Review article

Latin American consensus recommendations for management and treatment of neuromyelitis optica spectrum disorders in clinical practice

Edgar Carnero Contentti, Juan Ignacio Rojas, Edgardo Cristiano, Vanessa Daccach Marques, José Flores-Rivera, Marco Lana-Peixoto, Carlos Navas, Regina Papais-Alvarenga, Douglas K. Sato, Ibis Soto de Castillo, Jorge Correale

A R T I C L E  I N F O

Keywords:
Neuromyelitis optica spectrum disorder
Consensus recommendations
Diagnosis
Antibody testing
Latin America
Clinical practice

A B S T R A C T

Background: During the last two decades, neuromyelitis optica spectrum disorder (NMOSD) has undergone important changes, with new diagnostic markers and criteria, better recognition of clinical phenotypes, better disease prognosis and new therapeutic approaches. Consequently, management of NMOSD patients in Latin American (LATAM) has become more complex and challenging in clinical practice. In making these consensus recommendations, the aim was to review how the disease should be managed and treated among LATAM patients, in order to improve long-term outcomes in these populations.

Methods: A panel of LATAM neurologists who are experts in demyelinating diseases and dedicated to management and care of NMOSD patients gathered virtually during 2019 and 2020 to make consensus recommendations on management and treatment of NMOSD patients in LATAM. To achieve this consensus, the RAND/UCLA methodology for reaching formal consensus was used.

Results: The recommendations focused on diagnosis and differential diagnoses, disease prognosis, tailored treatment, identification of suboptimal treatment response and special circumstances management. They were based on published evidence and expert opinions.

Conclusions: The recommendations of these consensus guidelines seek to optimize management and specific treatment of NMOSD patients in LATAM

1. Introduction

During the last 25 years, neuromyelitis optica (NMO) spectrum disorder (NMOSD) has undergone important changes, with new diagnostic criteria, better recognition of clinical phenotypes, identification of anti-aquaporin-4 antibodies (AQP4-ab), better assay methods, and disease prognosis as well as new therapeutic approaches (Wingerchuk et al., 2015; Flanagan, 2019; Lana-Peixoto and Talim, 2019; Flanagan and Weinsenker, 2014; Weinsenker and Wingerchuk, 2017; Sato et al., 2014a, b; Lennon et al., 2005). However, there remain significant unmet needs with its management, in terms of disease diagnosis, wider symptom control and specific treatment (Wingerchuk et al., 2015; Flanagan, 2019; Lana-Peixoto and Talim, 2019; Flanagan and Weinsenker, 2014; Weinsenker and
Wingerchuk, 2017; Sato et al., 2014a, b; Lennon et al., 2005).

Latin America (LATAM) is a large region of the American continent that extends from Mexico (32° North latitude) to the Argentinian and Chilean Patagonia in South America (56° South latitude), including the Caribbean Islands (Alvarenga et al., 2017). LATAM inhabitants are a heterogeneous, multiethnic group of individuals. They have diverse variants and genetic proportions among Mestizos, the most representative ethnic population, who themselves are the product of centuries of interracial mixing between Native Americans (or Amerindians), White Caucasian Europeans, and Black Africans (Alvarenga et al., 2017; Papais-Alvarenga et al., 2015). NMO prevalence in LATAM ranged from 0.37/100,000 (Volta Redonda city) to 4.2/100,000 inhabitants (Caribbean Islands) and NMOSD (Alvarenga et al., 2017; Papais-Alvarenga et al., 2015; Hor et al., 2020), which is not a classic demyelinating disease (Kawachi and Lassmann, 2017), represented 11.8% of all inflammatory diseases of the central nervous system (CNS) in a large multicenter study from South America (Alvarenga et al., 2017; Papais-Alvarenga et al., 2015; Hor et al., 2020; Kawachi and Lassmann, 2017; Rivas-Alonso et al., 2018; Rivera et al., 2008; Soto de Castillo et al., 2019). NMO has shown to be significantly different to MS as regards gender, ethnicity, morbidity and genetic susceptibility in this region (Kawachi and Lassmann, 2017; Rivas-Alonso et al., 2018; Rivera et al., 2008; Soto de Castillo et al., 2019). Unfortunately, there are no data on access and utilization of NMOSD care services in LATAM, unlike MS (Carnero Contentti et al., 2020).

Consequently, management of NMOSD patients has become more complex and challenging in clinical practice. Local and regional factors need to be considered when recommending how the disease should be managed and treated. Costs involved in diagnosis acquisition, medications, and long-term care of the disease are challenging for a region where developing healthcare systems are not designed or prepared to adopt adequate NMOSD care as part of their budgetary or societal responsibilities. Therefore, in making these consensus recommendations, the aim was to review how NMOSD (particularly AQP4-ab positive patients) should be managed and treated in LATAM in order to improve long-term outcomes in these populations in clinical practice.

2. Methods

A panel of LATAM experts in neurology who are dedicated to diagnosis and care of NMO patients gathered virtually during 2019 and 2020 to make consensus recommendations about management and treatment of NMO in LATAM. To achieve consensus, the RAND/UCLA methodology for reaching formal consensus was used (Alvarenga et al., 2017; Papais-Alvarenga et al., 2015; Hor et al., 2020). The method for developing practice guidelines through formal consensus is both a consensus method and a guideline method (Bell et al., 2014; Santorl et al., 2008; Rand Corporation 2001). As a consensus method, the purpose is to formalize the degree of agreement among experts by identifying and selecting, through iterative ratings with feedback, the proposals on which experts agree and those points on which they disagree or are undecided. The guideline methods are subsequently based on agreement proposals. As a practice guideline method, the purpose is to draft several recommendations that address questions of interest in clinical practice (Hor et al., 2020). This is a rigorous and explicit method based on involvement of user representatives and professionals in the field to which the guidelines relate, and on use of an external peer review phase, transparency, independence of development and management of conflicts of interest.

The first step in the process consisted of inclusion of working group experts. Experts were selected based on their experience in managing patients with NMO in different regions of LATAM. The working group was then divided into: a) a steering group, constituted by three professionals, including two chairpersons of the steering group (E.C.C and J.C) and a project manager; and b) a rating group of eight professionals who, in their daily practice, are directly involved in patient care. After the working group had been formed, the procedure consisted of the following phases:

1. Systematic review and synthesis of the literature: A systematic search of the literature, without language restrictions, was carried out on MEDLINE and EMBASE for the period 1990-2019. The search terms were “NMOSD”, together with the modifiers “treatment”, “diagnosis”, “personalized”, “care”, “pharmacovigilance”, “response”, “suboptimal”, “biomarkers”, “aquaporin-4 antibodies”, “magnetic resonance imaging (MRI)”, “precision”, “response”, “diagnosis”, “centers” and “guidelines”. Relevant clinical papers were distributed to the working group for review and summarization so that they could respond to the proposals and recommendations for discussion.

2. Development of proposal list: A list of proposals developed by the steering group was submitted to the rating group in the form of a questionnaire. At this stage, the proposals complemented or contradicted each other insofar as they considered all opinions expressed by the group members during the work sessions.

3. Rating: Initially, the statements on which the members of the rating group agreed were identified. For statements in which there was no agreement, two more rounds of votes were conducted, with interim feedback sessions based on the published evidence (see supplementary data 1). This phase concluded with selection of the proposals on which there was a consensus within the rating group. Existence of a consensus was defined as a situation in which 70% of the respondents agreed, and lack of consensus, in which ≥ 30% disagreed. The rules for rating and analysis of the scores were defined at the outset and were communicated to the rating group, prior to the first round. At every stage of the rating phase, members of the rating group were able to comment about their response to each statement. All the comments made were also analyzed in a qualitative manner to include comments in the next rating phase.

4. Drafting the initial version of the guideline: The steering group and the project manager drafted the first version of the consensus that was to be submitted to the peer review group based on the consensus proposals.

5. Peer review: An analytical report was drafted, drawing together all scores and comments from the peer review group members and, where applicable, from the participants in the public consultation.

6. Finalization: The final version of the evidence reports, the consensus recommendations and a summary of the guideline were drawn up. The validated versions of these documents were disseminated.

2.1. Recommendations regarding disease diagnosis and immunological tests

-To achieve a confident diagnosis of NMO, there must be clinical involvement in at least one of the six CNS regions: optic nerve, spinal cord, area postrema of the dorsal medulla, brainstem, diencephalon or cerebrum.

Previously, involvement of both the optic nerve and spinal cord was mandatory in order to make the diagnosis of NMO in accordance with the 2006 NMO diagnostic criteria, in the absence of brain symptoms (Wingerchuk et al., 2007, 2006). The 2015 International Panel for NMO diagnostic criteria (IPND) (Wingerchuk et al., 2015) added area postrema (APS), brainstem (BSS), acute diencephalic syndrome (ADS) and symptomatic cerebral syndrome (SCS), to optic neuritis (ON) and acute transverse myelitis (ATM). This established the spectrum and validity of the clinical syndromes that are reported in clinically diagnosed NMO, thereby defining new core clinical criteria (Wingerchuk et al., 2015). More precise definition of the clinical presentations of NMO to allow it to be diagnosed in the presence of at least one of the six core clinical characteristics, along with detection of AQP4-ab and ruling out alternative diagnoses (Wingerchuk et al.,
2015). In patients who are negative for AQP4-ab or whose status is unknown, the IPND criteria are more stringent and MRI criteria must also be fulfilled.

**The 2015 International Panel for NMOSD diagnostic criteria should be applied to LATAM patients who are suspected of having NMOSD, in order to make diagnosis**

In the 2015 IPND criteria (Wingerchuk et al., 2015), revisions of the previous 2006 criteria were recommended (Wingerchuk et al., 2006) (Figure 1). These new criteria defined a uniform concept combining NMO and NMOSD, and consequently the term NMO was retained by using NMOSD (Wingerchuk et al., 2015). The panel emphasized the serological status (including negative and unknown status), the clinical implications of AQP4-ab and presence of highly suggestive MRI lesions. These factors reflect wider NMOSD phenotypes, thus facilitating earlier and more accurate NMOSD diagnosis (Wingerchuk et al., 2015).

Although the 2015 IPND criteria have not been validated in LATAM, it was demonstrated that they increase the rate and speed of NMOSD diagnosis in comparison with the 2006 NMO criteria, in two LATAM cohorts (Carnero Contentti et al., 2018; Fragoso et al., 2019). This result is in line with other reports worldwide (Hamid et al., 2017; Hyun et al., 2016).

