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

Friedemann Paul, MD, Romain Marignier, MD, PhD, Jacqueline Palace, DM, Georgina Arrambide, MD, PhD, Nasrin Asgari, MD, PhD, DMSc, Jeffrey L. Bennett, MD, PhD, Bruce A. C. Cree, MD, PhD, MAS, Jérôme De Seze, MD, PhD, Kazuo Fujihara, MD, Ho Jin Kim, MD, PhD, Rebecca Hornby, PhD, Saif Huda, MD, DPhil, Najib Kissani, MD, Ingo Kleiter, MD, Satoshi Kuwabara, MD, PhD, Marco Lana-Peixoto, MD, PhD, Lisa Law, MSc, M. Isabel Leite, MD, DPhil, Lekha Pandit, MD, PhD, Sean J. Pittock, MD, Chao Quan, MD, PhD, Sudarshini Ramanathan, FRACP, PhD, Dalia Rotstein, MD, MPH, Albert Saiz, MD, PhD, Douglas Kazutoshi Sato, MD, PhD, and Adi Vaknin-Dembinsky, MD, PhD

Supplementary Material

eAppendix 1: Targeted literature review—methods

A targeted literature review was carried out using the electronic database, Embase, as well as online sources such as PubMed and Google. Search terms used for Embase are presented in eTables 1 and 2. Relevant studies were those meeting the following criteria: (a) population: patients with AQP4-IgG seropositive NMOSD or mixed populations of patients with AQP4-IgG seropositive and seronegative NMOSD; (b) intervention: eculizumab, inebilizumab, or satralizumab; (c) outcomes: efficacy, safety, and tolerability, and outcomes related to route and frequency of treatment administration; (d) any comparator or study design. No date limit was applied to the searches, and only English language articles were considered. The targeted literature review was performed by Oxford PharmaGenesis, Oxford, UK, an independent consultancy which received funding from F. Hoffmann-La Roche Ltd.

eTable 1 Electronic Search Strings (Embase) Used for Targeted Literature Review: Searching for Evidence for Satralizumab, Eculizumab, or Inebilizumab

#	Search terms	Results
1	(satralizumab or Enspryng).ti,ab.	50
2	(eculizumab or Soliris).ti,ab.	3483
3	(inebilizumab or Uplizna).ti,ab.	37
4	or/1-3	3540
5	(Neuromyelitis Optica or Neuromyelitis Optica Spectrum Disorder).ti,ab.	7881
6	(NMOSD or NMO).ti,ab.	6846
7	Neuromyelitis Optica/	5399
8	or/5-7	10013
9	4 and 8	124

Searches were run on December 2, 2020.

Abbreviation: NMOSD = neuromyelitis optica spectrum disorder.

eTable 2 Electronic Search Strings (Embase) Used for Targeted Literature Review: Searching for General Treatment Guidance for NMOSD

#	Search terms	Results
1	(Neuromyelitis Optica or Neuromyelitis Optica Spectrum Disorder).ti,ab.	7881
2	(NMOSD or NMO).ti,ab.	6846
3	Neuromyelitis Optica/	5399
4	or/1-3	10013
5	(guideline$ or recommend$).ti,ab.	1379152
6	decision-making.ti,ab.	190175
7	(taper$ or switch$ or initiat$).ti,ab.	1080945
8	or/5-7	2522912
9	(novel or satralizumab or Enspryng or eculizumab or Soliris or inebilizumab or Uplizna).mp.	1714879
10	4 and 8 and 9	96

Searches were run on December 2, 2020.

Abbreviation: NMOSD = neuromyelitis optica spectrum disorder.

eAppendix 2: Proto-Statement Questionnaire for the NMOSD Delphi Consensus

1. In your opinion, what are the most important considerations when choosing therapies for patients with NMOSD? (please limit to five items)
2. At what stage should patients with NMOSD start newly approved therapies?
3. Should the decision for a patient to start a newly approved therapy be dependent on aquaporin-4 serostatus?
4. What should inform the decision to give a newly approved therapy as monotherapy or in combination with immunosuppressant therapy?
5. Which criteria would you apply when selecting one of the newly approved drugs (e.g., mode of action, patient's disease history)?
6. Should patients receiving off-label immunosuppressants and/or oral corticosteroids and who are free of relapses be treated with newly approved therapies?
7. What considerations should be made when combining newly approved therapies with immunosuppressant therapy including steroids (e.g., replacement with monotherapy, steroid tapering)?
8. What factors should inform the decision to switch maintenance therapies?
9. What treatment pathways should be followed if a patient with NMOSD has previously received any of the newly approved therapies, rituximab or tocilizumab prior to switching?
10. Would the use of biomarkers be useful for informing treatment decisions? If so, which biomarkers?
11. How important is patient preference when it comes to treatment decision-making in NMOSD?
12. How important is quality of life and patient-reported outcomes when it comes to treatment decision-making in NMOSD?
13. How should treatment considerations differ for patients with comorbidities (e.g., overlapping autoimmune diseases such as Sjogren's, Lupus, rheumatoid arthritis, psoriasis arthritis, thyroiditis, myasthenia gravis or non-autoimmune co-morbidities such as type 2 diabetes mellitus) than those without?

