to a center with PLEX.
2 In the availability of a single modality, a repeated course can be considered, in refractory cases.

3.1. Preventing NMOSD relapses

The following applies to patients with the diagnosis of NMOSD as per

IPND 2015 criteria. Patients with MOGAD or other disorders are not included in this section and will be addressed separately. As NMOSD is a chronic relapsing disease where relapses can be severe and devastating, relapse prevention using immunosuppression is the cornerstone in preventing disability and maintaining a good quality of life. Of importance, treatments aimed to prevent relapses should be started early, as soon as the diagnosis is confirmed. A delay in initiation of immunosuppression puts the patient at risk of disabling relapse and side effects of corticosteroids.

3.2. Rituximab

Rituximab is a widely used chimeric monoclonal antibody that exerts its action by depleting lymphocytes from B cell lineage via the binding to CD20 on the cell surface. This binding initiates a cascade of events leading to the lysis of the B lymphocytes by mechanisms of complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) (Cerny et al., al.). The use of Rituximab in NMOSD was first reported in 2005 in a small open-label study (Cree et al., 2022a). Since then, there have been multiple reports, case series, and small clinical trials confirming rituximab efficacy in the prevention of NMOSD relapses (Nikoo et al., 2022; Tahara et al., 2022; Damato et al., 2022).

We recommend the following:

Dosing

Giving two doses of Rituximab, 1000 mg each, 2 weeks apart. The dose of follow-up infusions is variable across institutions and practices. A single dose of 1000 mg IV is commonly used in the literature for NMOSD patients (Damato et al., 2022).

With B cell depletion, rituximab might trigger NMOSD relapses, we recommend that patients who received oral prednisone in the first month (30–40 mg) are tapered until discontinuation.

Monitoring of blood CD19 levels is commonly used to guide the need for retreatment with Rituximab. About 17% of NMOSD patients will repopulate their B cells before 6 months (Greenberg et al., 2022).

Secondary hypogammaglobulinemia results from chronic depletion of antibody-producing cells. Very low levels are associated with recurrent infections. There management of hypogammaglobulinemia in the context of rituximab therapy is variable among practitioners. but there is agreement that immunoglobulin replacement with IVIG is indicated for patients with very low IgG levels and severe or recurrent infections. In this meeting, we discussed the following IgG cut-offs and threshold for immunoglobulins replacement (see Table 1).

Precautions

Latent infections such as tuberculosis, hepatitis B, and C, in addition to any relevant infection, must be excluded before treatment initiation. Evaluation by a specialist is warranted for any suspicion of the above conditions or positive screening tests. In addition to CD19 level, patients must be assessed for symptoms of infection, allergic reactions, or side effects that could be attributed to rituximab. Regular monitoring of blood counts, renal and liver functions are also recommended.

Monitoring

i Giving two doses of Rituximab, 1000 mg each, 2 weeks apart, the following regimen, is a single dose of 1000 mg IV i*ii. To avoid relapses following rituximab infusion, maintain* oral prednisone in the first month (30–40 mg).

ii The subsequent doses can be administrated either according to CD19 level, or every 6 months.

iii Replacement with IVIG is indicated for patients with very low IgG levels and severe or recurrent infections. In this meeting, we discussed the following IgG cut-offs and threshold for immunoglobulin replacement (see Table 1).

Table 1
Consensus recommendations based on expert opinion are to consider IgG repletion with IVIG, based on serum levels of IgG (mg/dL).

Serum total IgG level (mg/dL)	Recommendation
>500	unlikely to need replacement
300–500	heavily dependent on infection history; may use responses to vaccines to judge
150–300	consider replacing with IVIG, especially if a clearly documented history of recurrent infections
<150	recommend replacing with IVIG regardless of infections

3.3. Inebilizumab

Inebilizumab is a humanized monoclonal antibody that binds to the CD19 molecule which is present on the surface of B lymphocytes (Schiopu et al., 2022). In a phase 2/3 placebo-controlled study (N-Momentum), Inebilizumab delayed the time to a confirmed NMOSD with a hazard ratio of 0.27 (ARR by 77.3%) (Cree et al., 2022).