**In the LATAM population, in addition to multiple sclerosis (MS), ruling out other regional diseases (local infections and nutritional diseases) that could mimic NMOSD is recommended.**

To rule out other regional diseases that mimic NMOSD, careful and detailed medical and epidemiological history-taking and physical examination are crucial (Thompson et al., 2018; Kim et al., 2017; Fragoso et al., 2017; Zatjirua et al., 2011; Delgado-García et al., 2019; Gray et al., 2011; Li et al., 2017; Lana-Peixoto et al., 2018; von Glehn et al., 2012; Cristiano et al., 2020). As shown in Table 1, in LATAM populations, certain infectious and nutritional diseases have higher prevalence, thus mimicking NMOSD, both clinically and on MRI (Thompson et al., 2018; Kim et al., 2017; Fragoso et al., 2017; Zatjirua et al., 2011; Delgado-García et al., 2019; Gray et al., 2011; Li et al., 2017; Lana-Peixoto et al., 2018; von Glehn et al., 2012; Cristiano et al., 2020). Fig. 1. This schematic diagram illustrates different NMOSD phenotypes according to the 2015 diagnostic criteria for NMOSD and the 2018 MOG international experts consensus recommendations. Abbreviations: AQP4-ab: anti-aquaporin-4 antibodies, TM: transverse myelitis, ON: optic neuritis, APS: area postrema syndrome, BSS: brainstem syndrome, ADS: acute diencephalic syndrome, SCS: symptomatic cerebral syndrome, MOG-ab: anti-myelin oligodendrocyte glycoprotein antibodies, LETM: longitudinally extensive transverse myelitis, ADEM: Acute disseminated encephalomyelitis, NMOSD: neuromyelitis optica spectrum disorders. * Given that positivity for both AQP4-ab and MOG-ab is extremely rare using recommended assays, if core clinical characteristics or ADEM-like and/or cortical signs are observed both antibodies should ideally be tested (if available).
testing had become available (Jarius et al., 2012). Misdiagnosis may earlier and more precise diagnosis and adequate treatment.

A referral to a neurologist with experience in diagnosing of demyelinating diseases, to ensure an

Cristiano et al., 2020).

Li et al., 2017; Lana-Peixoto et al., 2018; von Glehn et al., 2012;

Table 1

<table>
<thead>
<tr>
<th>General aspect</th>
<th>Causes</th>
<th>Clinical features to diagnosis</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious diseases</td>
<td>Neurotuberculosis</td>
<td>• Most common manifestation is tuberculous meningitis</td>
<td>Mantoux tuberculin skin test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tuberculomas, cerebral miliary tuberculosis, tuberculous encephalopathy and tuberculosis abscess may mimic NMOSD at least at the onset of infection</td>
<td>Interferon gamma release assays, if available</td>
</tr>
<tr>
<td></td>
<td>Neurosyphilis</td>
<td>• Although optic neuritis and transverse myelitis due to syphilis is rare, it could mimic to NMOSD.</td>
<td>Chest X-ray or Chest CT VDRL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Screening for neurosyphilis is relevant in bilateral optic neuritis and LETM patients because is treatable</td>
<td>To confirm with FTA-ABS test</td>
</tr>
<tr>
<td></td>
<td>Neurocysticercosis</td>
<td>• Most common presentation is related to epilepsy</td>
<td>Neuroimaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• MRI could mimic ‘open-ring’ Gd enhancement and NMOSD lesions</td>
<td>Immunological</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Calcified lesions in imaging examinations can aid in the differential diagnosis of MS and NMOSD</td>
<td>CSF and serum tests</td>
</tr>
<tr>
<td></td>
<td>Schistosomiasis</td>
<td>• Signs and symptoms of increased intracranial pressure, ataxia, delirium, seizures, visual impairment</td>
<td>Stool or urine samples</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Transverse myelitis, including acute transverse myelitis or subacute myeloradiculopathy of the lumbar sacral region is the most commonly reported neurological manifestation of both S. mansoni and S. haematobium infection</td>
<td>Serological test</td>
</tr>
<tr>
<td></td>
<td>Dengue-virus infection</td>
<td>• Recently become important in the diagnostic workup for brain and spinal demyelination on LATAM populations</td>
<td>Antibodies for dengue in blood and CSF samples</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Main neurological presentation is encephalopathy/encephalitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Although transverse myelitis/LETM, cerebellar syndrome and ADEM due to dengue is rare, it could mimic to NMOSD.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human T-cell lymphotropic virus type 1 (HTLV1)</td>
<td>• Main presentation is progressive spastic paraparesis</td>
<td>Blood or CSF immunological tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spinal cord clinical picture usually reflects impairment of the dorsolateral columns, which can also be identified by MRI as long-segment hyperintensity on T2 of the lateral columns</td>
<td></td>
</tr>
<tr>
<td>Nutritional deficits</td>
<td>Vitamin B12 deficiency</td>
<td>• Subacute combined degeneration of the spinal cord may manifest as associations of progressive motor, sensitive and autonomic dysfunction (erectile impotence, urine and fecal incontinence), gait, ataxia, mental disturbances and optical impairment</td>
<td>Vitamin B12 levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spinal cord MRI shows symmetric bilateral hyperintensity within the dorsal columns (the inverted ‘V’ sign)</td>
<td>Complete blood count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dietary deficiency (vegan/vegetarian diet or excessive alcohol intake), malabsorption (history of surgery, drugs, infections), pernicious anemia.</td>
<td>Others:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spinal cord MRI findings are similar to patients with vitamin B12 deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Folate deficiency</td>
<td>• Chronic and slowly progressive myelopathy, with gait impairment because of sensory ataxia</td>
<td>Folate levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spinal cord MRI findings are similar to patients with vitamin B12 deficiency</td>
<td>Complete blood count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dietary, malabsorption and bariatric surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Copper deficiency</td>
<td>• Chronic and slowly progressive myelopathy, with gait impairment because of sensory ataxia and lower limb spasticity</td>
<td>Copper serum levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spinal cord MRI findings are similar to patients with vitamin B12 deficiency</td>
<td>Zinc serum levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• History of zinc supplementation, gastric band surgery or malabsorption syndrome.</td>
<td>Complete blood count</td>
</tr>
<tr>
<td></td>
<td>Demyelinating disease Multiple sclerosis</td>
<td>• Unilateral optic neuritis, partial transverse myelitis, brainstem/cerebellar syndrome and cerebral syndrome</td>
<td>24-hour urine test for copper</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ovoid/round lesions adjacent to a lateral ventricle, inferior temporal lobe lesion, U fibers lesions, Dowson’s finger-type lesions and partial spinal cord lesions can distinguish MS from distinct aquaporin-4 antibodies serostatus NMOSD</td>
<td>Brain and spinal MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24-hour urine test for copper</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CSF proteins and white blood cells</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OCB</td>
<td>OCT and VEPs</td>
</tr>
</tbody>
</table>


Li et al., 2017; Lana-Peixoto et al., 2018; von Glehn et al., 2012; Cristiano et al., 2020).

-Patients with suspected NMOSD should be evaluated in a center with experience in diagnosing of demyelinating diseases, to ensure an earlier and more precise diagnosis and adequate treatment.

A referral to a neurologist with experience in NMOSD offers the opportunity to ensure that the diagnosis of NMOSD is correct. In a retrospective multicenter study in Europe, it was reported that 42.5% of NMO patients were misdiagnosed as having MS, mostly before AQP4-Ab testing had become available (Jarius et al., 2012). Misdiagnosis may have a significant impact on NMOSD care and on the costs to the healthcare system in our region. Accumulated disability as a result of failure to provide swift treatment for relapses may result in long-term neurological sequelae and delays in diagnosing NMOSD. In addition, there needs to be improved patient referral and understanding the impact of the relapses, as well as highly suggestive MRI lesions, together with an integrated multidisciplinary team approach towards limiting patient disability (Wingerchuk et al., 2015; Flanagan et al., 2019; Lana-Peixoto and Talim, 2019; Flanagan and Weinshenker, 2014; Weinschenker and Wingerchuk, 2017). An integrated approach to
clinical, laboratory and imaging examinations will enable accurate and precise differential diagnoses in suspected NMOSD patients (Wingerchuk et al., 2015; Flanagan, 2019; Lana-Peixoto and Talim, 2019; Flanagan and Weinschenker, 2014; Weinschenker and Wingerchuk, 2017; Mutch et al., 2014). Optical coherence tomography (OCT) can be a useful additional emerging tool in differentiating NMOSD from MS. Thus, OCT has shown that thinning of both peripapillary retinal nerve fiber layer and ganglion cell/inner plexiform layer after an ON relapse is more severe in AQP4-ab-positive NMOSD and MOG-ab-associated disease than in MS, in line with the clinical experience of poor vision outcomes in NMOSD (Bennett et al., 2015; Sotirchos et al., 2019; Oertel et al., 2017).

2.2. AQP4-ab, anti-myelin oligodendrocyte glycoprotein antibodies (MOG-ab) and lumbar puncture (PL) test statements

-Patients with suspected NMOSD should be tested for serum AQP4-ab.

Identification of the autoantibody biomarker AQP4-ab in 2004 was an important milestone in differentiating NMO from MS (Lennon et al., 2004;2005). Although the presence of AQP4-ab alone is not an absolute criterion for diagnosing NMOSD, it is frequently found (about 80%), in patients who fulfill the 2015 NMOSD criteria, when detected using an appropriate test, as reported in different large cohorts worldwide (Wingerchuk et al., 2015; Lennon et al., 2005; 2004; Prain et al., 2019; McCreary et al., 2018; Waters et al., 2012). Thus, detection of AQP4-ab is specific for confirming the NMOSD diagnosis in an appropriate clinical context (Wingerchuk et al., 2015). Nevertheless, analysis of AQP4-ab may not be widely available in LATAM using adequate laboratory techniques. It is also worth mentioning that the test results can be affected by a number of analytical, disease and treatment-related factors (Wingerchuk et al., 2015; Flanagan, 2019; Lana-Peixoto and Talim, 2019; Flanagan and Weinschenker, 2014; Weinschenker and Wingerchuk, 2017; Jarius and Wildemann, 2013; Takahashi et al., 2007; Fujihara and Sato, 2013; Margnieri et al., 2013). Thus, up to 20-30% of NMOSD patients, depending on the assay used, can be negative for AQP4-ab (Wingerchuk et al., 2015; Flanagan, 2019; Lana-Peixoto and Talim, 2019; Flanagan and Weinschenker, 2014; Weinschenker and Wingerchuk, 2017); these results higher in LATAM population (up to 35%; probably due to the methodology used (Carnero Contentti et al., 2020)).

