International Delphi Consensus on the Management of AQP4-IgG+ NMOSD

Recommendations for Eculizumab, Inebilizumab, and Satralizumab

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Abstract

Background and Objectives
Neuromyelitis optica spectrum disorder (NMOSD) is a rare debilitating autoimmune disease of the CNS. Three monoclonal antibodies were recently approved as maintenance therapies for aquaporin-4 immunoglobulin G (AQP4-IgG)–seropositive NMOSD (eculizumab, inebilizumab, and satralizumab), prompting the need to consider best practice therapeutic decision-making for this indication. Our objective was to develop validated statements for the management of AQP4-IgG–seropositive NMOSD, through an evidence-based Delphi consensus process, with a focus on recommendations for eculizumab, inebilizumab, and satralizumab.

Methods
We recruited an international panel of clinical experts in NMOSD and asked them to complete a questionnaire on NMOSD management. Panel members received a summary of evidence identified through a targeted literature review and provided free-text responses to the questionnaire based on both the data provided and their clinical experience. Responses were used to generate draft statements on NMOSD-related themes. Statements were voted on over a maximum of 3 rounds; participation in at least 1 of the first 2 rounds was mandatory. Panel members anonymously provided their level of agreement (6-point Likert scale) on each statement. Statements that failed to reach a predefined consensus threshold (≥67%) were revised based on feedback and then voted on in the next round. Final statements were those that met the consensus threshold (≥67%).
Neuromyelitis optica spectrum disorder (NMOSD) is a rare debilitating autoimmune disease of the CNS, characterized primarily by optic neuritis and longitudinal extensive transverse myelitis.¹⁻² It affects between 0.7 and 10 per 100,000 people, depending on geography and ethnicity, and is more common in women than men.³,⁴ NMOSD is recognized as a distinct disease from multiple sclerosis (MS), even though it may share similar clinical features, which can lead to misdiagnosis of NMOSD as MS.⁵,⁶ Patients with NMOSD experience long-term symptoms such as vision loss, weakness, sensory impairment, bladder and bowel dysfunction, neuropathic pain, and fatigue.⁷⁻¹⁰ Evidence suggests that 90% of patients with NMOSD will test seropositive for antiaquaporin-4 immunoglobulin G (AQP4-IgG),²,¹¹,¹² a circulating pathogenic autoantibody and a key diagnostic biomarker for NMOSD.¹³

Treatment of NMOSD involves the management of acute relapses, or attacks, and maintenance therapy to prevent further relapses.⁵,¹⁴ Before 2019, there were no approved therapies for AQP4-IgG–seropositive NMOSD; maintenance treatments, although empirically identified as being potentially beneficial in sustaining remission, were all off-label. These included rituximab, azathioprine, mycophenolate mofetil, methotrexate, tocilizumab, and oral corticosteroids. There are now 3 biologics approved as maintenance therapies specifically for adults, or adults/adolescents, with AQP4-IgG–seropositive NMOSD, in a range of countries: eculizumab, inebilizumab, and satralizumab.¹⁵⁻²⁸ However, there are no standard treatment recommendations for AQP4-IgG–seropositive NMOSD that provide clear guidance on the use of these approved biologics or their role in the context of existing off-label maintenance therapies. Previous recommendations have focused only on the utilization of off-label therapies,⁵,¹⁴ or where new therapies were included, recommendations regarding their use are limited.²⁹ As such, there is a clear and pressing need for new international recommendations for the management of AQP4-IgG–seropositive NMOSD.

Delphi consensus methods gather information from experts and allow for the development and validation of consensus statements that reflect the broad experience of key experts in a particular field.³⁰ Consensus statements may inform clinical treatment guidelines in a therapeutic or disease area, especially for rare diseases, where standard practice recommendations may not yet be established or may not be updated on a regular basis.³¹

We conducted an international Delphi process to generate and validate a series of evidence-based consensus statements for consideration in best practice therapeutic decision-making related to the use of eculizumab, inebilizumab, and satralizumab to treat patients with AQP4-IgG–seropositive NMOSD.

