



Seeing a difference in Neuromyelitis Optica Spectrum Disorder: integrating novel strategies into care

Transcript from a touchSATELLITE SYMPOSIUM

*Funded by an independent medical education request from Alexion.
This activity is provided by touchIME.*

THE EXPERTS:



PROF. JACKIE PALACE
(Chair)

Nuffield Department of Clinical Neurosciences, Oxford University, Oxford, UK



PROF. KAZUO FUJIHARA

Department of Multiple Sclerosis Therapeutics, Fukushima Medical University School of Medicine, Fukushima, Japan



PROF. SEAN PITTOCK

Center for Multiple Sclerosis and Autoimmune Neurology, and the Neuroimmunology Research Laboratory, Mayo Clinic, Rochester, MN, USA

Funded by an independent medical education request from Alexion. This activity is provided by touchIME.

November 2020

INTRODUCTION

Join Professor Jackie Place (chair), Professor Kazuo Fujihara and Professor Sean Pittock as they discuss the rationale for and latest data on novel therapies for neuromyelitis optica spectrum disorder and how to integrate them into patient care.

LEARNING OBJECTIVES

After watching this touchSATELLITE SYMPOSIUM you should be able to:

- Outline strategies for early and accurate diagnosis of neuromyelitis optica spectrum disorder (NMOSD)
- Describe how novel treatment options target the pathophysiology of NMOSD to prevent relapse
- Assess recent phase III results for novel therapies and how these may impact treatment decisions in NMOSD

TOPICS DISCUSSED:

- Does early detection reduce the burden of NMOSD?
- How do novel therapies work to reduce relapse?
- In the clinic with NMOSD: How can we translate the recent data to patient care?
- Audience Q&A

INTRODUCTION

For patients with the rare autoimmune condition neuromyelitis optica spectrum disorder (NMOSD), cumulative central nervous system damage occurs due to recurrent episodes of inflammation of the optic nerve, spinal cord or brain which can eventually result in blindness and paralysis, leading to significant disability. Early treatment to prevent disability related to recurrent attacks is crucial, but diagnosis may be delayed as it can be difficult to distinguish NMOSD symptoms from multiple sclerosis. Systemic immunosuppressants are widely used to prevent relapse, but in 2019 three new agents which target the pathophysiology of NMOSD were shown to effectively reduce attacks. The question now is: “How should we integrate newer agents into care for patients with NMOSD?”

Prof. Jackie Palace: Welcome to this symposium titled ‘Seeing a difference in neuromyelitis spectrum disorder’ and today we’re going to focus on how new and novel treatments affect our treatments in the clinic

So, this is our faculty, there is myself Professor Jackie Palace. We have Professor Kazuo Fujihara and Professor Sean Pittock joining us.

Agenda		
Time	Presentation	Speaker
08:00	Introduction and welcome	Prof. Jackie Palace
08:05	Does early detection reduce the burden of NMOSD?	Prof. Kazuo Fujihara
08:15	How do novel therapies work to reduce relapse?	Prof. Sean Pittock
08:30	In the clinic with NMOSD: How can we translate the recent data to patient care? Case-based discussion	Presenter: Prof. Jackie Palace Commentators: Profs. Sean Pittock and Kazuo Fujihara
08:45	Live Q&A	All faculty
08:55	Summary and close	Prof. Jackie Palace

NMOSD, Neuromyelitis optica spectrum disorder.

So, this is our programme today. Professor Kazuo Fujihara is going to tell us why diagnosing NMOSD early is important. Professor Pittock is going to run through the data on these new and novel treatments and how they reduce relapses. We’re then going to have a case-based discussion around how these new treatments are changing the strategy in the clinic when we’re deciding on treatments and then we’re going to end with a question and answer session and I encourage you to actively participate.

Learning objectives

Outline strategies for early and accurate diagnosis of neuromyelitis optica spectrum disorder (NMOSD)

Describe how novel treatment options target the pathophysiology of NMOSD to prevent relapse

Assess recent phase III results for novel therapies and how these may impact treatment decisions in NMOSD

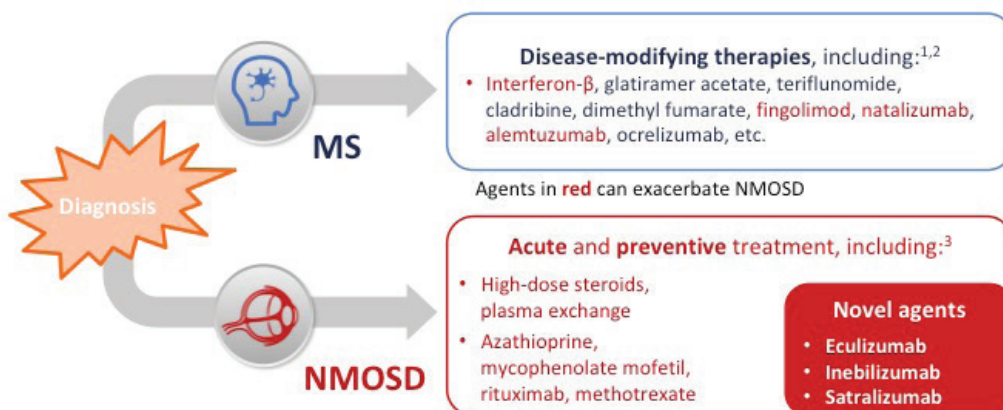
So, these are our learning objectives today. We're going to outline the strategies for diagnosing NMOSD early and accurately. We're going to describe how these new treatments target NMOSD relapses pathophysiologically. We're going to hear the phase III study results from these new treatments and then we're going to discuss how these new treatments impact on our algorithm.

Does early detection reduce the burden of NMOSD?

So now we have Professor Fujihara who's going to tell us about how early detection reduces the burden of NMOSD.

Prof. Kazuo Fujihara: Thank you very much for the introduction Jackie. I'm very happy to be here today. My talk is to address this question: "Does early detection reduce the burden of NMOSD?" My answer is of course yes, but to achieve the goal, we should understand the clinical manifestations, MRI and laboratory findings, diagnostic criteria, pathophysiology and the treatments available for this disease.

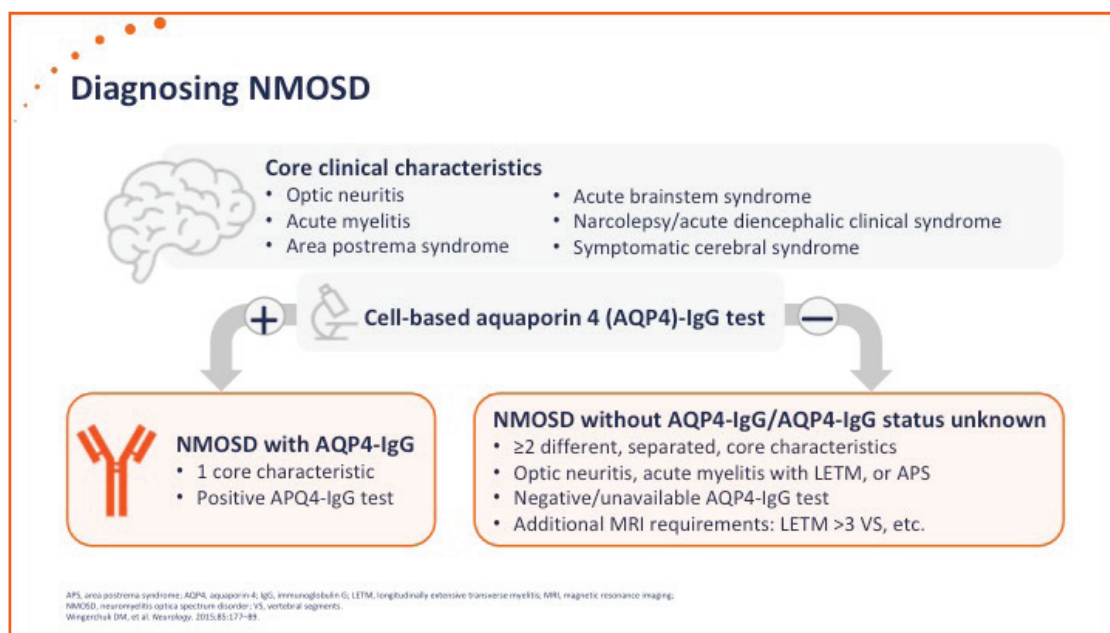
Treatment pathway for MS vs NMOSD



MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.
1. Montalban X, et al. *Mult Scler*. 2018;24:98–120. 2. AAN Practice Guideline Recommendations. Available at: www.aan.com/PracticeGuidelines/Neurology/PracticeGuidelines/MS (accessed July 2020).
3. Kessler RA, et al. *Curr Treat Options Neurol*. 2016;18:2.