-Serum AQP4-ab is best tested using cell-based assay (CBA) methods, whenever feasible, because of greater sensitivity and specificity.

Assay techniques for analyzing AQP4-ab status differ in their sensitivity and specificity (Waters et al., 2012; Fryer et al., 2014). In general, all AQP4-ab assays have been shown to be highly specific (97-100%) (Lennon et al., 2004; Prain et al., 2019; McCreary et al., 2018; Waters et al., 2012; Fryer et al., 2014). Direct fluorescence CBAs and fluorescence-activated cell sorting (FACS) assays have been shown to be the most sensitive and specific techniques for detecting serum AQP4-ab (Lennon et al., 2004; Prain et al., 2019; McCreary et al., 2018; Waters et al., 2012; Fryer et al., 2014). The sensitivity of CBAs was recently reported as being higher (92%) than those of the enzyme-linked immunosorbsorbent assay (ELISA) (60%) and tissue-based indirect immunofluorescence (IIF; 78%) among NMOSD patients in Australia and New Zealand who fulfilled the 2015 IPND diagnostic criteria (Prain et al., 2019). Serum was identified as being more sensitive than cerebrospinal fluid (CSF) for detecting AQP4-ab using FACS and commercial CBA methods (Majed et al., 2016). Therefore, serum is the most practical and cost-effective material for AQP4-ab testing.

-If CBA is not available, the ELISA technique is acceptable. However, patients without a typical clinical presentation of NMOSD should undergo a follow-up CBA: positive results would confirm NMOSD if ELISA is positive

CBA is strongly recommended, according to the 2015 IPND (a list of the referral centers where the authors work, performing AQP4-ab and MOG-ab detection through LATAM is showed in supplementary date 2) (Wingerchuk et al., 2015). ELISA may easily quantify the titer of AQP4-ab but has relatively low accuracy and has been shown to have higher false-positive rates in different studies conducted in Europe and Oceania, particularly among MS patients (Prain et al., 2019; McCreary et al., 2018; Waters et al., 2012; Jarius and Wildemann, 2013; Kim et al., 2012), when the titers are low. In addition, differential diagnoses are needed particularly if non-typical NMOSD clinical presentation or MRI lesions are found (Kim et al., 2017).

-To analyze AQP4-ab, serum samples should be taken before administering high-dose intravenous methylprednisolone (IVMP) or starting plasmapheresis (PLEX). However, treatment should not be deferred until the results are available.

Different clinical and serological conditions may lower the accuracy of AQP4-ab testing (Wingerchuk et al., 2015; Flanagan, 2019; Lana-Peixoto and Talim, 2019; Flanagan and Weinschenker, 2014; Weinschenker and Wingerchuk, 2017; Jarius and Wildemann, 2013; Takahashi et al., 2007; Fujihara and Sato, 2013; Margnieri et al., 2013). Likewise, it has been reported that serum AQP4-ab titers became lower after IVMP and PLEX treatment (Takahashi et al., 2007). Therefore, AQP4-ab samples should preferably be obtained during a relapse or before immunotherapy (Takahashi et al., 2007; Nishimura et al., 2018 Sep). However, patients with suspected NMOSD should not be given different treatment until the AQP4-ab result has been obtained, since relapses are usually severe and often lead to permanent disability if not treated promptly. Serum samples can be obtained and sent for analysis, and treatment can be started, while awaiting AQP4-ab results.

-AQP4-ab should be repeated after 3-6 months if the initial results were negative and suspicion of NMOSD is high (based on clinical and MRI features).

From expert opinions and reviews of the literature, negative findings from initial AQP4-ab testing lead to increased sensitivity of AQP4-ab detection in repeat testing 3-6 months later, especially if the initial test was performed during clinical remission, under immunosuppressant treatment (IST) or immediately following PLEX (Kim et al., 2017; Waters et al., 2012, 2014; Jarius et al., 2008; Palace et al., 2012; Trebst et al., 2014; Whitlam et al., 2017). Information from a few studies suggests that a slow increase in serum AQP4-ab titers occurs over time, even before a clinical relapse (Nagaishi et al., 2011). Special attention should be given to repeat AQP4-ab testing among seronegative patients with typical NMOSD manifestations, especially those with APS, neuropathic pain (Hyun et al., 2020; Asseyer et al., 2018) and paroxysmal painful tonic spasm (Carnero Contentti et al., 2016; Liu et al., 2017). These have been reported to occur more frequently in NMOSD than in MS and have a high impact on quality of life (Trebst et al., 2014; Whitlam et al., 2017; Beckman et al., 2019). Retesting AQP4-ab is especially recommended during a relapse and/or during treatment-free intervals, possibly 3-6 months after a previous examination and particularly with a more sensitive assay (Waters et al., 2014; Trebst et al., 2014; Whitlam et al., 2017).

-Clinical attacks of ON, ATM or APS in patients with systemic autoimmune disease (e.g. systemic lupus erythematosus [SLE] or Sjögren's syndrome [SS]) should be tested for AQP4-ab.

NMOSD is frequently associated with other systemic autoimmune diseases, particularly SS and SLE (Wingerchuk et al., 2007; Pittock et al., 2008; Birnbaum et al., 2017; Wingerchuk and Weinschenker, 2012). While antinuclear autoantibodies are often found in NMOSD patients (even in those who do not have clinical evidence of a systemic autoimmune disease), positivity for AQP4-ab in patients with systemic autoimmune diseases associated with cardinal manifestations of NMOSD such as ATM, ON or APS lead to the diagnosis of NMOSD (Wingerchuk et al., 2007; Pittock et al., 2008; Birnbaum et al., 2017; Wingerchuk and Weinschenker, 2012). Patients with SLE and SS...
but without symptoms of CNS involvement are consistently negative for AQP4-ab (Pittock et al., 2008; Birnbaum et al., 2017), which suggests that NMOSD is a separate entity from systemic rheumatic CNS diseases and that it may be attributable to a particular susceptibility for autoimmune diseases in those patients (Wingerchuk et al., 2007; Pittock et al., 2008; Birnbaum et al., 2017; Wingerchuk and Weinshenker, 2012).

- In patients with clinically suspected NMOSD with non-typical brain or spinal cord MRI lesions suggestive of MS, lumbar puncture with investigation of white blood cell count, protein levels, and oligoclonal bands (OCB) in CSF and serum is recommended, to evaluate differential diagnoses.

To avoid NMOSD misdiagnosis, evaluation of regional and non-regional differential diagnoses is crucial, as previously mentioned above. In this regard, CSF abnormalities are frequent during a NMOSD relapse and disappear during remission, but their role is still limited (Kim et al., 2017; Trebst et al., 2014). Mixed pleocytosis (lymphocytes, monocytes, polymorphonuclear and eosinophils cells), which might be elevated (up to 1000/mm³), and high protein levels are commonly found (Kim et al., 2011; Sellner et al., 2016; Ghezzi et al., 2004; Wingerchuk et al., 1999; Jarius et al., 2011). In contrast, CSF white blood counts higher than 50 cells/mm³ and protein content more than 100 mg/dl are very rare in MS patients, but are found in up to 35% of NMOSD patients (Kim et al., 2011, Sellner et al., 2016, Ghezzi et al., 2004, Wingerchuk et al., 1999, Jarius et al., 2011).

- The presence of OCB in CSF does not rule out the diagnosis of NMOSD.

While OCB in CSF occurs in 90% of Caucasian MS patients (Thompson et al., 2018), this is typically absent in NMOSD. However, OCB has been reported in up to 25-43% of NMOSD patients (17.1% in a LATAM cohort) (Carnero Contentti et al., 2020), particularly during a relapse. It can be transitory and mostly disappears in follow-up samples (Wingerchuk et al., 2007; Kim et al., 2017; Trebst et al., 2014; Whittam et al., 2017; Nagashi et al., 2011; Hyun et al., 2020; Assever et al., 2018; Carnero Contentti et al., 2016; Liu et al., 2017; Beekman et al., 2019; Pittock et al., 2008; Birnbaum et al., 2017; Wingerchuk and Weinshenker, 2012; Kim et al., 2011; Sellner et al., 2016; Ghezzi et al., 2004, Wingerchuk et al., 1999, Jarius et al., 2011). It is important to note that there are no reliable values on the real percentage of MS and NMOSD patients with OCBs in LATAM.

- In patients with suspicion of NMOSD who were negative for AQP4-ab (tested via CBA), performing MOG-ab is recommended.

- CBA must be used as the gold standard for evaluating MOG-ab in serum.

- The 2018 expert recommendations for MOG-ab-associated disease (Jarius et al., 2018) should be applied to LATAM patients who are suspected of having MOG-ab-associated disease, in order to make the diagnosis.

The role of MOG-ab in inflammatory CNS diseases has been reviewed (Sato et al., 2014a, b). Although these antibodies were associated with MS, their presence could not be reproduced in subsequent studies (Reindl and Waters, 2019). MOG-ab was found to be present in the serum of up to 40% of AQP4-ab-negative NMOSD patients (Jarius et al., 2016; Hamid et al., 2017), while in Brazil, these values were significantly lower (5/68; 7%) (Papais-Alvarenga et al., 2018). The presence of MOG-ab may discriminate between AQP4-ab-negative NMOSD patients and MS patients (Jarius et al., 2018, 2016; Reindl and Waters, 2019; Hamid et al., 2017; Papais-Alvarenga et al., 2018; Juryńczyk et al., 2019). Positivity for both AQP4-ab and MOG-ab is extremely rare when both assays are used (Juryńczyk et al., 2019). Indeed, several studies have clearly shown that MOG-ab-associated disease is a distinct entity from classical NMOSD, including two Brazilian cohorts (Sato et al., 2014; Jarius et al., 2016, 2018; Reindl and Waters, 2019; Hamid et al., 2017; Papais-Alvarenga et al., 2018; Juryńczyk et al., 2019; Waters et al., 2015; Reindl et al., 2020; Zamvil and Slavin, 2015; Narayan et al., 2018).