14. Should adolescents (age 12–17 years) with NMOSD be treated with newly approved therapies?
15. What are the main safety concerns that should be monitored in the short and long term?
16. In terms of safety outcomes, should specific subgroups of patients be monitored more closely than others? If so, which subgroups?
17. Do you think that guidance concerning meningococcal vaccinations for patients treated with eculizumab needs to be more specific for patients with NMOSD?
18. What are the most important research gaps in the current evidence for newly approved therapies for NMOSD?
19. Are there any further topics that you consider important but are not covered above?

eAppendix 3: Targeted Literature Review—Findings

After screening approximately 200 abstracts identified from the electronic and supplementary searches, 35 publications were considered relevant and were used to inform the Delphi consensus process. Of the 35 publications, 21 were related to the key randomized controlled trials (RCTs) for the therapies of interest: PREVENT (NCT01892345; eculizumab with or without immunosuppressive therapies); N-MOmentum (NCT02200770; inebilizumab as monotherapy); SAkuraStar (NCT02073279; satralizumab as monotherapy), and SAkuraSky (NCT02028884; satralizumab as add-on therapy to immunosuppressants).[e1-e21] One meta-analysis was identified that included 3 of these 4 RCTs (PREVENT, N-MOmentum, and SAkuraSky).[e22] One open-label study of eculizumab was identified that preceded the PREVENT trial.[e23] One cross-sectional survey was identified on the topic of patient experience in NMOSD.[e24] In addition, 11 review articles were identified that discussed key considerations related to therapies for NMOSD.[e25-e35]

eReferences—Reference List for the Targeted Literature Review

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eTable 3. Breakdown of Likert Responses for the Final NMOSD Delphi Consensus Statements

Final consensus statement (after all voting rounds)	Number of votes						
	Strongly agree	**Agree**	**Somewhat agree**	**Somewhat disagree**	**Disagree**	**Strongly disagree**	**Total**
Initiation of eculizumab, inebilizumab, or satralizumab							
Statement 1: In adults with NMOSD who are AQP4-IgG seropositive, eculizumab may be initiated at diagnosis, after first attack or after relapse due to failure of existing treatments	6	4	4	3	1	0	18
Statement 2: In adults with NMOSD who are AQP4-IgG seropositive, inebilizumab may be initiated at diagnosis, after first attack or after relapse due to failure of existing treatments	6	8	4	0	0	0	18
Statement 3: In adults and adolescents (≥12 years) with NMOSD who are AQP4-IgG seropositive, satralizumab may be initiated at diagnosis, after first attack or after relapse due to failure of existing treatments	8	6	3	1	0	0	18
Statement 4: The most important factors to inform decision-making for biologic NMOSD therapies are efficacy and safety	8	8	2	0	0	0	18
Statement 5: In addition to efficacy and safety, current clinical disease activity and relapse severity, acceptability of the therapy's route of administration, and whether the	11	6	1	0	0	0	18

Final consensus statement (after all voting rounds)	Number of votes						
	Strongly agree	**Agree**	**Somewhat agree**	**Somewhat disagree**	**Disagree**	**Strongly disagree**	**Total**
therapy could be beneficial for overlapping comorbidities are all important factors that contribute to the selection of a biologic NMOSD therapy							
Statement 6: For newly diagnosed patients with AQP4-IgG seropositive NMOSD, the choice between eculizumab, inebilizumab and satralizumab may be informed by patient preferences in dosing frequency, route of administration and acceptance of potential safety risks, including during pregnancy	5	9	4	0	0	0	18
Statement 7: When choosing between eculizumab, inebilizumab and satralizumab for patients with NMOSD who are AQP4-IgG seropositive, an important consideration is the patient's response to prior maintenance therapy; clinicians should choose a therapy with an alternative mode of action to previous failed therapies	10	6	1	0	1	0	18
Statement 8: While patients with AQP4-IgG seropositive NMOSD on off-label immunosuppressants (azathioprine, mycophenolate mofetil and oral steroids) or off-label biologics (rituximab and tocilizumab) are currently free of	7	7	2	2	0	0	18