We reached a consensus on the following:

Dosage

Inebilizumab should be initially given as two separate 300 mg IV infusions, 2 weeks apart, then one 300 mg infusion every 6 months.

Precautions: Similar to rituximab.

Monitoring: Similar to rituximab

Hypogammaglobulinemia Secondary to B Cell Depletion (similar to Rituximab)

3.4. Eculizumab

Eculizumab is a recombinant humanized monoclonal antibody that binds to human complement component 5 (C5) and inhibits its activation, and the subsequent formation of the membrane attack complex (MAC), a major contributor to cellular damage in some autoimmune disorders (Hillmen et al., 2022). The PREVENT trial was a randomized, double-blind, time-to-event trial examining the efficacy of eculizumab in patients with AQP4-NMOSD (Pittock et al., 2022). Adjudicated relapses occurred in only 3 patients out of the 96 (3%) on eculizumab compared to 43% of patients in the placebo arm. This translates to a 94% reduction in the annualized relapse rate compared to placebo. In this trial, one patient died from empyema and he was on both eculizumab and azathioprine. Meningococcal infections are also a concern with this medication. Of note, at the time of preparation of this report, eculizumab was not included in the Saudi Food and Drug Agency's (SFDA) list of registered medications and was not approved for the indication NMOSD.

We have agreed on the following:

Dosage

900 mg of eculizumab IV weekly for 4 weeks, followed by 1200 mg every 2 weeks.

Precautions

Administration of the first vaccination dose against *Neisseria meningitides* is required 2 weeks prior to starting eculizumab, the following vaccine dose can be given 8 weeks later, while the patient is on eculizumab. In urgent cases, administer vaccine(s) as soon as possible, and provide 2 weeks of antibiotic prophylaxis. The same recommendation can be applied when active infection with *Neisseria meningitides* is resolved. We recommend administrating the pneumococcal vaccine in immune-compromised patients or above the age of 60.

Monitoring

Periodic blood work for complete blood count (CBC), kidney and liver function is required (see label)

3.5. Satralizumab

Satralizumab is a humanized monoclonal antibody that, similar to

tocilizumab,[2] binds to subunits of the IL-6 receptor, perhaps with a higher affinity and longer half-life. Two clinical trials evaluated Satralizumab as monotherapy or as an add-on (Traboulsee et al., 2022; Kimbrough et al., 2022). In both studies, Satralizumab reduced the ARR by 79% as add-on therapy, and by 74% as monotherapy. Of note, in both clinical trials patients with AQP-4 negative AQP4 did not benefit from this Satralizumab. Satralizumab has been approved by the US FDA and EMA for patients with AQP4 positive NMOSD. At the time of preparation of this manuscript, Satralizumab was not in the approved medications by the SFDA.

We recommend the following:

Dosage

120 mg of Satralizumab should be given subcutaneously at 0, 2, 4 weeks, then every 4 weeks.

Precautions

Hepatitis B immune status, and other required vaccines must be updated. TB testing, baseline, CBC, kidney, renal functions, and lipid profile should be done before initiating treatment.

Monitoring

Periodic blood work for CBC, kidney and liver function, lipid profile, and blood sugar should be done.

3.6. Conventional Immunosuppressants

Prednisone, azathioprine, mycophenolate mofetil, methotrexate, mitoxantrone, and cyclophorid have been used in the management of NMOSD. Multiple studies, mostly observational, have shown their efficacy in the treatment of NMOSD (Kimbrough et al., 2022). We agree on their use on a case-by-case basis.

3.7. Our recommendations for the prevention of NMOSD relapses

3.7.1. AQP4+ NMOSD

All patients with AQP4+ NMOSD should receive long-term immunosuppression with a steroid-sparing medication. Consider an inhibitor of CD20, CD19, or IL6. Treatments such as azathioprine or mycophenolate mofetil can be considered if none of the above are available or contraindicated (see Table 2). Cost, availability, comorbidities, pregnancy planning, and logistics should be considered when choosing from the above treatments.

We recommend switching patients who fail azathioprine, mycophenolate, methotrexate, cyclophosphamide to rituximab, Inebilizumab, tocilizumab, or Satralizumab.