## Methods

### Overview

A modified Delphi consensus process was conducted, informed by a targeted literature review and clinical expertise. The Delphi panel comprised a steering committee of 3 members (one of whom was the nonvoting Chair of the panel). The steering committee have extensive expertise in NMOSD, especially for the newly approved therapies: they have been involved in the pivotal phase 3 trials for eculizumab, inebilizumab, and satralizumab. They also have broad knowledge of international, experienced clinicians in the field; thus, they were well placed to select the remaining panel members for this Delphi process. The steering committee selected panel members with 1 or more of the following credentials: they run specialized clinics for the treatment of
AQP4-IgG–seropositive NMOSD; they lead national cohort studies to investigate outcomes of AQP4-IgG–seropositive NMOSD; they have knowledge of newly approved therapies for AQP4-IgG–seropositive NMOSD through involvement in the pivotal trials. In total, 21 additional panel members were selected, resulting in 24 participants overall, 23 of whom were voting members (Table 1). Countries represented by the panel include Australia (1 panel member), Brazil (2), Canada (1), China (1), Denmark (1), France (2), Germany (2), India (1), Israel (1), Japan (2), Morocco (1), South Korea (1), Spain (2), UK (3), and United States (3). After the targeted literature review (eAppendix 1, links.lww.com/NXI/A859), the Delphi consensus participants contributed to several stages: (1) information gathering to obtain expert opinion on topics related to NMOSD management; (2) generation of a list of draft statements related to NMOSD management; and (3) voting on the statements to confirm if expert consensus was reached (Figure).

**Proto-statement Questionnaire**

The initial information gathering stage was performed using a proto-statement questionnaire. This comprised a series of open questions capturing free-text responses from the Delphi panel to gain information and expert opinion on a range of topics related to NMOSD management.

**Table 1** NMOSD Delphi Consensus Participants (n = 24) and Their Roles

<table>
<thead>
<tr>
<th>Participant (n)</th>
<th>Role/other details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair (1)</td>
<td>Responsible for agreeing the design of the Delphi consensus process, including selection of Delphi consensus panel members and the agreement threshold for statements questionnaire. Contributed to the development of the proto-statement questionnaire, initial statements, and revisions to statements that did not meet consensus. Did not participate in the voting stage of the Delphi process.</td>
</tr>
<tr>
<td>Steering committee member (3 [including the chair])</td>
<td>Responsible for agreeing the design of the Delphi consensus process, including selection of Delphi consensus panel members, questionnaire and statement development, and the agreement threshold for statements. Participated in the voting stage and/or questionnaire stage of the Delphi process.</td>
</tr>
<tr>
<td>Panel member (21)</td>
<td>Participated in the voting stage and/or questionnaire stage of the Delphi process. All Delphi panel members were identified based on their clinical expertise in the area of NMOSD and selected based on their willingness to participate and with an aim to create good representation for geographic location and gender.</td>
</tr>
<tr>
<td>Independent support</td>
<td>Support with consensus statement development and Delphi consensus voting rounds was provided by Oxford PharmaGenesis, Oxford, UK, an independent consultancy, which received funding from F. Hoffmann-La Roche Ltd.</td>
</tr>
</tbody>
</table>

**Figure** Overview of NMOSD Delphi Consensus Process

NMOSD = neuromyelitis optica spectrum disorder.
topics in NMOSD management (eAppendix 2, links.lww.com/NXI/A859). To support this stage, panel members were provided with an evidence summary from the targeted literature review. Responses were collected securely online, through Google forms, and were extracted anonymously into an Excel spreadsheet.

**Generation of Statements**

Key themes were identified from responses to the proto-statement questionnaire. Within these themes, draft statements were developed using information from the responses.

**Voting Rounds**

The draft statements were voted on over a maximum of 3 rounds (Figure). As with the proto-statement questionnaire, responses in each round were collected through Google forms and were extracted anonymously into an Excel spreadsheet. Participation in at least 1 of the first 2 rounds was mandatory for each Delphi panel member. In round 1, panel members anonymously voted their level of agreement with each statement, using a 6-point Likert scale (strongly agree, agree, somewhat agree, somewhat disagree, disagree, and strongly disagree). If panel members selected 1 of the 3 responses that disagreed with the statement, they had the option to provide free-text feedback to explain their reasons for disagreement. Panel members were given no other instructions regarding how they should provide responses. In all voting rounds, the percentage agreement was compared with a predefined consensus threshold (≥67%) previously used in Delphi processes. Statements that failed to reach the predefined consensus threshold were revised based on the feedback provided by those who disagreed with the statement. Revisions were approved by the steering committee (Table 1). In round 2, revised statements were voted on in the same way as in the first round. A third round took place if any of the revised statements still failed to meet the consensus threshold.

**Standard Protocol Approvals, Registrations, and Patient Consents**

Not required for this study.

**Data Availability**

All information and data pertaining to this study are included within this article. There is no further supplementary information that can be provided.

**Results**

**Overview**

Thirty-five articles were identified from the targeted literature review, including primary randomized controlled trial (RCT) data and review articles (eAppendix 3, links.lww.com/NXI/A859). Based on this evidence, and on feedback from the proto-statement questionnaire, 25 draft statements were developed.