Let me start with the treatment. As you all know, the treatment of NMOSD is different from multiple sclerosis (MS). Among the 20 or so disease-modifying therapies approved for MS in the United States, some drugs like interferon-beta, fingolimod, natalizumab and alemtuzumab can exacerbate NMOSD, so you should avoid treating your NMOSD patients with these MS drugs. Therefore, it is very important to differentiate NMOSD from MS in the early phase of the diagnostic workup.

For the immunological treatment for NMOSD, treatments are divided into two phases: acute phase and chronic phase to prevent relapse. For relapse prevention, several immunosuppressants have been used including azathioprine, mycophenolate mofetil, rituximab and so on. However last year, the first ever randomised controlled trials of monoclonal antibodies in NMOSD were published. All three monoclonal antibodies were found to be highly efficacious in preventing relapse and were relatively safe. These three monoclonal antibodies are eculizumab (anti-complement monoclonal), inebilizumab (anti-CD19 monoclonal) and satralizumab (anti-IL-6 receptor monoclonal). So, we have more treatment choices for this disease.

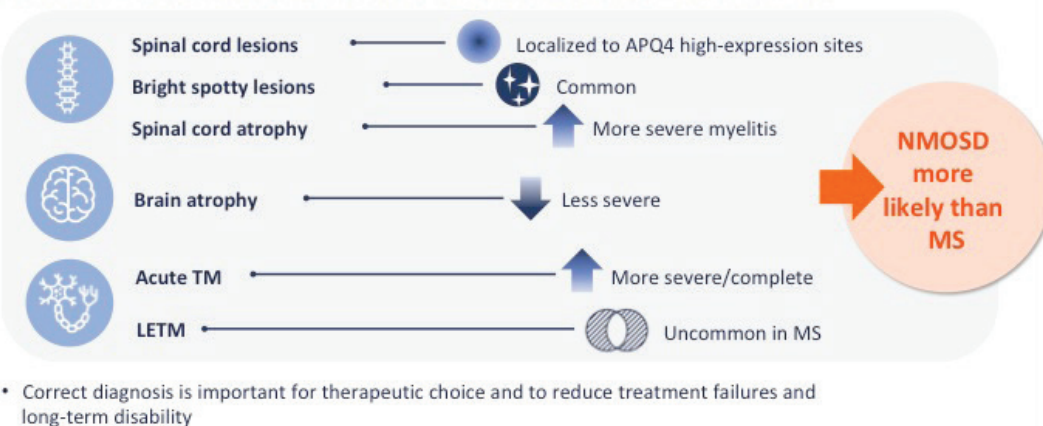


Next, the diagnosis of NMOSD. As you can see here, there are six core clinical characteristics: optic neuritis, acute myelitis, area postrema syndrome manifesting in intractable hiccups, and nausea and vomiting, as well as some brainstem and cerebral syndromes. As for the aquaporin-4 (AQP4)-IgG testing, ideally a cell-based assay should be used because a cell-based assay is the most sensitive and most specific.

To make a diagnosis of NMOSD with AQP4-IgG, your patients should have one of those six core clinical characteristics and the patients are positive for AQP4-IgG; as long as you can exclude an alternative diagnosis, you can make a diagnosis of NMOSD with AQP4-IgG. NMOSD without AQP4-IgG or AQP4-IgG serostatus unknown is more complicated and the criteria are more stringent. For example, you need two or more separate core clinical characteristics and one of them should be optic neuritis, acute myelitis or area postrema syndrome. The patient should also fulfil additional MRI criteria like spinal cord lesions longer than three vertebral segments. MOG antibody-positive NMOSD may be included in this category, but they can be heterogenous in nature.

Differentiating NMOSD from MS

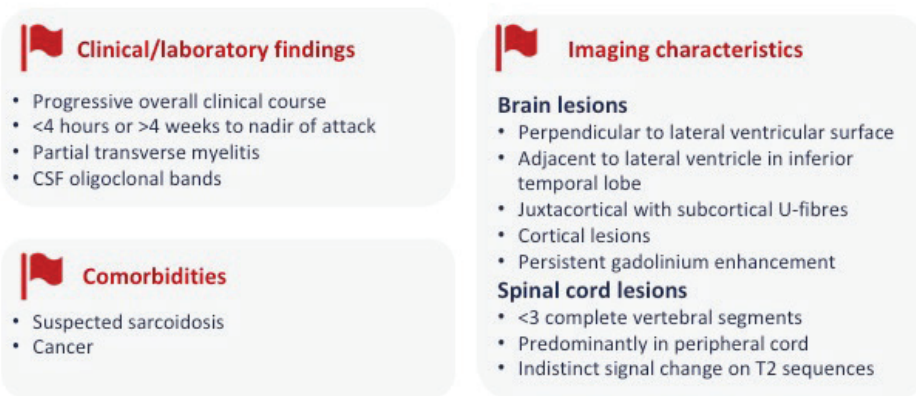
Symptom magnitude and disease history can help differentiate NMOSD from MS



AQP4, aquaporin-4; LETM, longitudinally extensive transverse myelitis; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; TM, transverse myelitis. Marrodan M, et al. *Biomolecules*. 2020;8:130.

Some MRI findings and clinical features may be helpful in differentiating NMOSD from MS. Spinal cord lesions may be localised to AQP4 high expression sites like periventricular regions and central grey matter of the spinal cord. Bright spotty lesions are commonly seen in NMOSD and spinal cord atrophy is more severe in NMOSD than in MS, but on the other hand, brain atrophy is less severe in NMOSD. Transverse myelitis is more severe and complete in NMOSD, but longitudinal extensive transverse myelitis is relatively uncommon in MS. So, these findings are useful for the differential diagnosis.