Add-on maintenance low-dose prednisone (5–20 mg/d) can be used in certain situations to increase efficacy. Care must be taken to evaluate, prevent and manage corticosteroid side effects. (see text and table).

Eculizumab should be considered in patients with highly aggressive disease (2 or more disabling relapses within 1year) or fails one of the monoclonal antibodies.

If eculizumab is not available, add-on azathioprine, mycophenolate, or methotrexate to tocilizumab or satralizumab, can be considered based on evidence from the SAkuraSky trial (Yamamura et al., 2022).

3.8. Seronegative NMOSD

Exploration of other possibilities is crucial, and revisiting the diagnosis is important, especially if there is continuing worsening or lack of response to immunotherapy.

Rituximab, inebilizumab, azathioprine, or mycophenolate mofetil can be considered as first-line therapy (Chan and Lee, 2022a).

Add-on maintenance low-dose prednisone (5–20 mg/d) can be used in certain situations to increase efficacy (Mealy et al., 2022). Care must be taken to evaluate, prevent and manage corticosteroid side effects.

Tocilizumab and Satralizumab appear to be ineffective in AQP4 IgG-NMOSD, therefore, they should not be used in those patients.

As seronegative NMOSD patients were not included in the eculizumab trial, its efficacy is not known in this population. We recommend using it only in exceptional scenarios, under expert guidance, and with careful monitoring of outcomes.

However, we do not encourage switching stable patients to other treatments for reasons not solely driven by efficacy.

Interferons, natalizumab, dimethyl fumarate, alemtuzumab, fingolimod, and teriflunomide should be avoided in such patients.

At this point, we recommend evaluation by a physician with expertise in neuroimmunology disorders.

3.9. Managing NMOSD in pregnant women

3.9.1. Relapses in pregnancy

We advise avoiding repeated courses of IV methylprednisolone during pregnancy

Plasma exchange appears to be safe during pregnancy and we encourage considering it in patients with moderate to severe relapses (Shosha et al., 2022).

3.9.2. Relapse prevention in pregnancy

As NMOSD relapses are commonly severe and disabling, all patients with APQ4 NMOSD should be under effective immunosuppression before, during, and after pregnancy.

Azathioprine may be continued alone or with a small dose of steroid. Some experts suggest monitoring WBC count on weekly basis and halving the dose at 32 weeks if WBC is less than 8.6 × 109/L.

For patients on Rituximab, conception can be attempted two months after the most recent dose. We recommend that rituximab be given intrapartum if B cells repopulate. Rituximab crosses the placenta in the 2nd and 3rd trimesters, therefore, the newborn should be evaluated by a paediatrician regarding immunity and the effect on vaccinations.

Reliable contraception must be used during treatment with mycophenolate mofetil, and the drug should be withdrawn 6 weeks before conception for a patient planning a pregnancy. Methotrexate should be withdrawn 6 months before a planned conception (Shosha et al., 2022).

Monthly IVIG can be considered a preventive method.

3.10. Anti-MOG associated diseases (MOGAD)

MOG-associated NMOSD is a very recently described phenomenon and experience is growing concerning its management. Patients who require long-term treatment are those with a relapsing disease or persistent MOG-IgG antibodies beyond 6 months. For acute attacks, we recommend treatment with IV methylprednisolone followed by oral corticosteroids, with PLEX reserved for more severe/refractory attacks. We have reached a consensus to continue oral corticosteroid treatment such as prednisone after the first attack for 3–6 months. Monthly IVIG, mycophenolate mofetil, azathioprine, and IL-6 inhibitors are options for relapse in prevention for patients with a high risk of relapses. Data on rituximab in MOG is conflicting but it appears to be less effective than in anti-AQP4+ NMOSD (Durozard et al., 2022).

3.10.1. Medications to avoid in NMOSD

Some disease-modifying therapies for MS can exacerbate NMOSD. The use of interferons, natalizumab, dimethyl fumarate, alemtuzumab, and fingolimod are not safe in patients with confirmed or suspected NMOSD (Kira, 2022). We agree that these medications should be avoided in NMOSD patients.