**Voting Participation and Consensus**

All 23 voting members of the Delphi panel participated in at least 1 round of the process and thus qualified for membership of the final Delphi panel. In round 1, the participation rate was 78%, with 18/23 panel members voting on the 25 draft statements. After this voting round, 23 of the 25 statements reached consensus. Only 2 statements failed to reach consensus (levels of agreement were 61.1% and 66.7%); these statements were revised based on feedback. In round 2, 21/23 panel members (participation rate, 91.3%) voted on the revised statements. During this voting round, both statements reached consensus. A third voting round was therefore not required.

**Consensus Statements**

**Overall Results**

In total, the Delphi panel agreed on 25 consensus statements. The statements are summarized, by theme, in Tables 2–6 and are discussed individually in the next sections. Detailed voting responses are summarized in eTable 3 (links.lww.com/NXI/A859).

**Initiation of Eculizumab, Inebilizumab, or Satralizumab**

Nine consensus statements are relevant to the initiation of eculizumab, inebilizumab, or satralizumab (Table 2).

Statement 1 reached consensus in round 1 of voting (77.8% of panel agreed). The efficacy of eculizumab for the treatment of AQP4-IgG-seropositive NMOSD was demonstrated in an adult study population in the PREVENT trial. Approximately 211 weeks after randomization, the rate of adjudicated relapse was 3% in the eculizumab group and 43% in the placebo group (hazard ratio [HR] 0.06; 95% confidence interval [CI] 0.02–0.20; p < 0.001).

Statement 2 reached consensus in round 1 of voting (100% of panel agreed). The efficacy of inebilizumab for the treatment of AQP4-IgG-seropositive NMOSD was demonstrated in an adult study population in the N-MOmentum trial during a study period of up to 197 days. In the AQP4-IgG-seropositive subgroup, the rate of attack, defined by prespecified attack criteria and adjudicated by committee, was 11% in the inebilizumab group and 42% in the placebo group (HR 0.227; 95% CI 0.121–0.423; p < 0.0001).

Statement 3 reached consensus in round 1 of voting (94.4% of panel agreed). Efficacy for satralizumab was demonstrated in adults and adolescents (≥12 years) in the SAkuraSky and SAkuraStar trials, during double-blind study periods of up to 224 weeks and 216 weeks, respectively. Among 55 patients in the SAkuraSky trial who were AQP4-IgG seropositive, the rate of protocol-defined relapse was 11% in those receiving satralizumab as add-on to baseline immunosuppressant therapy and 43% in those receiving placebo (HR 0.21; 95% CI 0.06–0.75). In the SAkuraStar, among 64 patients in the trial who were AQP4-IgG seropositive, the rate of protocol-defined relapse was 22% in those receiving satralizumab as monotherapy and 57% in those receiving placebo (HR 0.26; 95% CI 0.11–0.63).

**Table 2: Nine consensus statements are relevant to the initiation of eculizumab, inebilizumab, or satralizumab**

<table>
<thead>
<tr>
<th>Statement</th>
<th>Description</th>
<th>Consensus Reached</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Round 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Efficacy of eculizumab for NMOSD</td>
<td>77.8%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Efficacy of inebilizumab for NMOSD</td>
<td>100%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Efficacy of satralizumab for NMOSD</td>
<td>94.4%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Statement 4 reached consensus in round 1 of voting (100% of panel agreed). Efficacy and safety of treatment, as evidenced by RCT data, were the most common responses when panel members were asked to name the most important considerations when choosing therapies for patients with NMOSD. Other common responses were used to develop Statement 5.

Statement 5 reached consensus in round 1 of voting (100% of panel agreed). When panel members were asked to name the most important considerations for choosing therapies for patients with NMOSD, the most common responses after efficacy and safety of treatment were disease or relapse severity for the patient (mentioned by 47% of panel members); patient preference for treatment administration (47%); and comorbidities and other patient characteristics (24%).

Statement 6 reached consensus in round 1 of voting (100% of panel agreed). Based on the panel members’ clinical experience, the acceptance of safety risks by patients is an important factor in deciding their therapy. The panel members also agreed that patient preferences are highly relevant for choosing between eculizumab, inebilizumab, and satralizumab. The relevance is due to the differing administration route and schedule between treatments. Eculizumab is administered by IV infusion, every week during the initial phase and every 2 weeks during the maintenance phase. Inebilizumab is administered by IV infusion twice 2 weeks apart and once every 6 months. Satralizumab is administered by subcutaneous injection every 2 weeks during the initial phase and every 4 weeks thereafter. Frequency and route of administration of treatments are known to influence patient preferences in other diseases. In NMOSD, the importance of patients’ preference was demonstrated in a US cross-sectional survey that found that 13% of patients with NMOSD were concerned about discomfort during administration, 11% were concerned about inconvenience of treatment, and 7% were concerned about impact on pregnancy decisions.