The panel recommends that MOG-ab-associated disease should be diagnosed in patients with any clinical feature suggestive of NMOSD who are negative for AQP4-ab, particularly in cases of ON, ATN, brainstem encephalitis, encephalitis or any combination of these syndromes (Jarius et al., 2018; Reindl and Waters, 2019; Jarius et al., 2016; Hamid et al., 2017; Papais-Alvarenga et al., 2018; Juryńczyk et al., 2019). However, it must be taken into account that an indiscriminate MOG-ab testing will probably elevate the false-positive rate (Juryńczyk et al., 2019). In this regard, it is also critical to use an adequate measurement technique (Papais-Alvarenga et al., 2018; Juryńczyk et al., 2019).

A CBA using cells transfected with full-length human MOG, can detect specific autoantibodies, which recognize conformational epitopes of MOG has the highest sensitivity and specificity (Jarius et al., 2018; Juryńczyk et al., 2019; Waters et al., 2015; Reindl et al., 2020, Zamvil and Slavin, 2015), as well as high reproducibility between different referral centers (Planagan, 2019). Therefore, CBA using immunofluorescence or flow cytometry is currently recommended as the gold standard to measure MOG-ab (Jarius et al., 2018; Juryńczyk et al., 2019; Waters et al., 2015; Reindl et al., 2020; Zamvil and Slavin, 2015).

2.3. Recommendations for MRI and complementary tests at diagnosis and follow-up.

-To diagnose NMOSD, a standardized MRI protocol should be applied at diagnosis and follow-up.

Brain and spinal MRI have important roles in making differential diagnoses and are very important tools for identifying patients with NMOSD (Kim et al., 2015; Carnero Contentti et al., 2018). Most lesions observed on MRI in NMOSD patients are not typical for MS, and only 10%-20% of patients who have brain lesions will meet the Barkhof criteria for MS (Kim et al., 2015). Brain MRI findings can differentiate MS from different AQP4-ab serostatus NMOSD using T2-weighted and FLAIR sequences, including LATAM patients (Table 2) (Matthews et al., 2013; Carnero Contentti et al., 2019). These MRI features suggestive of MS were included in the 2015 IPND criteria for NMOSD as "red flags" (Wingerchuk et al., 2015). Another study from LATAM has shown significant differences in lesion distribution at disease onset as well as in brain volumes during follow-up between NMOSD and MS (Silveira et al., 2020). Adequate repositioning (manually or via an automated positioning system) is needed to allow consistent comparisons among follow-up scans.

Because MS and other local diseases may at disease onset mimic NMOSD, standardization of MRI protocols for demyelinating diseases across LATAM centers is very important, since this would enable uniform performance and correct interpretation of studies. The recommended brain protocol is shown in Table 2.

-At NMOSD diagnosis, spinal cord MRI is recommended, following a standardized imaging protocol.

NMOSD patients can present ATM at disease onset or during follow-up. Around 85% of acute lesions extend ≥ 3 spinal segments (LETM) (Ciccarelli et al., 2019), which helps to differentiate AQP4-ab-positive NMOSD from MS and to facilitate the differential diagnosis (Kim et al., 2015; Carnero Contentti et al., 2018, 2019; Matthews et al., 2013; Silveira et al., 2020; Ciccarelli et al., 2019). Use of an MRI scanner with a minimum field strength of 1.5-T is strongly recommended. Use of an MRI scanner with a minimum field strength of 1.5-T is strongly recommended.

-In patients with short-segment myelitis (STM) on MRI (lesions affecting < 3 segments on sagittal spinal cord MRI) and normal or non-typical brain lesions for MS, AQP4-ab testing should be performed.

While STM was observed in 8% of NMOSD patients in LATAM (Carnero Contentti et al., 2018), it has been reported in up to 19.8% of
NMOSD patients worldwide (Jarius et al., 2012; Flanagan et al., 2015; Hu et al., 2018; Huh et al., 2017). The length of the lesion depends on the timing of the MRI scan (Carnero Contentti et al., 2018; Flanagan et al., 2015). Additionally, no significant differences in distribution lesion frequencies on axial topography (central vs. peripheral) were described in NMOSD patients who experienced STM (Jarius et al., 2012; Carnero Contentti et al., 2018; Flanagan et al., 2015; Hu et al., 2018). Although STM is rare in NMOSD, it should be considered as an initial manifestation to avoid NMOSD misdiagnosis or delay in making the NMOSD diagnosis and implementing specific treatment. Thus, AQP4-ab should be performed if MS has not been diagnosed (Flanagan et al., 2015).

- In patients with STM on MRI and normal or non-typical brain lesions for MS, who are negative for AQP4-ab, MOG-ab testing should be performed.

STM has been reported at least once over the course of the disease in around 44%–52% of all MOG-disease patients (Jarius et al., 2018, 2016; Reinl and Waters, 2019; Hamid et al., 2017; Papais-Alvarenga et al., 2018; Juryńczyk et al., 2019; Mariotto et al., 2017). Therefore, in patients who do not fulfill the 2017 diagnostic criteria for MS (Thompson et al., 2018) or who are negative for AQP4-ab, MOG-ab should be performed in order to allow a specific diagnosis (Jarius et al., 2018).

- In patients with ON, orbital MRI following a standardized protocol is recommended in order to facilitate differential diagnosis and to assess typical NMOSD lesions.

At disease onset, ON has a broad range of differential diagnoses (Amaral et al., 2020; Carnero Contentti et al., 2019; Petzold et al., 2014). Although orbital MRI is not required for the ON diagnosis, both orbital and brain MRI are necessary for evaluating differential diagnoses between different autoimmune and inflammatory optic neuropathies as well as compressive / neoplastic optic nerve affection, and detecting asymptomatic demyelinating lesions. Differentiation is critical for treatment choice and further patient management (Petzold et al., 2014). Orbital MRI is increasingly being relied on to confirm the ON diagnosis when the clinical diagnosis is uncertain (McKinney et al., 2013; Bursztyn et al., 2019; Srikajon et al., 2018). Orbital MRI in association with fat-suppression techniques has been shown to have higher sensitivity and specificity in detecting lesions suggestive of NMOSD (McKinney et al., 2013). Bilateral optic nerve involvement, posterior nerve predominance (especially with extension into the optic chiasm) or extensive lesions of the optic nerve (more than half of its length) are all suggestive of NOMSD, and they are different from those observed in MS (Wingerchuk et al., 2015; Kim et al., 2015; Carnero Contentti et al., 2018). The recommended orbital protocol is shown in Table 2.

### 2.4. Recommendations for disease prognosis

- **Number of relapses and their severity in NMOSD patients, during the first two years, predicts medium/long-term disability (5 to 10 years).**

Phenotypically, a secondary progressive clinical course in NMOSD is uncommon (Wingerchuk et al., 2007) and 90% of NMOSD patients have a relapsing course (Sellner et al., 2010; Ghezzi et al., 2004; Wingerchuk et al., 1999; Jarius et al., 2016). NMOSD patients have reported mean annualized relapse rates (ARR) of 0.82–1.3 (Sellner et al., 2010; Ghezzi et al., 2004; Wingerchuk et al., 1999; Jarius et al., 2016; Kitley and Leite, 2012; Palace et al., 2019) with a median time to reach the first relapse of 10–17 months (Ghezzi et al., 2004; Jarius et al., 2016; Kitley and Leite, 2012; Palace et al., 2019; Papais-Alvarenga et al., 2015). Disability is relapse-related (Kitley and Leite, 2012; Palace et al., 2019), particularly represented by persistent paraplegia and blindness. Long-term outcomes from relapses were strongly correlated with the severity of the relapse at presentation, regardless of treatment timing (Banerjee et al., 2019; Seok et al., 2016) and the initial onset attack (Palace et al., 2019). A history of severe relapse before an initial treatment was an independent risk factor for relapse after adjusting treatments (Palace et al., 2019; Shi et al., 2019). Although it has been reported that the location of the first relapse had no impact on the subsequent disability (Palace et al., 2019), patients with cerebral or brainstem-onset relapses experienced the highest relapse risk (Drulovic et al., 2019). Additionally, ON at disease onset has been reported to be more likely to develop with severe visual disability, compared with other symptoms at onset (Palace et al., 2019).

NMOSD patients have reduced life expectancy, with death often attributable to relapse, especially due to high risk of respiratory failure, extension of cervical lesions into the brainstem or primary brainstem relapses (Sellner et al., 2010; Ghezzi et al., 2004; Wingerchuk et al., 1999; Kitley and Leite, 2012; Palace et al., 2019; Papais-Alvarenga et al., 2015; Banerjee et al., 2019; Seok et al., 2016; Shi et al., 2019; Drulovic et al., 2019; Papais-Alvarenga et al., 2008; Wingerchuk and Weinshenker, 2003). Higher relapse frequency during the first two years of disease was associated with both high risk of...
relapses (Palace et al., 2019) and mortality due to NMO (Hu et al., 2018). The estimated mortality rate in different series was 15-30% (Kitley and Leite, 2012; Palace et al., 2019; Wingerchuk and Weinschenker, 2003; Mealy et al., 2018). However, recent estimates allowed establishing a lower mortality rate, probably based on an earlier diagnosis. In contrast, older age at disease onset, association with other autoimmune diseases as well as Japanese and African ancestry were associated with a worse prognosis (Carnero Contentti et al., 2020; Kitley and Leite, 2012; Palace et al., 2019; Wingerchuk and Weinschenker, 2003; Mealy et al., 2018).

At disease onset, the presence of AQP4-ab in NMO patients predicts worse medium/long-term disability.

AQP4-ab-positive status predicts a high risk of relapses in untreated patients with an initial event of NMO (LETM and ON) over time, even within the first year (Mattioli et al., 2008; Weinschenker et al., 2006). Recently, a prospective study reported that AQP4-ab-positive NMO patients without IST have a risk of relapse of 94% at five years (Shi et al., 2019). Currently, there is no relationship between antibodies titers and clinical and radiological activity, thus diminishing the likelihood of a specific cut-off that may predict relapses (Jarius and Wildemann, 2013; Waters et al., 2014; Jarius et al., 2008).

2.5. Recommendations for relapse and disease management

-Early IVMP treatment (1 g daily for 3–5 days) in acute relapses is recommended.