3.10.2. Relapses and symptom treatment

Two Asian series report an incidence of 22–25% of PTS among patients with NMOSD (Kim et al., 2022; Liu et al., 2022). For NMOSD patients with bothersome PTS, we suggest a sodium channel blocker

[2] Tocilizumab is registered by the SFDA

Table 2
Additional management options for NMOSD.

	Dosing	Pre-treatment	Monitoring	Options for switching	Side effects
Azathioprine (AZA)	2.5–3 mg/kg/day given once or twice daily. Start 25 mg/d if TPMT is not available Prednisone bridge starting 1 mg/kg/day, then taper to not less than 30 mg/day until AZA is effective (typically within 6 months) then taper slowly to discontinue.	Check CBC, LFT, creatinine. Exclude TB and hepatitis B and C Check thiopurine S-methyltransferase enzyme (TPMT) status	CBC, LFT, creatinine; weekly for 1 month then every 2 weeks for 2 months, then monthly for 1 year. Frequency can be reduced thereafter. Increasing MCV can be used as a target	Rituximab Mycophenolate mofetil	Transaminitis, hypersensitivity, neoplasms (skin, lymphoma), nausea, anemia, pancreatitis
Mycophenolate mofetil (MMF)	1000 mg bid (up to 3000 mg/d) (start low and increase to target dose over 2 weeks) Prednisone bridge starting 1 mg/kg/day, then taper to not less than 30 mg/day until AZA is effective (typically within 3–6 months) then taper slowly to discontinue.	Check CBC, LFT, creatinine. Exclude TB and hepatitis B and C	Initially, monthly CBC, LFT, creatinine (weekly if no TPMT) until a stable dose Best benefit when absolute lymphocyte count is less than 1.5 k/ml	Rituximab	Abdominal pain, diarrhea, teratogenicity, infections, malignancy, bone marrow suppression, renal impairment
Methotrexate (MTX)	Orally, 15–25 mg/week Supplement folic acid 1 mg/day	Check CBC, LFT, creatinine. Exclude TB and hepatitis B and C	Monitor liver function regularly Avoid NSAIDs	Azathioprine Rituximab Mycophenolate mofetil	

[a]Two 1000 mg doses are given 14 days apart for adults, four weekly doses of 375 mg for children; repeat every six months. [b]Total cumulative dose not to exceed 140 mg/m2.
LVEF: left ventricular ejection fraction; MCV: mean corpuscular volume; NSAID: non-steroidal anti-inflammatory drugs; TPMT: thiopurine methyltransferase.

such as carbamazepine or oxcarbazepine as an initial treatment option. Lacosamide is effective in the case report and we recommend its use in patients who fail or don't tolerate carbamazepine (Baheerathan et al., 2022). Other antiepileptics such as lamotrigine, topiramate, or gabapentin can be considered in PTS given their mechanism of action but supporting evidence is lacking. For patients with continuous muscle spasms or spams in the context of a spastic limb, anti-spasticity measures such as GABAergic agonists (baclofen or tizanidine), botulinum toxin, can be considered based on our consensus.

4. Disclosure

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Disclaimer

Clinical practice guidelines are evidence-based decision-making tools for managing health conditions. They are based on the best available information at the time of writing; moreover, they are regularly updated. The present recommendations are not meant as fixed protocols and strict treatment guidelines. Additionally, they are not intended to replace the clinical judgment of practicing physicians; rather, they are only tools to help in the management of patients with neuromyelitis optica spectrum disorders. Treatment decisions must always be considered on a case-by-case basis; further, the prescribing physicians should personalize care and customize the treatment regimen to the patients' personal circumstances and medical history. Furthermore, physicians should consult the approved product monographs within their institution's formulary for each drug for the dosage, special warnings and precautions for use, contraindications, and monitoring of side effects and potential harms. Institution formulary restrictions should be considered when selecting treatment options. Parts of this manuscript have been posted before on the official website of the Ministry of Health in Saudi Arabia with the consent of the authors. The posted parts have been since removed but could explain the high similarity check.

Declaration of Competing Interest

Authors deny any conflict of interest.

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