Statement 7 reached consensus in round 1 of voting (94.4% of panel agreed). Panel members agreed that treatments with different modes of action to a failed therapy are not likely to be effective. For example, satralizumab and tocilizumab are both interleukin-6 receptor targeting antibodies. Patients for whom tocilizumab therapy has failed may not experience positive outcomes with satralizumab. Furthermore, rituximab, an anti–cluster of differentiation (anti-CD) 20 monoclonal antibody,
and inebilizumab, an anti-CD19 monoclonal antibody, have similar mechanisms of action (although anti-CD19 therapy targets a wider range of B cells and some plasma cells compared with anti-CD20 treatments). Alternative modes of action, such as through eculizumab, which is a complement component 5 (C5) inhibitor, may be considered for such patients.

Statement 8 reached consensus in round 1 of voting (88.9% of panel agreed). Panel members agreed that patients who are relapse-free on their current therapy do not need to be switched to new therapies. Because the registration trials for the approved biologics (eculizumab, inebilizumab, and satralizumab) excluded nonrelapsing, clinically stable participants, there is no evidence to suggest that patients should switch to eculizumab, inebilizumab, or satralizumab if they are relapse-free on their current therapy. However, panel members acknowledged that the availability of long-term real-world data in the future may modify this recommendation, especially when data become available that allow comparison of the long-term safety profiles of eculizumab, inebilizumab, and satralizumab with those of conventional, off-label maintenance therapies (alone or with other treatments).

Statement 9 reached consensus in round 1 of voting (88.9% of panel agreed). Whereas statement 8 concerned patients with no disease activity on immunosuppressants, statement 9 concerns patients who do have disease activity. Evidence suggests that people on immunosuppressants need additional treatment to control disease activity. In a retrospective observational analysis, data in 116 patients with NMOSD who were treated with immunosuppressants (azathioprine or mycophenolate mofetil) showed that approximately one-third of patients responded poorly to treatment, especially if they had a history of severe attacks. This evidence suggests that, for some patients with NMOSD, conventional immunosuppressants alone, such as azathioprine and mycophenolate mofetil, are not sufficient to prevent attacks. At the same time, evidence suggests that discontinuation of conventional immunosuppressants may increase the risk of relapse for patients with AQP4-IgG–seropositive NMOSD, even after 5 years of remission. Thus, use of the newly approved biologics as add-on therapy may be justified. However, further evidence, particularly from RCTs, is needed to confirm the benefit of adding the approved biologic therapies to conventional immunosuppressants and to better characterize the risks of additional adverse events from dual immunotherapies.

**Monotherapy vs Combination Therapy**

Three consensus statements are relevant to the use of eculizumab, inebilizumab, or satralizumab as monotherapy or in combination with other therapies (Table 3).

Statement 10 reached consensus in round 1 of voting (83.3% of panel agreed). Whereas Statement 9 acknowledges that the combination of immunosuppressants with approved biologics could be beneficial, Statement 10 reflects the overall recommendation given the current evidence, which is to use biologics as monotherapy, where possible, because the use of combination therapy may be associated with a higher risk of infection.

The original version of Statement 11 failed to reach consensus during round 1 of voting, with the level of agreement falling below the predefined threshold of 67% (only 11/18 Delphi panel members agreed). Finally, Statement 12 was revised to achieve consensus during round 2 of voting (83.3% of panel agreed).