Because of the risk of severe residual disability following relapses, therapies for acute relapses are very important and need to be started as early as possible. In AQP4-ab-positive ON patients even a 7-day delay in IVMP initiation was detrimental to vision (Wingerchuk et al., 2015; Flanagan, 2019; Lana-Peixoto and Talim, 2019; Flanagan and Weinschenker, 2014; Weinschenker and Wingerchuk, 2017; Palace et al., 2012; Trebst et al., 2014; Stiebel-Kalish et al., 2019). In addition, evaluation of occult infection or metabolic alterations to diagnose pseudo-relapses should be performed. Although there are no randomized controlled trials on large cohorts regarding treatment of acute relapses, NMO patients are typically treated with 1 g of IVMP for 3–5 consecutive days (Flanagan, 2019; Lana-Peixoto and Talim, 2019; Flanagan and Weinschenker, 2014; Weinschenker and Wingerchuk, 2017; Palace et al., 2012; Trebst et al., 2014) and we recommended this management. Complete recovery through use of IVMP has been reported in up to 35% of NMO relapses (Abboud et al., 2016; Kleiter et al., 2016; Kleiter et al., 2018; Songthammawat et al., 2019; Bonnan and Cabre, 2012; Bonnan et al., 2018; Kleiter et al., 2018; Weinschenker et al., 1999; Magaña et al., 2011). The clinical benefit of PLEX diminishes after day 20, whether or not IVMP has been administered; therefore, starting PLEX early is recommended.

Because it has been reported that the maximum improvement is observed when the delay in starting PLEX is minimized (< 5 days), such that the clinical benefits gradually diminish, the longer the delay in starting PLEX is (see also the preceding and next statements) (Abboud et al., 2016; Kleiter et al., 2016; Songthammawat et al., 2019; Bonnan and Cabre, 2012; Bonnan et al., 2018; Kleiter et al., 2018; Weinschenker et al., 1999; Magaña et al., 2011).

PLEX should be considered for NMO patients with persistent neurological deficits, even beyond day 20 (acute phase) and particularly within 90 days after the attack onset.

As previously mentioned, PLEX has been shown to be beneficial, if it is implemented as early as possible. However, in a Korean study, the response rates did not differ significantly between NMO patients treated within 20 days and those treated after 20 days (66.7% and 61.5%, respectively) (Lim et al., 2013). Although it might be appropriate to consider PLEX for NMO patients without improvement within 90 days, other clinical or radiological factors relating to ongoing disease activity should help guide in making this decision.

2.6. Recommendations for long-term relapse prevention

The following are recommendations for AQP4-ab-positive NMO patients. Treatment strategies for MOG-ab-associated disease and double-negative NMO patients, where there are still controversies regarding treatment strategies, were not considered.

-Early start of IST treatments to reduce disease activity and therefore to prevent NMO relapses is recommended.

Long-term relapse prevention treatment is recommended for all AQP4-ab-positive and negative patients who are diagnosed with relapsing NMO (Flanagan, 2019; Lana-Peixoto and Talim, 2019; Flanagan and Weinschenker, 2014; Weinschenker and Wingerchuk, 2017; Palace et al., 2012; Trebst et al., 2014). In an outcome prediction model among AQP4-ab-positive NMO patients, IST treatment significantly
considered, and the dose used could be increased until optimal mon
adequate adherence to treatment) and a relapse is confirmed after 6
“suboptimal treatment response”.
therapy within five years of starting are classified as having
mean corpuscular volume increase of at least 5
with RTX or MMF if available, while leaving AZA for milder disease or
treating NMOSD, the panel recommends starting treatment of NMOSD
all the currently published NMOSD guidelines that AZA is effective for
(Palace et al., 2012; Trebst et al., 2014; Sellner et al., 2010). In addi-
tion, there is no standard management strategy for selection of first-line
therapy or treatment switching. Based on these three new clinical
Trials (Pittock et al., 2019; Cree et al., 2019; Yamamura et al., 2019),
more appropriate treatment strategies can probably be defined in the
near future. The characteristics of recommended IST treatment options
for NMOSD patients in LATAM are summarized in Table 3.
-Azathioprine (AZA; 2-3 mg/kg/day divided into 2-3 doses per day) has been shown to be effective and safe for preventing relapses of
NMOSD and for decreasing disability, and therefore it can be used as
a treatment for NMOSD.
 AZA was shown to be effective and safe in previous studies that
evaluated NMOSD patients (Bichueti et al., 2010; Costanzi et al., 2011;
Elsone et al., 2014; Qiu et al., 2015), including in a Brazilian cohort
recently published (Bichueti et al., 2019). In a prospective randomized
controlled trial (Nikoo et al., 2017), use of AZA gave rise to significant
decreases in both mean annualized relapse rate (ARR; 54% of the pa-
tients became relapse free after one year) and disability measured using
EDSS (from 2.40 to 1.95). Regarding comparative effectiveness between
AZA, RTX and MMF, retrospective studies found that RTX and MMF
were more efficacious than AZA (Stellmann et al., 2017; Mealy et al.,
2014; Jeong et al., 2016). Although there is a general consensus across
all the currently published NMOSD guidelines that AZA is effective for
treating NMOSD, the panel recommends starting treatment of NMOSD
with RTX or MMF if available, while leaving AZA for milder disease or
situations in which neither RTX nor MMF is available.
-NMOSD patients under treatment with AZA at a target dose of
2.5-3.0 mg/kg/day adjusted to the total lymphocyte count (< 600-
1000/µL) and a mean corpuscular volume increase of at least 5
points from the baseline, who present a relapse after six months of
therapy within five years of starting are classified as having
“suboptimal treatment response”.
If AZA is used correctly (early initiation, adequate dosing and
adequate adherence to treatment) and a relapse is confirmed after 6
months of drug therapy, a suboptimal response to treatment should be
considered, and the dose used could be increased until optimal mon-
itoring doses are reached (lymphocytes count between 600-1000/µL or
a mean corpuscular volume> 5 points compared to baseline)
(Palace et al., 2012; Collongues et al., 2019; Mealy et al., 2014). The
predominantly relapsing and often severe disease course of the disease
supports the use of long-term preventive treatments in patients with
NMOSD (Wingerchuk et al., 2007; Palace et al., 2012; Trebst et al.,
2014; Sellner et al., 2010). Furthermore, the time to next attack can
increase naturally in the later stages of the disease (Kim et al., 2013)
suggesting the possible natural change in the disease activity over time
(Kim et al., 2011). However, the duration of preventive treatment in
NMOSD that is needed has not been adequately studied. Absence of new
clinical relapses during an extended period of preventive therapy (e.g.,
more than 2 years) is viewed as probable treatment success. The ab-
sence of validated therapeutic biomarkers for NMOSD have suggested that
AQP4-ab-positive patients who present with a first ever attack of
LETM should be treated with immunosuppression for five years
(Weinshenker et al., 2006; Kimbrough et al., 2012). This time period is
arbitrary but attempts to balance the potential benefits of therapy
during a period of higher relapse risk (the first 2-3 years after pre-
sentation) against the risks of long-term toxicity, especially treatment
related to malignancy.
-Mycophenolate mofetil (MMF, at a target dose of 2-3 g/day
divided into two doses per day) has been shown to be effective and
safe for preventing relapse of NMOSD and for decreasing dis-
ability, and therefore it can be used as a first-line treatment for
NMOSD patients.
-NMOSD patients under treatment with MMF at doses between
1500 and 3000 mg/day, adjusted based on the total lymphocyte count (> 1000/µL), who present a relapse after six months of drug
therapy within five years of treatment start are classified as having
a “suboptimal treatment response”.
MMF is widely available around the world but, compared with AZA,
it is more expensive (Bichueti et al., 2019). MMF has been shown to
be effective and safe in retrospective studies on NMOSD patients.
Compared with AZA, MMF showed fewer side effects with more efficacy
(Jacob et al., 2009; HüH et al., 2014; Montcuquet et al., 2017;
Huang et al., 2019, 2018; Yang et al., 2018; Chen et al., 2017). In a
recent systematic review and meta-analysis, MMF was ranked as a more
tolerable therapy, compared with AZA and RTX (Huang et al., 2019).
If a relapse is observed during MMF treatment, it is important to confirm
whether MMF is being optimally dosed or whether increasing it to a
maximum maintenance dose of 3000 mg/day is necessary. However, in
a recent study, it was reported that 50.7% of patients experienced re-
lapse under MMF treatment (Montcuquet et al., 2017). Nonetheless,
99.7% of them continued to receive MMF and 83% achieved stabi-
lization or improvement of EDSS by the end of the follow-up. It was
concluded that relapse under treatment should not be the only para-
meter for assessing treatment efficacy in NMOSD (Montcuquet et al.,
2017). In general, if a relapse (“suboptimal treatment response”)
(Abboud et al., 2016) or ≥ 2 relapses or ≥ 1 severe relapse (“poor
response”) (Kim et al., 2017) is confirmed while patients are on MMF or
AZA, they must switch the treatment.
-In NMOSD patients who receive AZA or MMF, oral steroid tapering
should be maintained for at least 4-6 months.
If AZA or MMF is added as long-term IST therapy, concomitant use
of oral steroids for six months and tapering over the next six months is
recommended in order to prevent relapses while another steroid-
sparing therapy reaches full efficacy (Flanagan, 2019; Lara-Peixoto and
Talim, 2019; Flanagan and Weinshenker, 2014; Weinshenker and
Wingerchuk, 2017; Palace et al., 2012; Trebst et al., 2014; Sellner et al.,
2010).
-Low doses of oral steroids (5–10 mg of prednisolone or its
equivalent) should be administered for a prolonged period in combi-
nation with MMF/AZA in NMOSD patients who have “suboptimal
treatment response”.
Although general agreement for this statement was obtained, some
of the panel members mentioned that “use of oral steroids should be
decided on a case-by-case basis”. On the one hand, they commented: “in
patients with partial response to AZA/MMF, oral steroids in combina-
tion may be an acceptable approach”, on the other hand, “suboptimal
therapeutic response should lead to prompt and immediate change in
immunotherapy and not to administering steroids in association”.
In a prospective 18-month cohort trial, it was reported that com-
bination of AZA with oral steroids led to benefits with regard to pre-
venting relapse and improving disability (Mandler et al., 1998). In
addition, low doses of oral steroids as monotherapy have been reported
as having long-term beneficial effects with regard to reducing relapses
Table 3
Recommended immunosuppressant treatment options for NMOSD patients from Latin America