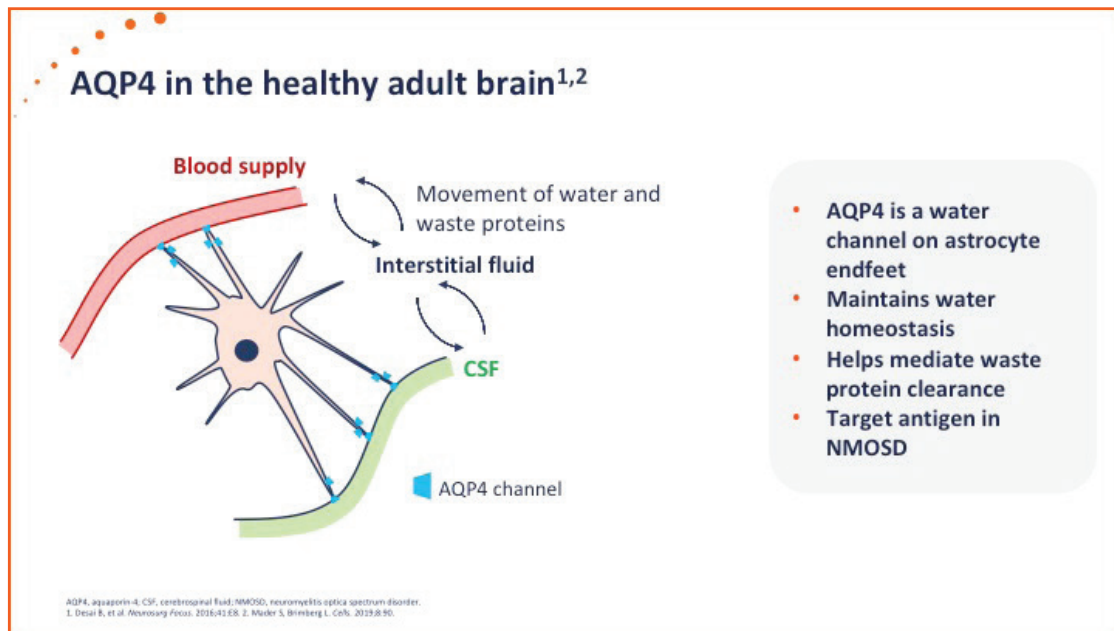
Red flags: atypical findings in NMOSD



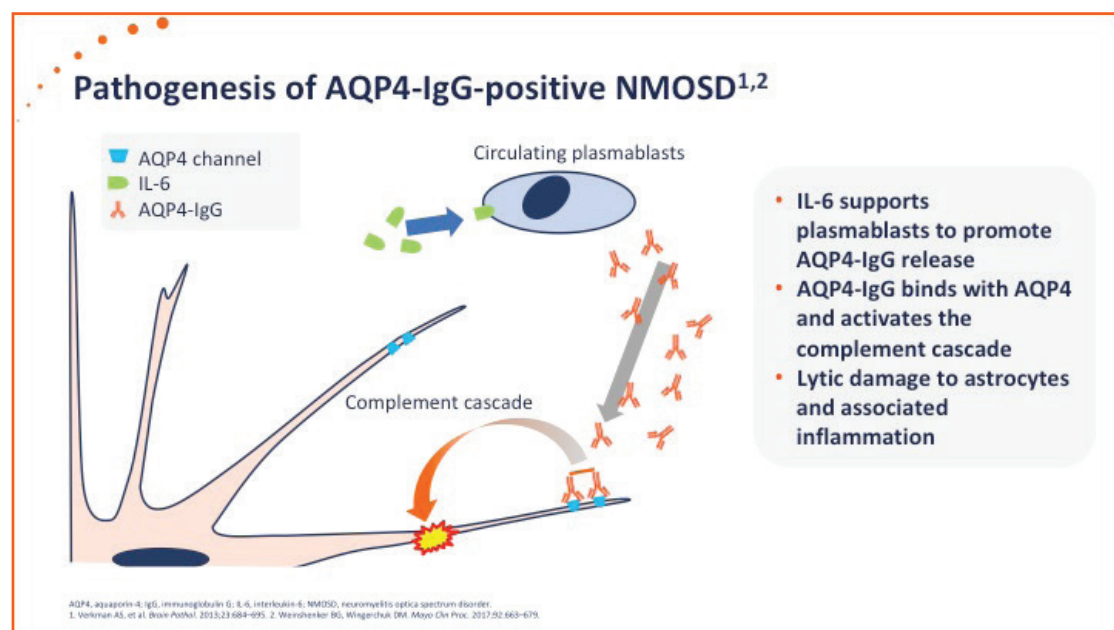
CSF, cerebrospinal fluid; NMOSD, neuromyelitis optica spectrum disorder. Wingerchik DM, et al. *Neurology*. 2015;85:177–89.

There are some red flags which are atypical findings in NMOSD. A progressive clinical course is uncommon in NMOSD. As I said, partial transverse myelitis is common in MS, but not common in NMOSD. If CSF oligoclonal bands are positive, you cannot exclude NMOSD, but only 10% of patients with NMOSD are oligoclonal band positive. If the patients have comorbidities, you should be careful. Sarcoidosis may mimic NMOSD and in some cancer patients, spinal cord lesions may be longer than three vertebral segments. Some brain lesions listed here are relatively typical in MS, so if you see these lesions in your patients, you should doubt the diagnosis of NMOSD.

Spinal cord lesions are usually longer than three vertebral segments so short spinal cord lesions are relatively uncommon in NMOSD. However, a recent Mayo Clinic study showed that spinal cord lesions in up to 15% of patients with onset NMOSD myelitis were shorter than three vertebral segments. So short spinal cord lesions do not necessarily exclude the diagnosis of NMOSD; spinal cord lesions in the periphery are uncommon in NMOSD.



What is AQP4, where is AQP4 localised and what are its functions? AQP4 is a water channel on astrocyte endfeet and it maintains water homeostasis, helps to mediate waste protein clearance and, of course, it's a target antigen in NMOSD.



What should we know about the pathogenesis of AQP4-IgG positive NMOSD? The circulating plasmablasts can release AQP4-IgG and are mainly supported by interleukin (IL)-6. AQP4-IgG binds with AQP4, which are expressed on the endfeet of the astrocytes, and since AQP4-IgG is mainly IgG-1, it can activate the complement cascade efficiently. As a result of the complement-mediated cytotoxicity, the astrocytes are damaged but the myelin and neurons are also damaged in NMOSD. In addition to this humoral immunity, cellular immunity involving lymphocytes, macrophages and granulocytes also contribute to the lesion formation.

Other biomarker candidates in NMOSD



Th17-related cytokines¹

- Levels of Th17 cells increased in NMOSD
- IL-6, IL-17 higher in NMOSD than MS
- Th17 cells and cytokines may be therapeutic targets



CXCL1, CXCL5, and CXCL7 in CSF³

- Neutrophil-related chemokines elevated in NMOSD but not MS
- Not correlated with clinical severity
- Potential for diagnostic use



GFAP and NfL²

- Increased in NMOSD
- CSF levels correlated with serum levels
- Likely to be biomarkers of disease activity
- Serum GFAP:NfL higher in NMOSD than MS



Exosomal microRNAs⁴

- Hsa-miR-122-3p and hsa-miR-200a-5p correlated with disease severity in NMOSD
- Potential as biomarkers for relapsing NMOSD

CSF, cerebrospinal fluid; CXCL, chemokine; GFAP, glial fibrillary acidic protein; IL, interleukin; MS, multiple sclerosis; NfL, neurofilament light chain; NMOSD, neuromyelitis optica spectrum disorder; RNA, ribonucleic acid; Th, T-helper.
1. Hou MM, et al. *Int Immunopharmacol*. 2019;75:105793. 2. Watanabe M, et al. *Neurology*. 2019;93:e1299-1311. 3. Liu Z, et al. *Ann Clin Transl Neurol*. 2020; doi: 10.1002/act5.51094. 4. Chen C, et al. *Front Immunol*. 2020;11:5064.

What are other biomarker candidates in NMOSD? Th-17-related cytokines like IL-6, IL-8, GM-CSF are very much upregulated in NMOSD. They may be the therapeutic targets in this disease. GFAP is an astrocyte protein and neurofilament lightchain (NfL) is a neurone-specific protein. If you detect these proteins in the blood and the CSF, they suggest astrocytic damage and neuronal damage, and their levels in the serum and the CSF are very high in NMOSD in comparison with MS and other conditions. Some chemokines are also upregulated in NMOSD. For example, CXCL1 is a neutrophilic chemoattractant. CXCL5 is expressed in eosinophils. Neutrophil-related chemokines are elevated in NMOSD but not in MS. Recent studies suggest that exosomal microRNAs may also be emerging biomarkers in NMOSD.

Phenotypic subgroups in AQP4-IgG-negative NMOSD



Principal component analysis of 36 clinico-radiologic parameters from 41 patients, validated in 45 patients

3 phenotypic subgroups

MS-like subgroup

- Dawson fingers
- Lesion touching lateral ventricle body
- ≥4 brain lesions
- Inferior temporal lesion
- Unmatched CSF oligoclonal bands
- Significantly higher myoinositol and formate than NMOSD-like subgroup

NMOSD-like subgroup

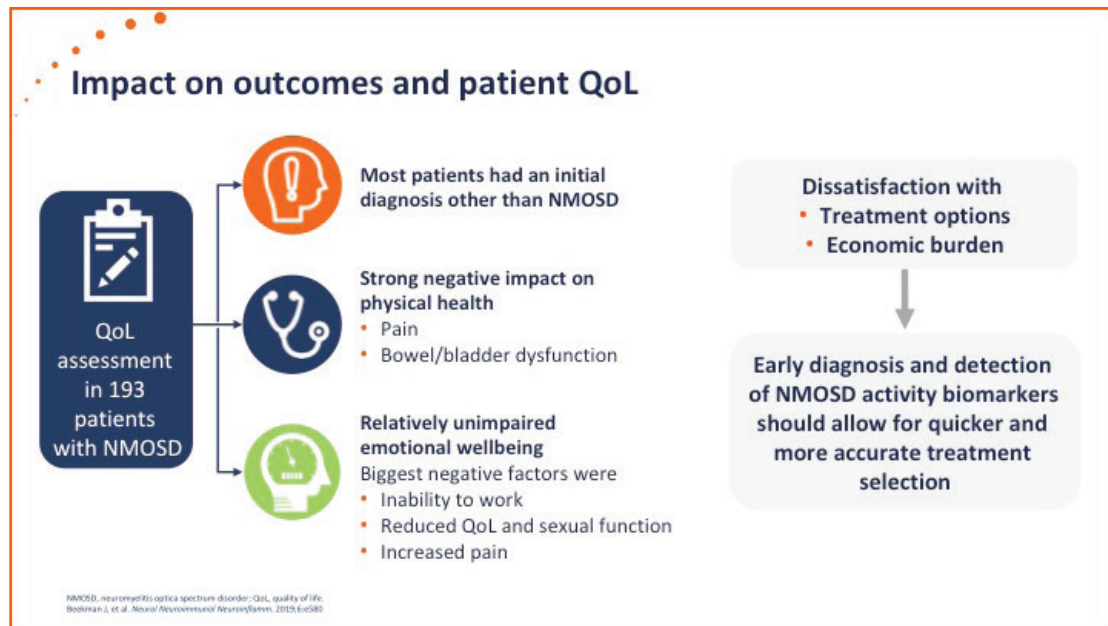
- Fulfills 2015 NMOSD criteria
- Predominant central cord involvement
- Simultaneous optic neuritis and transverse myelitis
- Tumefactive brain lesion
- EDSS ≥6 during attack

Low brain lesion subgroup

- ≤3 brain lesions

CSF, cerebrospinal fluid; EDSS, expanded disability status scale; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.
Yeo T, et al. *Neural Neuroimmunol Neuroinflamm*. 2019;6:e26.