**Table 3** NMOSD Delphi Consensus Statements on Monotherapy vs Combination Therapy and Switching Therapies

<table>
<thead>
<tr>
<th>Consensus statement</th>
<th>Level of agreement, i.e., n/N (%) of panel members who agreed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statement 10: Eculizumab, inebilizumab, or satralizumab should be given as monotherapy to patients with AQP4-IgG–seropositive NMOSD to reduce the risk of additional side effects of concomitant use with immunosuppressant therapies</td>
<td>15/18 (83.3%)</td>
</tr>
<tr>
<td>Statement 11: While monotherapy is preferred, evidence from randomized controlled trials shows that eculizumab or satralizumab may be combined with immunosuppressant therapies if the patient is already receiving immunosuppressants. Combination therapy should be considered in the context of the short-term and long-term safety and tolerability profiles of the immunosuppressants</td>
<td>18/21 (85.7%)</td>
</tr>
<tr>
<td>Statement 12: If eculizumab, inebilizumab, or satralizumab are initially combined with immunosuppressant therapy in patients with AQP4-IgG–seropositive NMOSD, patients should be closely monitored for side effects, and immunosuppressants should be slowly tapered, based on the expected onset of action of the new biologic therapy</td>
<td>17/18 (94.4%)</td>
</tr>
<tr>
<td>Statement 13: After initiation of eculizumab, inebilizumab, or satralizumab, and after allowing for onset of action, patients with AQP4-IgG–seropositive NMOSD should be switched to another of these 3 biologic therapies: if there is a severe relapse while on treatment; if serious treatment-related adverse events occur; or due to patient preference</td>
<td>16/18 (88.9%)</td>
</tr>
<tr>
<td>Statement 14: When switching between eculizumab, inebilizumab, and satralizumab, the new therapy can be started immediately after stopping the previous therapy, taking into consideration the mechanism and duration of action</td>
<td>18/21 (85.7%)</td>
</tr>
</tbody>
</table>

Abbreviations: AQP4-IgG = anti-aquaporin-4 immunoglobulin G; GFAP = glial fibrillary acidic protein; N/A = not applicable; NfL = neurofilament light chain; NMOSD = neuromyelitis optica spectrum disorder.

*Threshold for consensus was ≥67%. Statements 10, 12, and 13 achieved consensus during round 1; statements 11 and 14 achieved consensus during round 2, after revision.*
after cessation of the previous treatment in case the lack of washout period led to strong immunosuppression in the patient. Panel members also recommended allowing sufficient time to observe the onset of action of the previous therapy. For example, pivotal RCTs for each of the biologics allowed a follow-up of 24–48 weeks to observe their primary end points. The revised version of the statement, which reached consensus in round 2 of voting, acknowledges that the mechanism and duration of action of the previous therapy should be considered. In total, 18/21 Delphi panel members (85.7%) agreed with the revised Statement 14 during round 2 of voting.

**Patient Populations**

Two consensus statements are related to considerations for different patient populations when using eculizumab, inebilizumab, or satralizumab (Table 4).

Statement 15 reached consensus in round 1 of voting (100% of panel agreed). Comorbidities were considered important in several ways. Long-term oral corticosteroid use can increase the risk of infection and can exacerbate preexisting conditions such as type 2 diabetes mellitus, osteoporosis, and glaucoma; thus, switching to eculizumab, inebilizumab, or satralizumab earlier may be appropriate. If a patient has more than 1 autoimmune disease, the condition with more significant disease activity should guide the treatment decision-making. However, specific treatments could complement the treatment of overlapping autoimmune disease; for example, satralizumab would be complementary for the treatment of rheumatoid arthritis, while eculizumab would be complementary for the treatment of myasthenia gravis.

Statement 16 reached consensus in round 1 of voting (88.9% of panel agreed). The efficacy of satralizumab was demonstrated in adults and adolescents (≥12 years) in the SAkuraSky trial, which supported the European Medicines Agency (EMA) approval for this indication. In the subgroup analysis of adolescents only, with NMOSD of any type, the safety profiles of the satralizumab add-on therapy and placebo treatment arms were comparable. It should be noted that this analysis was based on a small sample size of 8 patients, and it would be valuable to confirm this evidence in larger study populations.

<table>
<thead>
<tr>
<th>Consensus statement</th>
<th>Level of agreement, i.e., n/N (%) panel members who agreed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statement 15: Comorbidity in patients with NMOSD and concomitant autoimmune diseases should be a consideration in the choice of biologic therapy (eculizumab, inebilizumab, or satralizumab)</td>
<td>18/18 (100%)</td>
</tr>
<tr>
<td>Statement 16: Adolescents (12 year or older) with AQP4-IgG–seropositive NMOSD should be treated with satralizumab. Treatment with eculizumab or inebilizumab may be considered if there is severe disease activity that is refractory to satralizumab, but clinical trial evidence is needed to support the use of these drugs in other scenarios</td>
<td>16/18 (88.9%)</td>
</tr>
</tbody>
</table>

Abbreviations: AQP4-IgG = anti-aquaporin-4 immunoglobulin G; NMOSD = neuromyelitis optica spectrum disorder.

*Threshold for consensus was ≥67%. Statements 15 and 16 achieved consensus during round 1.
populations. Data in adolescents are not currently available for eculizumab or inebilizumab.

**Safety**

Five consensus statements are related to the safety of eculizumab, inebilizumab, and satralizumab (Table 5).