<table>
<thead>
<tr>
<th>Medication, route and dosage</th>
<th>Mode of action</th>
<th>Efficacy/Effectiveness</th>
<th>Main examinations and monitoring</th>
<th>Most common and important side effects</th>
<th>Recommendations and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral steroids (OS): meprednisone / prednisone (Palace et al., 2012, Trebst et al., 2014, Sellner et al., 2010, Mandler et al., 1998, Watanabe et al., 2007)</td>
<td>Oral: Start at 60 mg once daily and then taper. Target dose: 30-60 mg once a day.</td>
<td>Inhibits purine synthesis resulting in the inhibition of DNA, RNA, and protein synthesis</td>
<td>Free of relapse: 34%–61% Follow-up (FU): 18–47 mo EDSS (stabilization or improvement): up to 90% during 5 years of FU</td>
<td>Leucopenia, diarrhea, vomiting and sepsis</td>
<td>AZA should be avoided if using AZA as a parallel product.</td>
</tr>
<tr>
<td>Azathioprine (AZA) (Palace et al., 2012, Trebst et al., 2014, Sellner et al., 2010, Bichetti et al., 2010, Costanzi et al., 2011, Bione et al., 2014, Qui et al., 2015, Bichetti et al., 2019, Nikoo et al., 2017, Skil remaining, Mealy et al., 2014, Jeong et al., 2016)</td>
<td>Oral: Start at 25 mg and then increase by 25 mg daily. Target dose: 2500-3000 mg/kg daily in divided doses.</td>
<td>Binding to intracellular receptors which then act to modulate gene transcription</td>
<td>ARRs was significantly lower (0.49 vs. 1.48 per year) in OS periods (19.3 mo) than in the non-OS periods (45.3 mo)</td>
<td>Systematically evaluate for blood pressure, glycemia, electrolytes and bone density.</td>
<td>If adding MMF or AZA, we recommended OS for at least 1 mo and then taper OS for at least 1 mo and then taper OS could be used during pregnancy.</td>
</tr>
<tr>
<td>Mycophenolate mofetil (MMF) (Palace et al., 2012, Trebst et al., 2014, Sellner et al., 2010, Jacob et al., 2009, Huh et al., 2014, Montcuquet et al., 2017, Huang et al., 2019, Huang et al., 2018, Yang et al., 2018, Chen et al., 2017)</td>
<td>Oral: Start at 500 mg twice daily for 1–2 weeks and then increase to 1 g twice a day. Target dose: 1500 mg twice a day.</td>
<td>Prodrug of mycophenolic acid, an inhibitor of inosine-5′-monophosphate dehydrogenase (antimetabolite)</td>
<td>Free of relapse: 46%–73% FU: 20–27 mo EDSS (stabilization or improvement): up to 90% during 5 years of FU</td>
<td>Leucopenia, diarrhea, vomiting and sepsis</td>
<td>MMF should be combined with OS until its full effect (at least 4–6 months).</td>
</tr>
<tr>
<td>Rituximab (RTX) (Palace et al., 2012, Trebst et al., 2014, Sellner et al., 2010, Skil remaining, Mealy et al., 2014, Jeong et al., 2016, Kim et al., 2013, Kimbrough et al., 2012, Montcuquet et al., 2017, Huang et al., 2019, Huang et al., 2018, Damato et al., 2016, Torres et al., 2015, Zephir et al., 2015, Collongues et al., 2016, Jacob et al., 2008, Gao et al., 2019, Rodi et al., 2011, Kim et al., 2019, Shaygannejad et al., 2019, Marcinnò et al., 2019)</td>
<td>Intravenous: 1 g with re-treatment at 2 weeks or 375 mg/m2 body surface area once weekly for 4 weeks.</td>
<td>Chimeric monoclonal antibody against human CD20</td>
<td>Free of relapse: 52%–88% FU: 24–60 mo. EDSS (stabilization or improvement): up to 97% during 5 years of FU</td>
<td>Minor infections (urinary and respiratory tract) Non-serious infusion-related reactions</td>
<td>We recommend use concurrently of OS for at least 1 mo and then tapering. Monitoring B cells (CD19+/CD20+/CD27+) could be useful to plan retreatment. RTX could be used during pregnancy or overlapping syndrome (NMOSD and MS).</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Medication, route and dosage</th>
<th>Mode of action</th>
<th>Efficacy/Effectiveness</th>
<th>Main examinations and monitoring</th>
<th>Most common and important side effects</th>
<th>Recommendations and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eculizumab (ECZ)</strong> <em>(Pittock et al., 2019)</em></td>
<td>Intravenous 900 mg weekly during the first four doses starting on day 1, followed by 1200 mg every 2 weeks starting at week 4.</td>
<td>Humanized monoclonal antibody, which inhibits the terminal complement protein C3</td>
<td>Free of relapse: 96.1% FU: 96-weeks Relapse reduction: 93.1% EDSS (stabilization or improvement): not differences vs placebo</td>
<td>Pretreatment: ECG, pregnancy tests, chest X-ray, immunogenicity as measured by HAHA CBC, complete chemistry panel and urinalysis</td>
<td>Minor infections (respiratory tract, nasopharyngitis and urinary), headache. Non-serious infusion-related reactions. Increased risk of meningococcal and encapsulated bacterial infection. PREVENT trial was a randomized, placebo-controlled, time-to-event trial in AQP4-ab-positive NMOSD patients (add-on therapy). All NMOSD patients must receive meningococcal vaccination 14 days prior to the first dose.</td>
</tr>
<tr>
<td><strong>Sotralizumab</strong> <em>(Yamamura et al., 2019, See et al., 2020)</em></td>
<td>Subcutaneous 120 mg at weeks 0, 2, and 4 and then every 4 weeks</td>
<td>Humanized anti interleukin 6 receptor (IL-6R) monoclonal antibody type IgG2 (recycling technology)</td>
<td>Free of relapse: 81% (+ AQP4-ab) and 72% (- AQP4-ab) FU: 96-weeks Relapse reduction: 58% EDSS (stabilization or improvement): NA</td>
<td>CBC, LE, complete chemistry panel and urinalysis serological antibody testing for HIV, HBV, HCV and latent TBC. Pregnancy test</td>
<td>Minor infections Non-serious infusion-related reactions. We show data from pooled analysis from two phase 3, randomized, double-blind, placebo-controlled studies in + and - AQP4-ab NMOSD patients. Sakura-Sky was an add-on therapy study (with AZA, MMF or OS). Sakura-Start was a monotherapy study.</td>
</tr>
<tr>
<td><strong>Inebilizumab</strong> <em>(Cree et al., 2019)</em></td>
<td>Intravenous 300 mg in 2 doses on open-label days 1 and 15 and then 300 mg every 6 mo</td>
<td>Humanized monoclonal antibody against CD19</td>
<td>Free of relapse: 87.6% FU: 28-weeks Relapse reduction: 73% EDSS (stabilization or improvement): OR= 0.37</td>
<td>Pre-treatment: CBC, lymphocyte count, LE and serological antibody testing for HIV, HBV, HCV and VZV.</td>
<td>Minor infections (urinary and respiratory tract) Non-serious infusion-related reactions. Arthralgia.</td>
</tr>
<tr>
<td><strong>Tocilizumab (TCZ)</strong> <em>(Zhang et al., 2020, Lotan et al., 2019)</em></td>
<td>Intravenous 8 mg/kg every 4 weeks</td>
<td>Humanized monoclonal antibody against the interleukin-6 receptor</td>
<td>Free of relapse: 91.5% FU: 48-weeks Relapse reduction: NA EDSS (stabilization or improvement): OR= 0.34</td>
<td>Pretreatment: CBC, LE and latent TBC evaluation CBC and LE every 1-2 mo for 3 mo and then quarterly. Blood pressure</td>
<td>Anemia, infusion-related reactions, infections (TBC, opportunistic), elevated LE, hypertension. TANGO was a randomized, open-label, parallel-group study comparing TCZ vs AZA in + and - AQP4-ab NMOSD patients. TCZ could be considered in pregnant women with severe NMOSD.</td>
</tr>
</tbody>
</table>

ARR: annualized relapse rate; DNA: deoxyribonucleic acid; RNA: ribonucleic acid; mo: month/s; CBC: complete blood cell count; LE: liver enzymes (aspartate aminotransferase and alanine aminotransferase); TMPT: thiopurine methyltransferase enzyme; MCV: mean corpuscular volume; HIV: human immunodeficiency virus; HBV: hepatitis B-virus; HCV: hepatitis C-virus; VZV: varicella zoster-virus; TBC: tuberculosis; NMOSD: neuromyelitis optica spectrum disorders; MS: multiple sclerosis; ECG: electrocardiogram; HAHA: Human Anti-human Antibody; NA: not available.
in NMOSD. Relapses were significantly more frequently with 10 mg/d or less, than with over 10 mg/day (OR = 8.75) (Watanabe et al., 2007).

- Induction protocol with RTX should be based on infusion of doses of 375 mg/m² of body surface area, administered as an i.v. infusion once a week for four weeks, or 1000 mg i.v. with re-treatment at 14 days.

- Maintenance protocols with 1000 mg of RTX with a re-treatment at 14 days or one infusion of 1000 mg or one infusion of 375 mg/m² repeated every six months have been shown to be safe and effective for preventing NMOSD relapses and therefore can be used as the standard protocol for treating NMOSD patients.

RTX is not widely available in LATAM. Compared with AZA or MMF, it is more expensive (Bichuetti et al., 2019). RTX has been shown to be effective and safe in prospective and retrospective studies on NMOSD patients (Collongues et al., 2019; Stellmann et al., 2017; Mealy et al., 2014; Jeong et al., 2016; Montcuquet et al., 2017; Huang et al., 2019; Kim et al., 2017, 2015, 2011; Ciron et al., 2018; Damato et al., 2016; Torres et al., 2015; Zephir et al., 2015; Collongues et al., 2016; Jacob et al., 2008; Gao et al., 2019; Bedi et al., 2011). Several comparative studies have demonstrated that RTX is more effective than AZA and MMF in decreasing relapse severity and preventing relapses (Collongues et al., 2019; Stellmann et al., 2017; Mealy et al., 2014; Jeong et al., 2016; Montcuquet et al., 2017; Huang et al., 2019; Kim et al., 2017, 2015, 2011; Ciron et al., 2018; Damato et al., 2016; Torres et al., 2015; Zephir et al., 2015; Collongues et al., 2016; Jacob et al., 2008; Gao et al., 2019; Bedi et al., 2011).