Recently, researchers have started to focus on AQP4-IgG-negative NMOSD. An Oxford group led by Jackie [Palace], recently did a principal component analysis of 36 clinical MRI parameters in patients with this disease and they found that there are three phenotypic subgroups in this category: MS-like subgroup, NMOSD-like subgroup and low brain lesion subgroup. The MS-like subgroup has MRI lesions which are typically seen in MS and their metabolomic study demonstrated that there was a significantly higher level of myoinositol and formate in this group than in the NMOSD-like subgroup. So, these two groups may be different from the viewpoint of pathology. The NMOSD-like subgroup has features consistent with the diagnosis of NMOSD. The low brain lesion subgroup is characterised by three or less brain lesions. So seronegative NMOSD may be heterogenous by nature.



Finally, a recent study analysed quality of life in more than 190 patients with NMOSD. Very importantly, most patients had an initial diagnosis other than NMOSD; that means the diagnosis of NMOSD was delayed. A strong negative impact on physical health was seen in these patients. Pain and bladder or bowel dysfunction were also annoying symptoms. But on the other hand, emotional wellbeing was relatively unimpaired, but the biggest negative factors were inability to work, reduced quality of life, sexual function and increased pain. The patients' quality of life is quite low, and they are not satisfied with the treatment options and economic burden. So, early diagnosis is critically important in order to start early treatment with appropriate drugs and we should use biomarkers for early diagnosis and to monitor disease activity.

Thank you very much for your attention.

How do novel therapies work to reduce relapse?

Prof. Sean Pittock: Hello, I'd like to thank Prof. Jackie Palace for the invitation to speak today. Following on from what Prof. Fujihara has mentioned, we will be talking about how novel therapies work to reduce relapse. I will be covering some of the mechanisms that were discussed in Prof. Fujiharas' lecture and then discussing the phase III trials that have been performed in NMOSD. We will be talking about the results of these trials as well as some of the potential side effects of these medications.

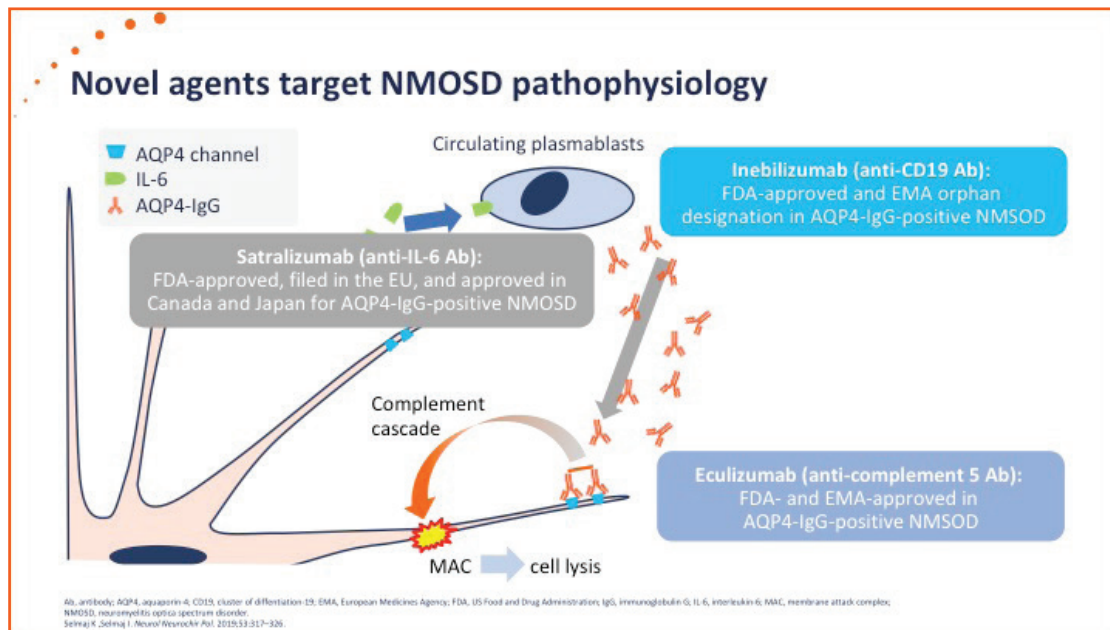
Treatment goals in NMOSD^{1,2}

-  NMOSD attacks require aggressive immunosuppressive therapy
-  Prevention of NMOSD attacks and relapse is crucial to limit damage accumulation, BUT relapse clusters and intermittent attacks are difficult to predict
-  Traditional approach to treatment relied on
 - Immunosuppression: steroids, azathioprine, methotrexate and mycophenolate mofetil
 - B-cell targeted therapy with rituximab

NMOSD, neuromyelitis optica spectrum disorder
1. Dische F, et al. *Neural Neuroimmunol Neuroinflamm*. 2020;7:e640. 2. Weischenberg BG, Wingerchuk DM. *Mayo Clin Proc*. 2017;92:663-679.

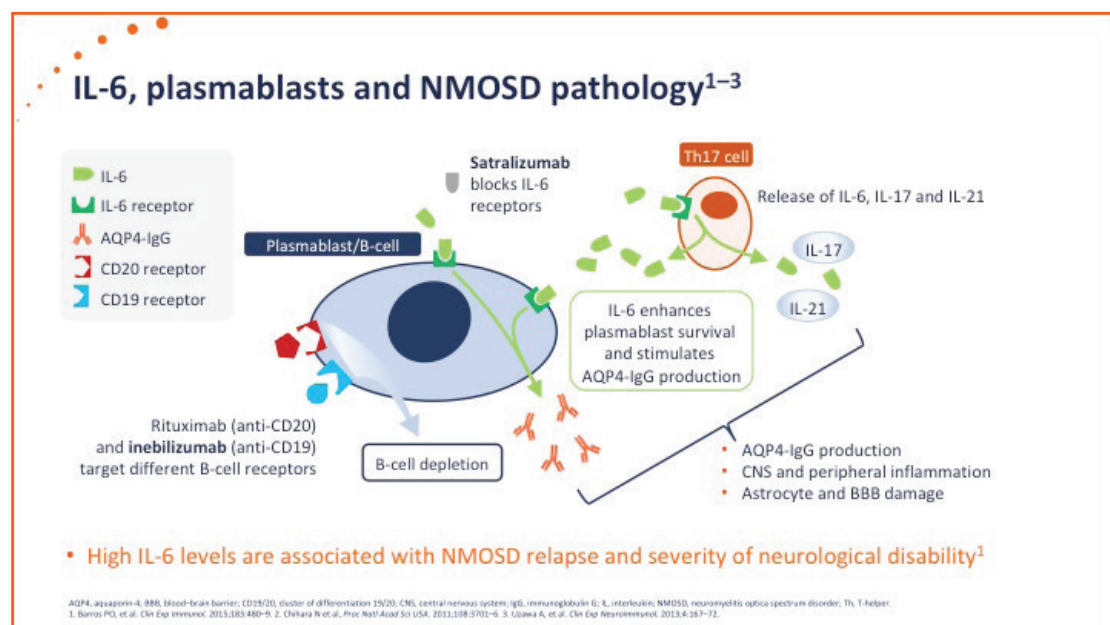
So, what are the treatment goals in NMOSD? We know that NMOSD attacks require aggressive immunosuppressive therapy. The reason they require aggressive therapy as Professor Fujihara has pointed out, is that NMOSD attacks can be severe and disabling. They can result in blindness and paraplegia. Prevention of NMOSD attacks and relapses is crucial to limit damage accumulation. Relapses cluster and intermittent attacks are difficult to predict.