Statement 17 reached consensus in round 1 of voting (100% of panel agreed). The Delphi panel members suggested that infections were the main safety concern to be monitored over time, particularly opportunistic infections, meningococcal meningitis, herpes zoster, and progressive multifocal leukoencephalopathy. The risk of these infections is emphasized in the EMA and US Food and Drug Administration (FDA) labels of eculizumab, inebilizumab and satralizumab. Moreover, monitoring individual patients reporting significant infections such as these to the manufacturer and other post-marketing databases (e.g., US FDA) would also be helpful in enabling wider monitoring of potential safety issues associated with these therapies.

Statement 18 reached consensus in round 1 of voting (83.3% of panel agreed). Patients with comorbidities that influence the risk of infection, adolescents, older people, pregnant women, and patients with significant immunosuppression were the most commonly mentioned subgroups when panel members were asked whether certain patient types should be monitored more closely than others.

Statement 19 reached consensus in round 1 of voting (100% of panel agreed). Many panel members noted that pregnancy and family planning is a key consideration for their patients. Current literature suggests that multidisciplinary teams should be involved in the overall treatment and care of pregnant women with NMOSD.51 Reviews of eculizumab treatment during pregnancy suggest there are no major safety concerns.52,53 Evidence is less clear for inebilizumab and satralizumab. A review of inebilizumab suggested that treatment could be linked to transient hematologic abnormalities in the fetus if given during the second or third trimester of pregnancy, in the same way as ocrelizumab or rituximab can lead to these abnormalities; however, this has not been formally investigated. Little evidence is available for satralizumab use during pregnancy. Potentially, evidence for tocilizumab use in rheumatoid arthritis during pregnancy could be indicative of satralizumab use, given the similarities between the 2 treatments for mechanism of action.53-55 Overall, recommendations in the literature emphasize that more evidence is needed for the newly approved NMOSD therapies during pregnancy and lactation, and a long-term follow-up of infants is also recommended.52,53 Plans to generate such evidence are under way: the US Food and Drug Administration mandated a worldwide single-arm pregnancy safety registry study to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women with NMOSD exposed to satralizumab and inebilizumab during pregnancy.56,57

Statement 20 reached consensus in round 1 of voting (88.9% of panel agreed). In the PREVENT trial, all patients treated with eculizumab received the meningococcal vaccine, and there were no cases of meningococcal infection during the trial.34 Based on this clinical evidence, and their own experience, panel members agreed that all vaccinations, not only a meningococcal vaccine, should be up to date before treatment. This may include COVID-19 vaccination. It is not clear

<table>
<thead>
<tr>
<th>Table 5 NMOSD Delphi Consensus Statements on Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consensus statement</strong></td>
</tr>
<tr>
<td>Statement 17: Patients with AQP4-IgG-seropositive NMOSD treated with eculizumab, inebilizumab, or satralizumab should be monitored in the short-term and long-term for infections</td>
</tr>
<tr>
<td>Statement 18: Some patients with AQP4-IgG-seropositive NMOSD treated with eculizumab, inebilizumab, or satralizumab should be clinically monitored more frequently (more than twice per year); these include patients with comorbidities that influence the risk of infection, adolescents, older people, pregnant women, and patients with significant immunosuppression</td>
</tr>
<tr>
<td>Statement 19: Available data regarding the use of eculizumab, inebilizumab, or satralizumab in patients with NMOSD during pregnancy are currently limited; further research is needed to gain a better understanding of the risk of complications in the short-term and long-term and will inform patient decision-making on family planning and treatment pathways</td>
</tr>
<tr>
<td>Statement 20: Patients with NMOSD who are AQP4-IgG-seropositive should be up to date with all vaccinations before initiating new biologic therapies (eculizumab, inebilizumab, or satralizumab) unless there are exceptional circumstances</td>
</tr>
<tr>
<td>Statement 21: Guidance concerning meningococcal vaccinations for patients treated with eculizumab should be clarified for patients with AQP4-IgG-seropositive NMOSD to ensure clinicians know how to cover all serogroups and when to schedule booster vaccinations and reassess vaccination status</td>
</tr>
</tbody>
</table>

Abbreviations: AQP4-IgG = antiaquaporin-4 immunoglobulin G; NMOSD = neuromyelitis optica spectrum disorder.

a Threshold for consensus was ≥67%. Statements 17–21 achieved consensus during round 1.
the extent to which new biologic therapies may interfere with vaccination efficacy, in a similar way to other therapies such as tocilizumab, anti-CD20 monoclonal antibodies, azathioprine, and mycophenolate mofetil. More evidence is needed to investigate potential interference with vaccine efficacy by eculizumab, inebilizumab, or satralizumab.