Final consensus statement (after all voting rounds)	Number of votes						
	Strongly agree	**Agree**	**Somewhat agree**	**Somewhat disagree**	**Disagree**	**Strongly disagree**	**Total**
relapse or tolerability issues, there is no need to initiate eculizumab, inebilizumab or satralizumab							
Statement 9: There is evidence that patients with NMOSD who experience disease activity while treated with immunosuppressants and/or oral steroids would benefit from the addition of biologic therapies (eculizumab, inebilizumab or satralizumab)	8	5	3	1	1	0	18
Monotherapy vs combination therapy							
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	2	10	3	1	1	1	18
Statement 11: Whilst 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- and long-	4	8	6	0	3	0	21

Final consensus statement (after all voting rounds)	Number of votes						
	Strongly agree	**Agree**	**Somewhat agree**	**Somewhat disagree**	**Disagree**	**Strongly disagree**	**Total**
term safety and tolerability profiles of the immunosuppressants							
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	4	11	2	1	0	0	18
Switching therapies							
Statement 13: Following 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 three biologic therapies if: there is a severe relapse while on treatment; serious treatment-related adverse events occur; or due to patient preference	5	9	2	2	0	0	18
Statement 14: When switching between eculizumab, inebilizumab or satralizumab, the new therapy can be started immediately after stopping the previous therapy,	5	10	3	1	2	0	21

Final consensus statement (after all voting rounds)	Number of votes						
	Strongly agree	**Agree**	**Somewhat agree**	**Somewhat disagree**	**Disagree**	**Strongly disagree**	**Total**
taking into consideration the mechanism and duration of action							
Patient populations							
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)	5	7	6	0	0	0	18
Statement 16: Adolescents (≥12 years old) 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 use of these drugs in other scenarios	2	7	7	2	0	0	18
Safety							
Statement 17: Patients with AQP4-IgG seropositive NMOSD treated with eculizumab, inebilizumab or satralizumab should be monitored in the short- and long-term for infections	14	3	1	0	0	0	18
Statement 18: Some patients with AQP4-IgG seropositive NMOSD treated with eculizumab, inebilizumab or	9	6	0	3	0	0	18

Final consensus statement (after all voting rounds)	Number of votes						
	Strongly agree	**Agree**	**Somewhat agree**	**Somewhat disagree**	**Disagree**	**Strongly disagree**	**Total**
satralizumab should be clinically monitored more frequently (more than twice per year): these include patients with comorbidities that influence risk of infection, adolescents, older people, pregnant women and patients with significant immunosuppression							
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- and long-term and will inform patient decision-making on family planning and treatment pathways	11	6	1	0	0	0	18
Statement 20: Patients with NMOSD who are AQP4-IgG seropositive should be up to date with all vaccinations prior to initiating new biologic therapies (eculizumab, inebilizumab or satralizumab) unless there are exceptional circumstances	7	8	1	2	0	0	18
Statement 21: Guidance concerning meningococcal vaccinations for patients treated with eculizumab should be clarified for patients with AQP4-IgG seropositive	12	4	1	0	1	0	18

Final consensus statement (after all voting rounds)	Number of votes						
	Strongly agree	**Agree**	**Somewhat agree**	**Somewhat disagree**	**Disagree**	**Strongly disagree**	**Total**
NMOSD to ensure clinicians know how to cover all serogroups and when to schedule booster vaccinations and reassess vaccination status							
Use of biomarkers and patient-reported outcomes							
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 routine use of biomarkers to support treatment decision-making in patients with AQP4-IgG seropositive NMOSD	7	8	1	2	0	0	18
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	2	12	2	1	1	0	18
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	9	6	0	3	0	0	18

Final consensus statement (after all voting rounds)	Number of votes						
	Strongly agree	**Agree**	**Somewhat agree**	**Somewhat disagree**	**Disagree**	**Strongly disagree**	**Total**
Research gaps							
Statement 25: Research priorities in the area of NMOSD are the investigation of: (i) prognostic biomarkers of relapse and disease progression; (ii) predictive biomarkers to assess treatment response; (iii) the role of imaging; (iv) head-to-head evidence; and (v) long-term outcomes associated with the use of eculizumab, inebilizumab and satralizumab, gathered via clinical trials and real-world data	13	2	0	2	0	1	18

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%.