Traditional approaches have relied on immunosuppressant therapies: steroids oftentimes chronic, azathioprine, methotrexate and mycophenolate mofetil, and more recently B-cell targeted therapies with rituximab. The problems with these treatments are that they have significant potential side effects over the longer term and they also have limited efficacy. We know in retrospective studies that approximately 40% to 80% of patients will relapse at last follow-up when using these medications. It was thus identified that there was a great need for better therapies and also for proven therapies as none of these therapies have been proven in a phase III trial. Importantly, understanding the mechanism of NMOSD, the immunopathology of the disorder, has allowed us to identify potential novel targets for therapy.

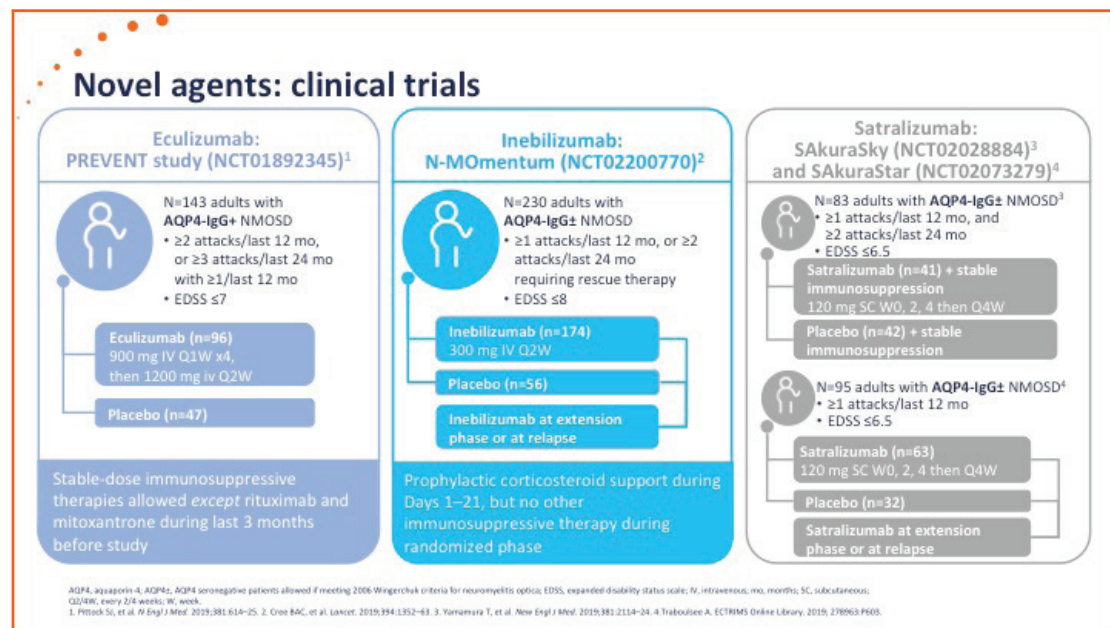


Here you can see three novel targets. Firstly, IL-6 is known to be increased in the spinal fluid and serum in patients during attacks. IL-6 drives plasmablasts, drives antibody production and thus is an ideal target in this disease. The cells that make antibodies, the plasmablasts, are also a potential target. B cells also drive T cells and T cells may also have a role in this disease, so targeting these cells makes sense. When the antibodies bind to the target cell, in other words when the antibodies bind to the water channel on the astrocyte, they activate complement and complement once activated results in the cleavage of C5 to C5A and C5B. Preventing this from occurring will prevent the membrane attack complex being formed and prevent the inflammatory effects of C5A, and thus this also represents a novel target.

From the IL-6 perspective, anti-IL-6 antibodies of satralizumab have been studied in two trials which we will discuss. Inebilizumab is an anti-CD19 antibody and we will also discuss this trial. Eculizumab, an anti-complement 5 antibody has been studied in a phase III trial and we will also discuss this trial.



So just giving you an overview. We know that high IL-6 levels are associated with NMOSD relapse and severity of neurological disability. IL-6 enhances plasmablast survival and stimulates AQP4-IgG production. Th-17 cells release IL-6, IL-17 and IL-21 and these cytokines drive AQP4-IgG production, CNS and peripheral inflammation and astrocyte and blood-brain barrier damage. Blocking IL-6 or targeting CD19 potentially will reduce this process and potentially impact this disease.



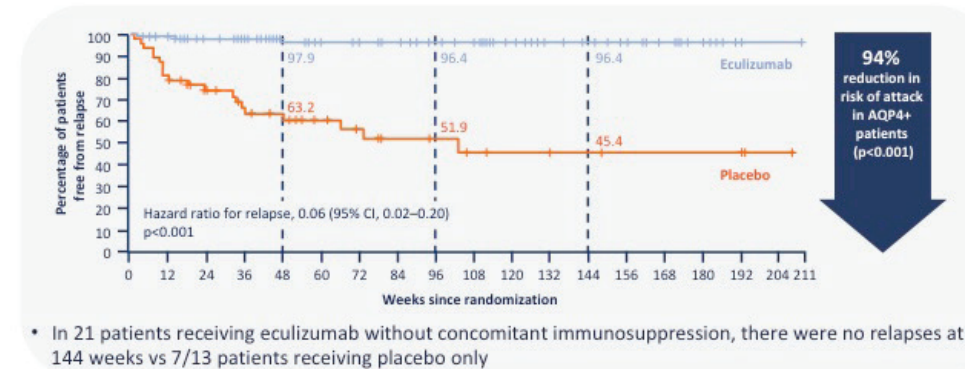
Here I'm going to discuss the four clinical trials that have been performed to date. The eculizumab trial or PREVENT study enrolled 143 adult patients with AQP4-IgG antibody-positive disease. The requirements for inclusion are shown: patients had to have ≥2 attacks in the last 12 months or ≥3 attacks in the last 24 months. These patients had severe disease and very frequent attacks. They were randomised in a 2:1 fashion and you can see the medication dosage that they received and the mode of administration and the frequency of that administration. Patients were allowed to have a stable dose of immunosuppressant therapies, except that patients could not have rituximab or mitoxantrone for the past three months before the study. Patients were allowed to have concomitant immunosuppressant therapies during this trial.

In the inebilizumab trial—also known as the N-MOMentum trial—230 patients were enrolled. For this trial and both the satralizumab trials, patients could have AQP4-antibody-positive, but also AQP4-antibody-seronegative NMOSD. Both the inebilizumab and satralizumab trials allowed enrolment of patients if they had ≥1 attack in the past 12 months or ≥2 attacks in the past 24 months. In the inebilizumab trial, patients had to have an EDSS of ≤8. Inebilizumab was dosed at 300 mg intravenously every two weeks and then that was repeated every six months and patients were randomised in a 3:1 fashion. If they had an attack, they went into an open label extension. Prophylactic corticosteroid support was allowed during days 1 to 21 in that study, but no other immunosuppressant therapy was allowed during the randomised phase.

For the satralizumab trials, there were two. The SAkuraSky randomised patients in 1:1 fashion. Patients were also allowed to be on stable immunosuppression. In the SAkuraStar study, 95 patients were randomised in a 2:1 fashion, they received 120 mg of subcutaneous satralizumab during week 0–4 and then every 4 weeks thereafter. In the SAkuraStar study, patients went on to or moved into the satralizumab extension phase at relapse.

Eculizumab: effect on relapse

PREVENT study

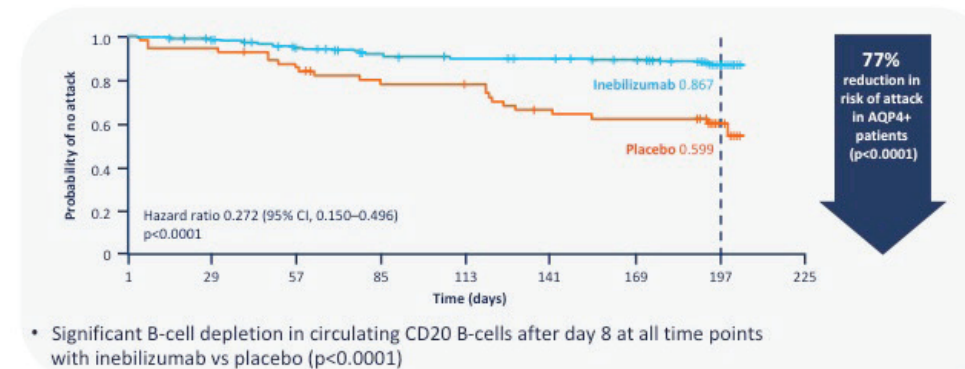


AQP4+, aquaporin-4 positive; CI, confidence interval.
Figure reproduced with permission from Pittock SJ, et al. *N Engl J Med*. 2015;381:614–25.