Although some recommendation guidelines have suggested that RTX may be used as a first-line treatment (Palace et al., 2012; Trebst et al., 2014; Selliner et al., 2010), its high cost and the lack of head-to-head studies limit access to this treatment in many LATAM countries (Bichuetti et al., 2019). In this regard, some neurologists only use RTX treatment in patients who fail to respond or do not respond to first-line treatments like AZA or MMF (Collongues et al., 2016). Notably, RTX may decrease the invisible costs of NMOSD patients who potentially would have experienced poor responses to AZA or MMF, since its use will reduce the number of hospitalizations because of decreased ABR, less use of paraclinical examinations like MRI and laboratory tests, less use of IVMP and less need for rehabilitation due to relapses (Palace et al., 2012; Trebst et al., 2014; Selliner et al., 2010).

There is no standardized RTX protocol for NMOSD. No differences in efficacy between induction protocols have been reported, given that retreatment was properly performed based on pre-planned B cell monitoring (Kim et al., 2011). To minimize potential side effects during follow-up, recent guidelines on use of RTX for treating NMOSD recommended use of 1000 mg every 6 months during follow-up (Collongues et al., 2019; Ciron et al., 2018; Kim et al., 2019).

One alternative to a fixed-dosage protocol every 6 months is to monitor memory B cell counts (CD19+/CD20+/CD27+) at three and six months and at any time if relapse is confirmed (Costanzo et al., 2011; Kim et al., 2013). If easy access to CD27+ cell counts is not possible, the first strategy consists of repeating RTX infusions every six months without other paraclinical monitoring of its effects (Collongues et al., 2019; Ciron et al., 2018; Kim et al., 2019). Monitoring CD19+ cells during the follow-up is less arduous than pre-planned monitoring (Kim et al., 2011). If a relapse is confirmed while IST treatment is underway with correct use and dosage (Mealy et al., 2014; Kim et al., 2017), these patients should be switched to a drug with a different mechanism of action because persistence of disease activity exists. Definitions of effective therapeutic protocols for NMOSD patients resistant to IST drugs are still required.

NMOSD patients under treatment with RTX who present a relapse after 1 to 5 months are considered to have a "suboptimal treatment response".

If the NMOSD diagnosis is confirmed and RTX is chosen, this treatment should be started immediately following IVMP or PLEX treatment for relapse and oral steroids. It should be maintained for at least 1 month (Ciron et al., 2018) and then tapered off. Different strategies to evaluate long-term RTX management have been described (Collongues et al., 2019; Ciron et al., 2018; Kim et al., 2019). In general, the clinical response to RTX in NMOSD patients depends on the degree of B cell depletion, regardless of the dose of rituximab used (Kim et al., 2019). The degree and durability of B cell depletion in RTX treatment is variable (Cohen et al., 2017). The first strategy consists of repeating RTX infusions every six months without other paraclinical monitoring of its effects (Collongues et al., 2019; Ciron et al., 2018; Kim et al., 2019). Given that the full effect of RTX is delayed for at least one month after infusion, NMOSD patients who have a relapse after this period (1 to 5 months) are considered as having a "suboptimal treatment response". Another strategy is to monitor CD19+ cells during the follow-up. CD19+ cells in blood have been shown to provide a good measurement of the total number of circulating B cells, and some neurologists have suggested repeating RTX infusions when CD19+ cell counts exceed 0.01 × 10^9/L (Collongues et al., 2019; Kim et al., 2019; Pellkofer et al., 2011) or when they reach more than 0.1% of the total lymphocyte count (Mealy et al., 2014). Other investigators have suggested monitoring CD27+ cells in peripheral blood, with the aim of repeating the treatment only when CD27+ cell levels are more than 0.05% of PBMCs (Collongues et al., 2019; Kim et al., 2011, 2019), since the risk of re-activation of the disease seems to be correlated with re-emergence of memory B cells (Collongues et al., 2019; Kim et al., 2019). Monitoring RTX infusion through AQP4-ab titers in AQP4-ab-positive NMOSD patients is not recommended.

Although there is no clear definition for “suboptimal treatment response”, if a relapse is confirmed in these patients while on RTX, they should be switched to a drug with a different mechanism of action, such as new drugs (eculizumab, satralizumab, inebilizumab or tocilizumab) recommended a combination of steroids with IV antihistamine and paracetamol, but without clear evidence. All immunizations (especially influenza vaccine, pneumococcal vaccine, varicella zoster virus vaccine and hepatitis B and C vaccine) included in the vaccination schedule should be highlighted (Ciron et al., 2018; Kim et al., 2019).

In NMOSD patients who receive RTX, oral steroids should be maintained for at least 1-2 months after starting RTX.

If RTX is used following a relapse, concurrent use of oral steroids for at least 1 month, followed by tapering. This is because RTX treatment could be followed by relapses in the first month (Perumal et al., 2015), possibly because of induction of B-cell activating factor, thus resulting in a transient increase in AQP4-ab titers or lysis of B cells (Flanagan and Weinshenker, 2014; Perumal et al., 2015; Nakashima et al., 2011).

Regardless of the number and severity of relapses among NMOSD patients after treatment starts, occurrences of relapses at least six months of correct use of the specific treatment indicates that disease activity still persists and justifies modifying the therapeutic scheme to balance the risk and benefit.

Although there is a consensus that NMOSD patients need to receive long-term IST, the best treatment choice for each individual remains uncertain. No comparisons have been made among these drugs in head-to-head studies and the terms "suboptimal treatment response", "poor response" and "treatment failure" have not been clearly defined. Based on experience in clinical practice, if a relapse is confirmed while IST treatment is underway with correct use and dosage (Mealy et al., 2014; Kim et al., 2017), these patients should be switched to a drug with a different mechanism of action because persistence of disease activity exists. Definitions of effective therapeutic protocols for NMOSD patients resistant to IST drugs are still required.
commended in order to evaluate disease activity, since MRI shows ongoing inflammatory disease activity.

ment has been started is recommended at least once a year to identify effects, particularly cardiotoxicity and myelotoxicity, and because other and mitoxantrone (Lotan et al., 2019) have been shown to

Table 3 approved for NMOSD. Other treatments for NMOSD will probably be demonstrated good safety and tolerability profiles with a limited rate of side effects. At the present time, ecncizumab has become the first drug

2.7. Recommendations in special situations

Regarding the brain MRI at six months after starting a specific treatment, the panel did not reach any consensus for recommending this. The panel members commented that brain MRI is not necessary if clinical relapses are not present during this period, unlike MS. However, future studies and evidence could modify this recommendation. The panel also did not reach any consensus regarding the necessity for an annual spinal cord MRI (routine) after starting a specific treatment, for identifying ongoing disease activity. The panel highlighted the absence of benefit from monitoring clinically silent lesions spinal cord MRI for NMOSD patients, as seen in MS (Comi et al., 2017).

For NMOSD patients whose phenotype is indeterminate between MS and NMOSD (overlapping syndrome), RTX is recommended.

When diagnostic uncertainty exists between MS and NMOSD, particularly in anti-AQP4-ab-negative NMOSD patients, it should be considered that the published expert recommendations state that an NMOSD-suited IST strategy will be effective for both diseases (Weinshenker and Wingerchuk, 2017; Palace et al., 2012). Although RTX is an off-label treatment for both MS and NMOSD, it has been shown to be effective in diminishing the rate of relapses in both diseases, over variable follow-up durations.

Early IVMP treatment (1 g daily for 3–5 days) in situations of acute relapse during pregnancy (depending on relapse severity) is recommended.

Women with NMOSD can remain active during pregnancy and it has been reported that they are at increased risk of relapses during the first 3 months (Nour et al., 2016; Fragozo et al., 2013; Klawitter et al., 2017; Shimizu et al., 2016; Huang et al., 2017) and 6 months (Kim et al., 2012) postpartum compared with pre-pregnancy. Furthermore, they can present poor pregnancy outcomes, particularly if they are AQP4-ab-positive (Shimizu et al., 2016; Delgado-García et al., 2018). Nevertheless, higher rates of miscarriage and preeclampsia are still controversial (Nour et al., 2016; Delgado-García et al., 2018; Salvador et al., 2019). During pregnancy, a personalized treatment regimen is required, because there are no treatment guidelines based on controlled clinical studies for this situation. We recommend treatment of acute NMOSD relapses during pregnancy or breastfeeding, consisting of IVMP 1 g day for 3-5 days (mothers should wait for 1-4 hours before they start breastfeeding again). In addition, oral steroids may be con

demyelinating lesions more sensitively than do clinical manifestations (Kim et al., 2016; Geraldes et al., 2018). As observed in a LATAM population (Carrero Contentti et al., 2018), several studies have shown that T2-signal abnormalities in the brain exist in up to 80% of NMOSD patients at presentation or during follow-up (Wingerchuk et al., 2007; Kim et al., 2015; Carrero Contentti et al., 2018; Matthews et al., 2013; Geraldes et al., 2018). In general, these lesions are often clinically silent (Wingerchuk et al., 2007), commonly not classically oval shaped (i.e. unlike those reported in MS), and typically are not visible on T1-weighted images (Wingerchuk et al., 2007; Kim et al., 2015; Carrero Contentti et al., 2018; Matthews et al., 2013; Comi et al., 2017; Pittock et al., 2006). The association that brain MRI lesions might have as a predictor of future disease activity and disability is still unclear. Recently, the central vein sign (CVS); in which MS lesions are developed around small veins was reported as a specific marker for MS diagnosis (Sati et al., 2016; Gaitán et al., 2020). A sensitivity of 68.1% and specificity of 82.9% for distinguishing MS from not MS using a 35% CVS proportion threshold has been reported (Sinnecker et al., 2019). Recently, a Class III study provided evidence that the proportion of lesions with the CVS was significantly higher in MS than in AQP4-ab-positive NMOSD patients (80% vs 32%, p < 0.001) (Cortese et al., 2018). If more than 54% of the lesions on any given scan show the CVS, then the patient can be given a diagnosis of MS with an accuracy of 94% (Cortese et al., 2018).

