Neuromyelitis optica spectrum disorder (NMOSD) is a rare, debilitating, autoimmune disease of the central nervous system.

- Anti-aquaporin-4 immunoglobulin G (AQP4-IgG) seropositive NMOSD is the more common form of NMOSD, accounting for approximately 80% of cases.
- Three approved monoclonal antibodies have emerged as effective maintenance therapies for AQP4-IgG seropositive NMOSD: eculizumab, inebilizumab, and satralizumab.
- There are no standard treatment recommendations that provide clear guidance on the use of the approved therapies or their role in the context of existing off-label maintenance therapies.
- There is a clear and pressing need for new international recommendations for the management of AQP4-IgG seropositive NMOSD.
- Delphi consensus methods are a robust approach for establishing best practice.
- Delphi consensus methods gather information from experts and allow the development and validation of consensus statements that reflect the broad experience of key experts in a particular field.

**Objective**

To develop validated statements on AQP4-IgG seropositive NMOSD, management, as an evidence-based consensus process, with a focus on recommendations for the use of eculizumab, inebilizumab, and satralizumab for the treatment of patients with AQP4-IgG seropositive NMOSD.

**Methods**

- A modified Delphi process was conducted, informed by a targeted literature review and clinical experience (Figure 1).
- A panel of 24 clinical experts in NMOSD was recruited.
- One expert acted as Chair (non-voting role) and steering committee member.
- Two experts acted as additional members of the steering committee (voting role).
- Twenty-one experts participated to complete the membership of the Delphi panel (voting role).
- The Delphi panel was asked to vote on the statements over a maximum of three rounds.
- Participation in at least one of the first two voting rounds was mandatory.
- Final statements were all those that had met the consensus threshold at the end of the process.

**Results**

**Supporting evidence and development of statements**

- The first 25 statements were designed to be relevant to the use of eculizumab, inebilizumab and satralizumab to treat NMOSD; the majority of these articles related to the NMOSD disease and its treatment.
- A consultation paper was developed with four key questions.
- Following the review of questionnaire responses from the Delphi panel members, which were informed by evidence from the literature and their own clinical experience, 25 proposed statements were developed.

**Voting results**

- Voting on the 25 proposed statements was completed in two rounds (Figure 2).
- The final 25 statements that met consensus are presented in Table 1.

**Discussion and conclusions**

A well-established consensus method was used to develop statements that offer practical recommendations from experts related to the treatment of patients with AQP4-IgG seropositive NMOSD with eculizumab, inebilizumab, and satralizumab.

- A geographically diverse panel of experts was recruited to support the use of these statements internationally.
- The level of panel participation remained high from the initial questionnaire and through both voting rounds.
- Levels of agreement were high, with all but one statement obtaining over 80% agreement and 11 statements obtaining over 90% agreement.
- Consensus statements generated by a Delphi process can be a significant step towards standardized care. The NMOSD Delphi statements address all major areas of practice and consideration and could be the most recently approved management guidelines for this disease.
- In conclusion, it is hoped that these consensus statements will be valuable for informing decision-making in the treatment of patients with AQP4-IgG seropositive NMOSD, with the aim of optimizing patient outcomes and supporting the development of standardized practice guidelines.

**References**

- Level of agreement: n/N (%)

**NMOSD Delphi panel**

Friedemann Paul was the non-voting Chair of the NMOSD Delphi panel. Romain Marignier and Jacqueline Palace were voting Steering Committee members. Other voting members of the NMOSD Delphi panel comprised Georgina Arzamendi, Naain Askari, Jeff Bennett, Bruce Cree, Jérôme De Seze, Katsuhiko Fujihara, Saff Hadji, Ho-Jin Kim, Najib Kissani, Ingo Klaiber, Satoshi Kubwara, Marco Lanza-Picolet, Isabel Lelat, Leila Pandit, Sean Pitblado, Chiay Cuan, Sudarshan Ramanathan, Dalia Rotstein, Albert Saiz, Douglas Sato and Adi Vaknin-Dembinsky.

**Table 1. Final NMOSD Delphi consensus statements and results in the voting rounds**

<table>
<thead>
<tr>
<th>Consensus statements*</th>
<th>Level of agreement, n/N (%)</th>
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<tbody>
<tr>
<td><strong>Monotherapy versus combination therapy</strong></td>
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<tr>
<td>Eculizumab monotherapy should be given as the initial regimen with AQP4-IgG seropositive NMOSD to reduce the risk of additional side effects of concurrent use with immunomodulatory therapies (Statement 10).</td>
<td>16/18 (88.9)</td>
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<tr>
<td>Eculizumab, inebilizumab or satralizumab should be added to immunomodulatory therapies if the patient is already receiving immunomodulatory treatments. Combination therapy should be considered in the context of the drug’s long-term safety and tolerance profiles of the immunomodulators (Statement 11).</td>
<td>17/18 (94.4)</td>
</tr>
<tr>
<td>In adults with AQP4-IgG seropositive NMOSD, eculizumab should be initiated at diagnosis, after first attack or after relapse due to failure of existing treatments (Statement 12).</td>
<td>17/18 (94.4)</td>
</tr>
<tr>
<td>Patients with AQP4-IgG seropositive NMOSD should be treated with satralizumab. Treatment with eculizumab or inebilizumab may be considered if the patient is already receiving immunomodulatory treatments.</td>
<td>18/18 (100.0)</td>
</tr>
<tr>
<td>Switching therapies</td>
<td></td>
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<tr>
<td>If eculizumab, inebilizumab or satralizumab are initiated, patients with AQP4-IgG seropositive NMOSD should be switched to another of these three biologic therapies if: there is a severe relapse while on treatment; serious treatment-related adverse events occur; or due to lack of efficacy.</td>
<td>18/21 (85.7)</td>
</tr>
<tr>
<td>Contraindication to patients with NMOSD and coexistent conditions such as pregnancy should be considered in the context of the therapeutic benefits of biologic medications (Statement 14).</td>
<td>18/18 (100.0)</td>
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<tr>
<td>Use of biologic agents and patient-reported outcomes</td>
<td></td>
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<tr>
<td>Treatment-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 inform decision-making (Statement 20).</td>
<td>15/18 (83.3)</td>
</tr>
<tr>
<td>Research gaps</td>
<td></td>
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<tr>
<td>Research proponents in the area of NMOSD is the investigation of 1) prognostic biomarkers of relapse and disease progression; 2) predictive biomarkers to assess treatment efficacy longitudinally; and 3) long-term outcomes in AQP4-IgG seropositive NMOSD (Statement 4).</td>
<td>15/18 (83.3)</td>
</tr>
<tr>
<td>NMOSD, neuromyelitis optica spectrum disorder</td>
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