So, what were the results of these trials? For eculizumab, here you can see the survival curve showing that at 96 weeks, 96.4% of patients who were treated with eculizumab were relapse-free compared with 51.9% of patients receiving placebo. That is a 94% reduction in the risk of attack in the AQP4 antibody-positive patients. In 21 patients receiving eculizumab without concomitant immunosuppression, there were no relapses at 144 weeks versus 7 of 13 patients receiving placebo having relapse.

Inebilizumab: effect on relapse

N-MOMentum study

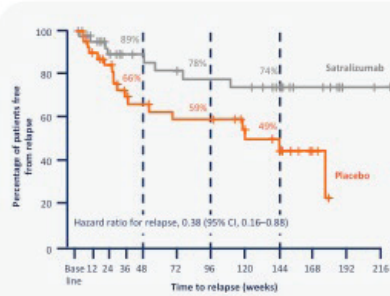


AQP4+, aquaporin-4 positive; CI, confidence interval.
Figure reproduced with permission from Cree BAC, et al. *Lancet*. 2015;384:1352–63.

For inebilizumab, a 77% reduction in the risk of attack in the AQP4 antibody-positive patients was noted. There was significant B-cell depletion in circulating CD20 B-cells after day 8 at all time points with inebilizumab versus placebo.

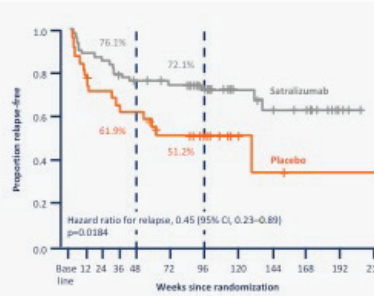
Satralizumab: effect on relapse

SAkuraSky study¹



- No significant difference vs placebo in AQP4 IgG-negative population (n=14)

SAkuraStar study²



- 55% reduction in relapse vs placebo

Pooled analysis³

75% reduction in risk of attack in AQP4+ patients

AQP4+, aquaporin-4-positive; CI, confidence interval; IgG, immunoglobulin G. Figures reproduced with permission from: 1. Yamamura T, et al. *New Engl J Med* 2019;381:2114-24; 2. Traboulzon A. *ECTRIMS Online Library* 2019; 278963-P003. 3. Haidoux Z, et al. *Invent Ophthalmol Vis Sci* 2020;61:3173.

For satralizumab, we can look at both the SAkuraSky study and the SAkuraStar study. In the SAkuraSky study, you can see that at 96 weeks, 78% of patients treated were relapse free compared with 59% of patients in the placebo arm. In the SAkuraStar study 72.1% of patients were relapse free in the treatment group with 51.2% of patients in the placebo arm having been relapse free. Overall combining both studies, a 75% reduction in the risk of attack in AQP4 antibody-positive patients was noted.

Novel agents: safety

Eculizumab: PREVENT study ¹			Inebilizumab: N-MOMentum study ²			Satralizumab: SAkuraSky study ³		
Most common AEs	Eculizumab (n=96), n (%)	Placebo (n=47), n (%)	Most common AEs	Inebilizumab (n=174), n (%)	Placebo (n=56), n (%)	Most common AEs	Satralizumab (n=41), n (%)	Placebo (n=42), n (%)
Upper RTI	28 (29)	6 (13)	UTI	20 (11)	5 (9)	Nasopharyngitis	10 (24)	7 (17)
Headache	22 (23)	11 (23)	Arthralgia	17 (10)	2 (4)	Upper RTI	10 (24)	8 (14)
Nasopharyngitis	20 (21)	9 (19)	IRR	16 (9)	6 (11)	Headache	10 (24)	4 (10)
Nausea	16 (17)	12 (26)	Back pain	13 (7)	2 (4)	UTI	7 (17)	7 (17)
UTI	13 (14)	10 (21)	Headache	13 (7)	4 (7)	Constipation	2 (5)	7 (17)
Limb pain	11 (11)	10 (21)	Nasopharyngitis	13 (7)	6 (11)			
• SAEs: 26% (eculizumab) vs 28% (placebo) • 1 related death (eculizumab) due to respiratory infection • 2 discontinuations due to AEs (both placebo) • No cases of meningococcal infection			• SAEs: 5% (inebilizumab) vs 9% (placebo) • No deaths during randomized controlled period; 2 deaths during extension phase (1 potentially treatment-related) • 2 discontinuations due to AEs (inebilizumab)			• SAEs: 17% (satralizumab) vs 21% (placebo) • No deaths or anaphylactic reactions • 8 discontinuations due to AEs (3 satralizumab and 5 placebo) • IRRs more frequent with satralizumab than in the placebo group (12% vs 5%)		

AE, adverse event; IRR, infusion related reaction; RTI, respiratory tract infection; SAE, serious AE; UTI, urinary tract infection. 1. Pittsack S, et al. *N Engl J Med* 2019;381:618-25. 2. Cree BAC, et al. *Lancet* 2019;394:1352-63. 3. Yamamura T, et al. *New Engl J Med* 2019;381:2114-24.

How safe were these agents? Here you can see the safety profiles noted in the three studies. For the eculizumab trial, common adverse events were upper respiratory tract infection and headache. Serious adverse events occurred in 26% of the eculizumab versus 28% in the placebo group. There was one related death from eculizumab due to respiratory infection. There were two discontinuations for adverse events, both were in the placebo group and there were no cases of meningococcal infection.

Serious adverse events were seen in 5% of inebilizumab and 9% of the placebo group. There were no deaths during the randomised controlled period in the inebilizumab trial. There were two deaths during the extension phase and one potentially treatment related. Two discontinuations for adverse events were seen in the inebilizumab trial. Most common adverse events in the inebilizumab trial were urinary tract infection and arthralgia.

For the satralizumab study, specifically looking at the SAKuraSky study, you can see the most common adverse events were nasopharyngitis, upper respiratory tract infection and headache. Serious adverse events occurred in 17% of the satralizumab and 21% of the placebo group. There were no deaths or anaphylactic reactions and there were eight discontinuations for adverse events, three in the satralizumab and five in the placebo group.

Summary

- Availability of biomarkers for diagnosis and to track disease state gives greater understanding of treatment needs**
- Preventing attacks prevents disability**
- Novel agents provide a more targeted way to prevent NMOSD attacks than relatively undirected immunosuppression**
 - Phase III trials with eculizumab, inebilizumab and satralizumab have shown reduction in likelihood of relapses and good safety profile

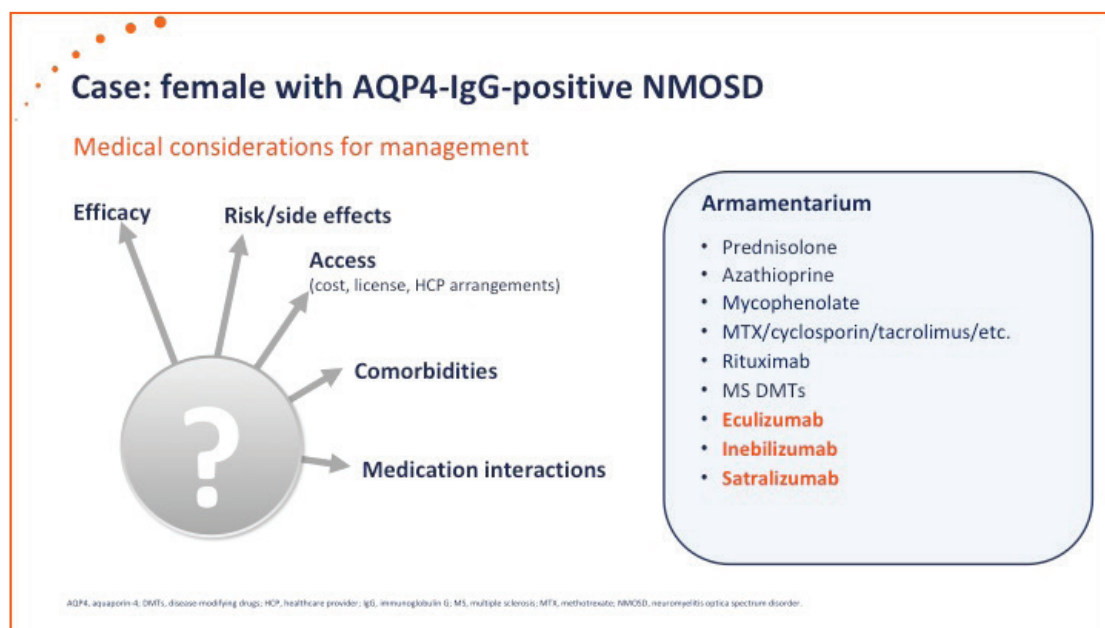
NMOSD, neuromyelitis optica spectrum disorder

In summary, these drug trials are great news for patients with NMOSD. 2019 saw the release of data for randomized controlled trials of three different drugs, all with different mechanisms of action. These studies show the importance of understanding mechanisms when trying to understand orphan diseases, but also when trying to identify novel therapies. Targeting IL-6, targeting CD19 and targeting complement showed evidence of significant reduction in the likelihood of having a relapse. Preventing relapses prevents disability in patients with NMOSD. Furthermore, the side-effect profile for all three drugs was very reassuring and these three drugs now offer great hope to patients with NMOSD. Physicians now have phase III trial data to support their decision making and to allow them to prescribe drugs that they can be confident will have a beneficial effect in their patients.