Women with NMOSD can remain active during pregnancy and it has been reported that they are at increased risk of relapses during the first 3 months (Nour et al., 2016; Fragozo et al., 2013; Klawitter et al., 2017; Shimizu et al., 2016; Huang et al., 2017) and 6 months (Kim et al., 2012) postpartum compared with pre-pregnancy. Furthermore, they can present poor pregnancy outcomes, particularly if they are AQP4-ab-positive (Shimizu et al., 2016; Delgado-García et al., 2018). Nevertheless, higher rates of miscarriage and preeclampsia are still controversial (Nour et al., 2016; Delgado-García et al., 2018; Salvador et al., 2019). During pregnancy, a personalized treatment regimen is required, because there are no treatment guidelines based on controlled clinical studies for this situation. We recommend treatment of acute NMOSD relapses during pregnancy or breastfeeding, consisting of IVMP 1 g day for 3-5 days (mothers should wait for 1-4 hours before they start breastfeeding again). In addition, oral steroids may be continued during pregnancy in NMOSD (Shosha et al., 2017; Borisow et al., 2012; Trebst et al., 2014; Sellner et al., 2010; Kimbrough et al., 2012; Trebst et al., 2014; Sellner et al., 2010;Collongues et al., 2019; Kimbrough et al., 2012).

Mitoxantrone has been shown to significantly reduce the rate of relapses in NMOSD patients (Kim et al., 2015). However, due to its side effects, particularly cardiotoxicity and myelotoxicity, and because other therapeutic alternatives with fewer side effects are available, its use should be considered very critically (Palace et al., 2012; Trebst et al., 2014; Sellner et al., 2010; Collongues et al., 2019; Kimbrough et al., 2012; Weinstock-Guttman et al., 2006). Panels of experts on NMOSD treatment have recommended that cyclophosphamide should only be used when other IST treatments fail or are not available (Palace et al., 2012; Trebst et al., 2014; Sellner et al., 2010; Kimbrough et al., 2012; Mok et al., 2008). The treatment may be applied in immunoablative doses (2000 mg/day for 4 days) or at a dose of 600 mg/m² (Palace et al., 2012; Trebst et al., 2014; Sellner et al., 2010; Collongues et al., 2019; Mok et al., 2008).

Routine brain MRI among NMOSD patients after specific treatment has been started is recommended at least once a year to identify ongoing inflammatory disease activity.

Follow-up brain MRI in NMOSD patients once a year is recommended in order to evaluate disease activity, since MRI shows demyelinating lesions more sensitively than do clinical manifestations (Kim et al., 2016; Geraldes et al., 2018). As observed in a LATAM population (Carrero Contentti et al., 2018), several studies have shown that T2-signal abnormalities in the brain exist in up to 80% of NMOSD patients at presentation or during follow-up (Wingerchuk et al., 2007; Kim et al., 2015; Carrero Contentti et al., 2018; Matthews et al., 2013; Geraldes et al., 2018). In general, these lesions are often clinically silent (Wingerchuk et al., 2007), commonly not classically oval shaped (i.e. unlike those reported in MS), and typically are not visible on T1-weighted images (Wingerchuk et al., 2007; Kim et al., 2015; Carrero Contentti et al., 2018; Matthews et al., 2013; Comi et al., 2017; Pittock et al., 2006). The association that brain MRI lesions might have as a predictor of future disease activity and disability is still unclear. Recently, the central vein sign (CVS); in which MS lesions are developed around small veins was reported as a specific marker for MS diagnosis (Sati et al., 2016; Gaitán et al., 2020). A sensitivity of 68.1% and specificity of 82.9% for distinguishing MS from not MS using a 35% CVS proportion threshold has been reported (Sinnecker et al., 2019). Recently, a Class III study provided evidence that the proportion of lesions with the CVS was significantly higher in MS than in AQP4-ab-positive NMOSD patients (80% vs 32%, p < 0.001) (Cortese et al., 2018). If more than 54% of the lesions on any given scan show the CVS, then the patient can be given a diagnosis of MS with an accuracy of 94% (Cortese et al., 2018).

Women with NMOSD can remain active during pregnancy and it has been reported that they are at increased risk of relapses during the first 3 months (Nour et al., 2016; Fragozo et al., 2013; Klawitter et al., 2017; Shimizu et al., 2016; Huang et al., 2017) and 6 months (Kim et al., 2012) postpartum compared with pre-pregnancy. Furthermore, they can present poor pregnancy outcomes, particularly if they are AQP4-ab-positive (Shimizu et al., 2016; Delgado-García et al., 2018). Nevertheless, higher rates of miscarriage and preeclampsia are still controversial (Nour et al., 2016; Delgado-García et al., 2018; Salvador et al., 2019). During pregnancy, a personalized treatment regimen is required, because there are no treatment guidelines based on controlled clinical studies for this situation. We recommend treatment of acute NMOSD relapses during pregnancy or breastfeeding, consisting of IVMP 1 g day for 3-5 days (mothers should wait for 1-4 hours before they start breastfeeding again). In addition, oral steroids may be continued during pregnancy in NMOSD (Shosha et al., 2017; Borisow et al., 2012; Trebst et al., 2014; Sellner et al., 2010; Collongues et al., 2019; Kimbrough et al., 2012).
2018; Mao-Draayer et al., 2020) at the lowest possible dose, typically less than 20 mg/day, using steroids that do not cross the placenta. In several studies, IVMP (short-term treatment) was used during pregnancy without apparent complications affecting the fetus, except for low birth weight (Nour et al., 2016; Fragoso et al., 2013; Klawiter et al., 2017; Shimizu et al., 2016; Huang et al., 2017; Kim et al., 2012; Delgado-Garcia et al., 2018; Salvador et al., 2019; Shosha et al., 2017; Borisow et al., 2018; Mao-Draayer et al., 2020).

Early PLEX treatment in situations of acute relapse during pregnancy (depending on relapse severity) should be considered.

PLEX may be used during pregnancy to treat relapses of NMOSD, particularly for episodes in women who do not respond to corticosteroids (Jacob et al., 2008; Gao et al., 2019; Bedi et al., 2011; Kim et al., 2019; Shaygannejad et al., 2019; Marciño et al., 2018; Perumal et al., 2015). PLEX and immunoadsorption seem to be relatively safe during pregnancy and can be used after evaluating the risk-benefit relationship (Shosha et al., 2017; Borisow et al., 2018; Mao-Draayer et al., 2020).

On the other hand, monthly IVIG seem to be a relatively safe option if needed (e.g. in cases of contraindication for IVMP or PLEX), but very little evidence of efficacy exists (Shosha et al., 2017; Borisow et al., 2018; Mao-Draayer et al., 2020).

Immunosuppressive therapy with AZA or RTX during pregnancy should be continued if the patient has had attacks of NMOSD within the past 3 years.

Given that some studies have demonstrated that women with NMOSD with more active disease may have more complications, IST treatment is recommended (Nour et al., 2016; Shosha et al., 2017; Borisow et al., 2018; Mao-Draayer et al., 2020).

Based on expert opinion, AZA and RTX treatment should be continued in NMOSD patients with active disease (i.e. those with frequent and disabling relapses) throughout pregnancy and the postpartum period after careful risk-benefit evaluation (Shosha et al., 2017; Borisow et al., 2018; Mao-Draayer et al., 2020). For RTX, conception immediately after the last infusion might be acceptable. Retreatment should be administered if no pregnancy is confirmed within six months and re-dosing, if severe relapses occur during pregnancy (Mao-Draayer et al., 2020). For AZA, continuing with a dose of 2.5 mg/kg/day or in combination with low doses of oral steroids seems to be safe and reasonable if disease activity exists (Shosha et al., 2017).

More than 2000 cases of AZA use during pregnancy have been reported (Shosha et al., 2017; Borisow et al., 2018; Mao-Draayer et al., 2020). Although reduced rates of preterm birth, low birth weight and cardiac septal defects were informed, these defects might have been due to underlying diseases in the mother, which might have led to taking AZA (Shosha et al., 2017; Borisow et al., 2018; Mao-Draayer et al., 2020).

RTX treatment during the first trimester has been studied in mothers with a variety of conditions (mainly non-Hodgkin lymphoma and rheumatoid arthritis). In this population, miscarriages, congenital cardiac septal defects were informed, these defects might have been due to underlying diseases in the fetus would occur. In a French consensus on RTX use, it was recommended that effective contraceptive methods during and for six months after RTX treatment should be used (Ciron et al., 2018).

Funding

This research did not receive any specific grant.

Declaration of Competing Interest

EC has received reimbursement for developing educational presentations, educational and research grants, consultation fees and/or travel stipends from Biogen, Genzyme, Merck and Novartis.

JRF has received honoraria from Novartis as a scientific advisor. He has received travel grants and attended courses and conferences on behalf of Merck-Serono Argentina, Novartis Argentina

EC has received reimbursement for developing educational presentations, educational and research grants, consultation fees and/or travel stipends from Biogen, Novartis, Genzyme, Merck and Roche.

VDM has received reimbursement for developing educational presentations, educational and research grants, consultation fees and/or travel stipends from Biogen Idec, Merck-Serono, Novartis, Roche, Sanofi-Genzyme, Teva.

JRF has nothing to disclose.

MLP has received reimbursement for developing educational presentations, educational and research grants, and travel stipends from Biogen Idec, Roche, Novartis and Sanofi-Aventis.

CN has nothing to disclose.

RPA has received reimbursement for developing educational presentations, educational and research grants, consultation fees and/or travel stipends from the following pharmaceuticals industries: Teva, Novartis, Roche, Merck, Biogen and Sanofi.

DKS has received research support from CNPq/Brazil (425331/2016-4 and 308636/2019-8), FAPERGS/MS/CNPq/SESRIS (17/2551-0001391-3) PPSUS/Brazil, TEVA, Merck and Euroimmun AG for investigator-initiated studies; has received speaker honoraria from Biogen, Novartis, Genzyme, TEVA, Merck, Roche and Bayer and has participated in advisory boards for Shire, Roche, TEVA, and Merck. ISC has received reimbursement for developing educational presentations, educational and research grants, consultation fees and/or travel stipends from the following pharmaceuticals industries: Teva, Bayer, and Biogen. JC is a board member of Merck-Serono Argentina, Novartis Argentina, Genzyme LATAM, Genzyme global, Biogen-Idec LATAM and Merck-Serono LATAM. He is part of the Steering Committee for the clinical trials of Ofatumumab (Novartis Global). JC has received reimbursement for developing educational presentations for Merck-Serono Argentina, Merck-Serono LATAM, Biogen-Idec Argentina, Genzyme Argentina, Novartis Argentina, Novartis LATAM, Novartis Global and Roche Argentina, as well as professional travel/accommodation stipends.

Acknowledgement

We would like to thank Prof. Brian G. Weinshenker (Department of Neurology, Mayo Clinic, USA) for his valuable recommendations and support provided during the development of this project.

Supplementary materials


References


E. Carnero Contentti, et al.

Multiple Sclerosis and Related Disorders 45 (2020) 102428