Statement 21 reached consensus in round 1 of voting (94.4% of panel agreed). The label for eculizumab typically contains recommendations on vaccinations required before treatment. For example, in the United States and EU, it is recommended that all patients on eculizumab receive the required meningococcal vaccines at least 2 weeks before initiating eculizumab (full details available in the treatment labels). In some countries, for example, UK, antibiotic cover is also required. A previous review of eculizumab has called for clarification of the recommendations for vaccination in patients with NMOSD. Items that require clarification include the following: timing and frequency of meningococcal vaccination; whether prophylactic antibiotics are recommended and for how long; and whether patients already on immunosuppressants require antibiotics to allow for attenuated immune response.

Use of Biomarkers and Patient-Reported Outcomes

Three consensus statements are relevant to the use of biomarkers and patient-reported outcomes regarding treatment with eculizumab, inebilizumab, or satralizumab (Table 6). Statement 22 reached consensus in round 1 of voting (88.9% of panel agreed). Results from biomarker analyses of N-MOmentum trial data showed that elevated serum GFAP at baseline was significantly associated with a greater likelihood of NMOSD attack, and serum NfL level after an attack had a significant correlation with Expanded Disability Status Scale score. Panel members agreed that these biomarkers have the potential to be useful for predicting patient outcomes; however, more evidence is needed, especially for patients with NMOSD treated with satralizumab or eculizumab, for which there was no evidence related to biomarkers identified in the literature review.

Statement 23 reached consensus in round 1 of voting (88.9% of panel agreed). In results reported in their primary clinical trial publications, neither eculizumab nor satralizumab was associated with significant improvement in quality of life, although post hoc analyses of the PREVENT trial suggested a positive impact of eculizumab treatment on patients’ quality of life. The short duration of trials may have affected the primary results. Quality-of-life measures were not captured for inebilizumab in the N-MOmentum trial.

Statement 24 reached consensus in round 1 of voting (83.3% of panel agreed). In responses to the proto-statement questionnaire, some panel members doubted the reliability of current measures of quality of life, such as the 36-item Short-Form Health Survey and EuroQol 5-dimension 5-level (EQ-5D 5L), in a patient population with NMOSD. As such, panel members agreed that new, validated patient-reported outcome measures for NMOSD would be valuable for assessing the benefit of the newly approved biologic therapies.

Research Gaps

One consensus statement is relevant to current research gaps regarding the use of eculizumab, inebilizumab, and satralizumab (Table 6).

Statement 25 reached consensus in round 1 of voting (83.3% of panel agreed). This statement was based on responses to an item in the proto-statement questionnaire, which asked, “What are the most important research gaps in the current

<table>
<thead>
<tr>
<th>Consensus statement</th>
<th>Level of agreement, i.e., n/N (%) panel members who agreed</th>
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<tr>
<td>Statement 22: While serum glial fibrillary acidic protein (GFAP) and serum neurofilament light chain (NfL) have been shown to be markers of disease activity for NMOSD, more evidence is needed to support the routine use of biomarkers to support treatment decision-making in patients with AQP4-IgG-seropositive NMOSD</td>
<td>16/18 (88.9%)</td>
</tr>
<tr>
<td>Statement 23: Health-related quality-of-life outcomes in patients with AQP4-IgG-seropositive NMOSD are important to measure, but current evidence from clinical trials is not sufficient to influence therapy decision-making</td>
<td>16/18 (88.9%)</td>
</tr>
<tr>
<td>Statement 24: There is a strong need for sensitive, well-validated patient-reported outcomes that can be used to evaluate quality-of-life outcomes for NMOSD therapies</td>
<td>15/18 (83.3%)</td>
</tr>
<tr>
<td>Statement 25: Research priorities in the area of NMOSD are the investigation of the following: (1) prognostic biomarkers of relapse and disease progression; (2) predictive biomarkers to assess treatment response; (3) the role of imaging; (4) head-to-head evidence; and (5) long-term outcomes associated with the use of eculizumab, inebilizumab, and satralizumab, gathered through clinical trials and real-world data</td>
<td>15/18 (83.3%)</td>
</tr>
</tbody>
</table>

Abbreviations: AQP4-IgG = anti-aquaporin-4 immunoglobulin G; GFAP = glial fibrillary acidic protein; NfL = neurofilament light chain; NMOSD = neuromyelitis optica spectrum disorder.