In the clinic with NMOSD: How can we translate the recent data to patient care?

Prof. Jackie Palace: So now we come on to the case-based discussion to explore how we translate what we've heard into our clinics.

So, I'd like to start with a female, she's 35, she works full time, she has two children of school age and a year ago she had an attack of transverse myelitis and she was found to be positive for AQP4 antibodies and her TPMT levels were low. So, she had five days of intravenous methylprednisolone for this attack and she recovered almost fully but was not completely back to baseline. She had a reducing course of prednisolone and has been maintained on 10 mg of prednisolone ever since and she's been completely relapse free. However, she feels the prednisolone is making her anxious, she can't tolerate this, and she wants to discontinue it.

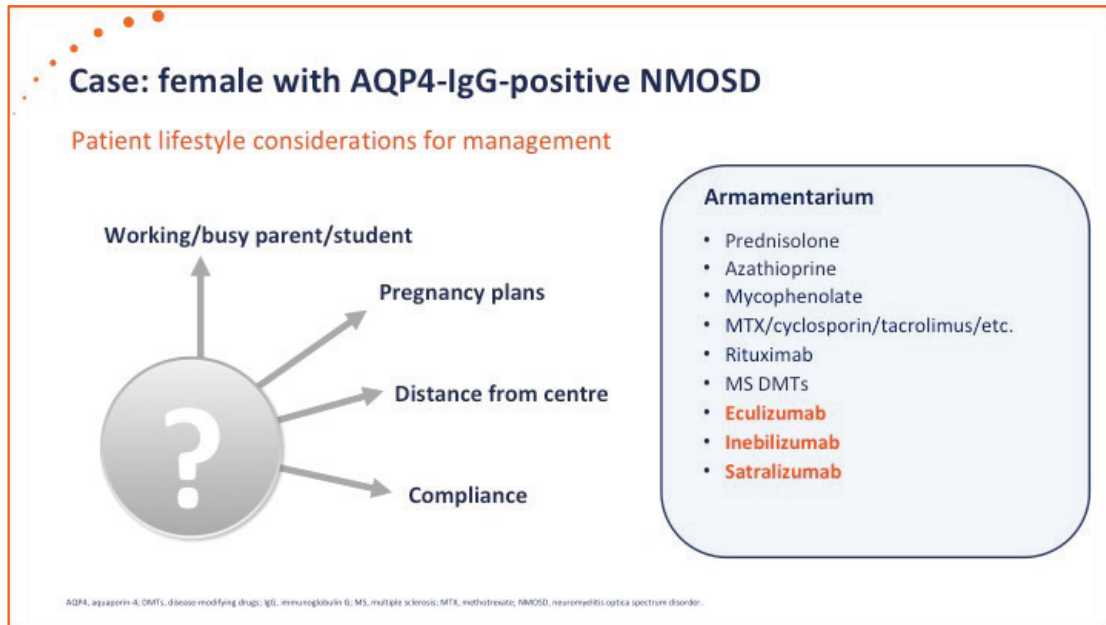


So, when we think about what treatments we're going to use in the clinic, there are many different factors we have to consider and the medical considerations include: how efficacious the drug is; what the risks and side effects are—and there's often a balance between these two; do we have a licence in our country and what's the healthcare provider agreement? Will they pay for it and do they have access to the drugs. Then we do have to consider any patient comorbidities that might affect our choice. And also, are they on any medications that might interact?

So, what sort of treatments might we be considering? Well, we have prednisolone— this is what she was on. The commonest steroid-sparing agents that we use are azathioprine and mycophenolate. There are many others such as methotrexate, cyclosporin and tacrolimus. We commonly use rituximab. Is there any role for MS disease-modifying therapies (DMTs)? Then we have the three new treatments now: eculizumab, inebilizumab and satralizumab.

So I wondered, Kazuo, if you might talk us through how these factors might affect your treatment choice in this patient.

Prof. Kazuo Fujihara: Thank you Jackie. So first of all, this patient is positive for AQP4 antibody and we know that some disease-modifying drugs for MS like interferon-beta, fingolimod, natalizumab, alemtuzumab, and possibly dimethyl fumarate as well can exacerbate NMOSD. So, we should avoid using disease-modifying drugs for MS in patients with NMOSD. And secondly, her TPMT levels were low and this enzyme may put the patient at greater risk for potential life-threatening bone marrow toxicity, so maybe we should not use azathioprine because the TPMT level is low. And thirdly, she has been receiving 10 mg of corticosteroid and she has been relapse free since onset. It seems to be successful, but on the other hand she feels that the prednisolone is making her anxious. Anxiety could be a psychiatric side effect of her corticosteroid and she wants to discontinue it, so maybe we had better think about something else for her treatment.



Prof. Jackie Palace: Ok, thank you. So, if we carry on, if we think about other considerations, there are lifestyle considerations as well that might affect our choice. So is the person working, are they very busy with children, or are they a student and away at university? Do they plan to become pregnant? Do they live miles from the centre or just around the corner? Do they have difficulty complying with the treatment?

So, I'd like to ask Sean if he could talk through how these factors might also influence his choice.

Prof. Sean Pittock: Thank you very much Jackie. I think you make a good point. These are issues that commonly arise in the clinic and they are very important to address. I'm going to focus my answer on the new drugs because, certainly in my practice, I'm generally using these novel therapies, which are proven in phase III trials to be of benefit. And there are some significant differences that need to be taken into account when looking at these three agents and the issues that you've raised here are very important. Unfortunately for many of these issues we don't have any good answers yet. If we take the first, certainly a working busy parent or student, there are obviously a lot of issues that need to be considered here. As you know, with eculizumab for example, this is a medication that has extremely good efficacy, as we discussed earlier, but it is a medication that has to be given as an intravenous infusion every two weeks. Satralizumab is a medication that has to be given subcutaneously every month and then inebilizumab is given as two infusions, two weeks apart every six months. So you can see there that there is a potential attraction to a drug that has to be given every six months for somebody who has a very busy lifestyle. But also to include the issue of distance from centre, people who work or spend a long period of time away from home may not be an ideal candidate for a drug that has to be given either every month or every two weeks. Also for drugs that have to be given by infusion, access to home infusion services or living nearby an infusion centre is going to be an important issue to consider.

With regard to pregnancy, unfortunately none of these drugs have been studied, or the safety of these drugs, has been studied in pregnancy in NMOSD. One of the issues, I think, is that in these studies, pregnancy was actually an exclusion criterion and all patients had to be on birth control. Eculizumab has been looked at in PNH (paroxysmal nocturnal haemoglobinuria) and haemolytic uraemic syndrome. These disorders are problematic during pregnancy and it is an issue for those patients to discontinue eculizumab in pregnancy; what's been found is that in pregnancy eculizumab seems to be relatively safe in those conditions. It does not seem to get into the breast milk, and in addition it does not seem to impact the complement levels in the infants. However, I think it is difficult to say what the recommendation would be for patients who become pregnant or intend to become pregnant. In the NMOSD patients, prior to having these three new drugs available for treating patients, there was a variety of different approaches: some would use prednisone during pregnancy. Others would continue to potentially use drugs like azathioprine, which in the rheumatology literature may be reasonably safe in pregnancy. And others would treat patients with rituximab and then wait for approximately one month and then recommend patients become pregnant and then not re-dose the patient until they had delivered. The idea here is that the rituximab essentially gets used up within the first two to four weeks and then it's not present in the serum and is relatively safe to use in pregnancy. But at the end of the day, unfortunately, we cannot make any definite recommendations

regarding safety for any of these drugs in pregnancy and I think each case has to be managed individually.

And then compliance is obviously important. Patients that are not compliant with tablet medication, will they be compliant with intravenous or injectable medications? I suppose the less frequent a medication has to be given, possibly the more compliant a patient might be.