* Threshold for consensus was ≥67%. Statements 22–25 achieved consensus during round 1.
evidence for newly approved therapies for NMOSD?" Among free-text responses from 17 panel members, the use of biomarkers and/or imaging was mentioned most frequently (by 7 panel members). Data on biomarkers, particularly for those that may be predictive of the risk of relapse or disease progression, were considered vital for informing treatment decisions, given the choice of biologics available. Such data would build on existing knowledge in this area, largely learned from the N-MOmentum trial (see statement 22). The supportive role of imaging has also been investigated in the N-MOmentum trial, and results showed that imaging was valuable in confirming relapses.68 It would also be beneficial to understand the impact of genetic variations on treatment response to allow individualized therapeutic decision-making; for example, in Japanese patients, a rare variant has been shown to affect treatment response to eculizumab.69 According to the panel, additional gaps included evidence related to the following: long-term efficacy and safety (mentioned by 5 panel members); head-to-head trials (5); children younger than 12 years (3); transitioning between therapies (2); first-line setting (1), predicting complications (1); and patients with low disease activity (1). One response also suggested there is a pressing need for a multinational NMO registry.

Discussion

An evidence-based modified Delphi consensus process was performed, which generated 25 validated statements to help inform therapeutic decision-making for patients with AQP4-IgG–seropositive NMOSD. The statements offer practical recommendations from experts related to the treatment of patients with AQP4-IgG–seropositive NMOSD with eculizumab, inebilizumab, or satralizumab.

The use of a geographically diverse panel of experts who were recruited to ensure perspectives were captured in a range of countries provides strength to the statements. The process combined expert experience with clinical evidence from published studies to generate and validate the consensus statements. A well-established Delphi method was used,30,31 with the consensus threshold decided a priori. Participation was mandatory in at least 1 voting round, but in this Delphi process, there was a high participation rate in all rounds.

The resulting statements are specific to AQP4-IgG–seropositive NMOSD, which is the only type of NMOSD indicated for the recently approved biologics. The finalized statements cover a broad range of topics in AQP4-IgG–seropositive NMOSD, many of which may have an immediate practical application for clinicians, such as the timing of initiation of biologic therapies, sequence of therapies (including when to switch), and potential long-term risks involved with biologics and immunotherapies for different subtypes of patient with NMOSD.

Although the wide geographic spread of the Delphi panel members is a strength of the process, it may also be considered a limitation, given that the level of clinical experience with the approved NMOSD therapeutics may vary between voting participants, depending on access to eculizumab, inebilizumab, and satralizumab in their region. Because the participants were not given specific instructions to vote on their agreement within the context of their experience only, or in an idealized setting, the impact of varying experience cannot be determined in the resulting statements. However, despite these factors, it should be noted that the level of agreement was high, with all but 1 statement obtaining more than 80% agreement and 11 statements obtaining more than 90% agreement. Another limitation of the statements is that the perspectives of nonclinical stakeholders, such as patients and payers, are not reflected. Throughout the Delphi process, the cost of treatments was considered not as important as efficacy and safety as a factor in decision-making. However, to patients and payers, especially in developing countries, cost is likely to be considered more important.

Consensus statements generated by a Delphi process can be a significant step toward standardizing care. The current statements aim to provide valuable guidance to clinicians, though it should be noted that some statements may be limited by a lack of specificity; for example, we were not able to state a precise length of time to monitor the duration of action of the therapies or confirm the best definition of severe relapse. In these cases, further development of statements was restricted by the amount of supporting evidence available. Despite these limitations, the NMOSD Delphi statements still address an unmet need in NMOSD treatment, for which the existing recommendations do not yet consider the most recently approved maintenance therapies.5,14,29 However, more research is needed to improve individualized treatment strategy further. The Delphi panel agreed that one of the key evidence gaps relates to the use of biomarkers that are predictive of treatment response; such biomarkers could allow for an optimized treatment strategy based on patient data. Comparative evidence between eculizumab, inebilizumab, and satralizumab and between these biologics and off-label therapies such as tocilizumab and rituximab would be valuable to inform decision-making between the available treatments. In the absence of head-to-head RCT data, comparative evidence may come from indirect treatment comparisons or from analysis of observational cohort data. Overall, continued monitoring of real-world data of eculizumab, inebilizumab, and satralizumab in patients with NMOSD is important in furthering our understanding of their long-term safety, tolerability, and efficacy profiles. Finally, given the importance of patient preferences, as highlighted throughout the statements, more insights into patient preferences for NMOSD treatment would be valuable to better understand the patient perspective and meet patients’ needs.

In conclusion, the consensus statements developed in this Delphi process seek to address an unmet need for providing recommendations on the use of eculizumab, inebilizumab, and satralizumab to treat patients with AQP4-IgG–seropositive NMOSD.
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### References


International Delphi Consensus on the Management of AQP4-IgG+ NMOSD: Recommendations for Eculizumab, Inebilizumab, and Satralizumab
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