Summary: female with AQP4-IgG-positive NMOSD



- 35-year-old woman in full-time employment
- 2 school-age children
- TPMT levels low
- She wants to discontinue prednisolone

- What would make you consider switching to a different drug or class?
- What if she were AQP4-IgG-negative?
- What if she were MOG-IgG-positive?

Armamentarium

- Prednisolone
- Azathioprine
- Mycophenolate
- MTX/cyclosporin/tacrolimus/etc.
- Rituximab
- MS DMTs
- Eculizumab
- Inebilizumab
- Satralizumab

AQP4, aquaporin-4; DMTs, disease-modifying drugs; IgG, immunoglobulin G; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; MTX, methotrexate; NMOSD, neuromyelitis optica spectrum disorder; TPMT, thiopurine methyltransferase.

Prof. Jackie Palace: Ok, well thank you very much for that. So, we started with many different potential treatments that we might use with this lady, but we've heard how there are medical and lifestyle considerations that will narrow the choice down. I think it is important to think about the factors that actually make us consider switching to a different drug or a different class of drug. And we've heard in this lady how side effects are important, and we've also heard about pregnancy. But importantly, relapse is relevant. I'd like to ask Kazuo whether you always change the patient's background therapy if a patient relapses.

Prof. Kazuo Fujihara: It's really a practical and important question Jackie. First of all, I would like to check the dose of the drug. If the dose of the drug is not high enough, we may not expect its clinical efficacy. For example, azathioprine is not the treatment of choice for this patient as I mentioned before, but for azathioprine, if it's really working pharmacologically, we should see the increase in mean corpuscular volume or MCV by five or more. If it's less than that, we may have to think about dosing up. And as for calcineurin inhibitors like cyclosporin or tacrolimus, we should measure the trough level. If it's low, again we have to think about dosing up. Another choice might be add-on therapy. In the PREVENT trial of eculizumab and the SakuraSky trial of satralizumab, these agents were used as add-on therapies. The patients were receiving immunosuppression and then either eculizumab or satralizumab were added on and this showed greater efficacy than just baseline treatment. So that's another option. If the patients are experiencing relapse and the side effects are not tolerable, we may have to think about just switching to something else. For example, I think eculizumab showed its effects very quickly, so even if you were just switching to eculizumab, I think you can expect it to be effective immediately. Those are my considerations about this issue.

Prof. Jackie Palace: Thank you very much. There are a couple of other things I think we should consider. So, would it change our choice if this patient was AQP4 antibody-negative? Would it change our choice if the patient was MOG antibody-positive? So, Sean I wonder if you might comment on these particular issues.

Prof. Sean Pittock: Well thank you very much Jackie. So, I suppose the question relates to patients who are AQP4-IgG negative. Patients that are AQP4-IgG negative really do not have a disease that is immunopathologically the same as patients that have AQP4-IgG positive disease. Certainly they have a different disease when it comes to patients with MOG-IgG or disorders that we call MOGAD (MOG Antibody

Disease). It's important to note that in the inebilizumab trial as well as the satralizumab trial, patients who were AQP4-IgG negative were allowed to be enrolled if they fulfilled seronegative NMOSD criteria. In the inebilizumab trial, there were only 17 of those patients so we really cannot draw conclusions about efficacy in that group. In the satralizumab study, it appeared that the patients that were AQP4-IgG negative didn't really benefit much from the drug even though there are small numbers. We also know that at least for patients that have MOGAD, there are major issues to discuss because there are significant differences between that disease and NMOSD. For example, many patients who have MOGAD do not have relapses, so many patients will have monophasic illness and obviously we wouldn't want to be putting a patient that is not going to have another attack on a long-term maintenance immunosuppressant medication that could potentially have side effects.

It's unfortunately quite difficult to identify patients after their first attack of MOGAD and to predict those that are going to go on to have attacks. It also appears that patients that have MOGAD may respond a little differently to many of these drugs compared with patients with AQP4 antibody-positive NMOSD. Actually there are some that would argue that in MOGAD, because patients will oftentimes have a much better outcome in terms of their attacks—they seem to recover better from the optic neuritis attacks or from the transverse myelitis attacks, even though at the nadir of the attacks they can be quite severe—some people advocate just treating the attacks aggressively if they're only having relatively few attacks. Obviously if patients are having very frequent attacks, then you do want to do something to prevent those attacks and there's a variety of different treatments that can be used but eculizumab, inebilizumab and satralizumab have not been investigated in an adequate number of patients to make any comment regarding their usage.

Rituximab has been looked at by some and has not appeared to be as robust in terms of its benefit as seen in NMOSD that's AQP4 antibody-positive. As for, azathioprine and mycophenolate it's not clear what these result in. In my own practice, if I see a patient that either is having relapsing inflammatory disease—relapsing optic neuritis, relapsing transverse myelitis or a combination—in the setting of being AQP4-IgG negative or in the setting of being MOG antibody-positive, generally I will initiate a patient on an immunosuppressant medication and generally I tend to go for a combination of prednisone with something like mycophenolate mofetil and then I generally try to wean the patient down off the prednisone. I think there's something to be said about just treating attacks if they are very infrequent and potentially we know that, for example, for MOGAD optic neuritis, 95% of patients will have pain initially. So, you can potentially get in very early with a kind of rescue treatment.

In terms of the acute attacks in these conditions, the treatments are generally the same. We generally treat patients with intravenous methylprednisolone for five days and some will use plasmapheresis either immediately after or if there's no response to the steroids, or some will use plasmapheresis as their first go-to agent. There is some data coming out now that suggests that some of these disorders, certainly the MOGAD conditions may respond quite well to intravenous immunoglobulin. Again, we have no large trials, we have no phase III trials in these diseases and so I think we've still got a lot to learn about the optimal approach to the management of these conditions.

Prof. Jackie Palace: Thank you very much for that. So, now we come on to the question and answer session and we welcome questions from all of you out there.

Q&A

Prof. Jackie Palace: I'm going to run through some of the questions that people have sent in. I will try to prioritise them in order in case we don't have time. So, if we start with the question: "If a patient has already relapsed on rituximab, which of the new treatments would you select?" Kazuo would you like to comment on this question?

Prof. Kazuo Fujihara: Yes, this is a very important question clinically. Unfortunately, there has been no head-to-head comparison of the monoclonal antibodies, but the previous reports suggest that some patients who were treated with eculizumab or satralizumab were refractory to rituximab, so eculizumab and satralizumab may be a choice for the patients who did not respond to rituximab. Inebilizumab, which is a CD19 monoclonal antibody, also destroys B cells and we know that CD19 molecules are expressed in the wider range of B-cell lineage cells. So inebilizumab may have a greater activity to suppress the disease activity of NMOSD in comparison with rituximab, but we do not have the real data to confirm it. So, that's my view for the treatment for that kind of patient.

Prof. Jackie Palace: So the anti-CD19 isn't totally out of the question here; under certain circumstances you might try it as well. There is another question regarding anti-CD19 therapy asking, "Do you get hypogammaglobulinemia with anti-CD19 therapy?". Sean, do you want to comment on this?

Prof. Sean Pittock: Yes, certainly you can get hypogammaglobulinemias in these cases. As you know from the side-effect profile perspective, this did not seem to be a big issue. It's certainly something that I do monitor for in my practice. Generally it can occur but it's not a major issue. I do think it's something that warrants investigation, certainly if patients have an infection. Despite the broader effect that this drug has on B cells, interestingly, it doesn't seem to cause significant hypogammaglobulinemias, but it can be an issue.

Prof. Jackie Palace: Ok, one of the questions is: "Of all these three novel treatment options that we have, how are we choosing between them?". I know we have discussed quite a lot about this earlier on. I think another question is: "Does the mechanism of action impact on our choice?" Sean, do you want to start with this question?

Prof. Sean Pittock: I think if we argue that the mechanism of action is impacting on our choice, then I think we're giving ourselves a little too much credit in terms of understanding the mechanisms of the disease. For example, if you take all these three drugs, the reality is that this is antibody-mediated disease and yet these three drugs don't eradicate the antibodies in the patient serum. So yes, these drugs are working very, very favourably as I've discussed in my talk, but how they actually work is probably much more problematic. Yes, we've presented the thinking and current understanding of how these drugs work, but I expect it's much more complex than that. I think it is difficult to choose based on mechanism and there are many other issues that need to be considered. Obviously when you're deciding on a drug, and you've got three drugs available, I think one is efficacy; this is something that you want to look at. As I said, the efficacy ranges from about 75% risk reduction to 96% risk reduction for eculizumab. There are other issues to discuss, as we discussed earlier, relating to mode of administration, frequency of administration, access to outpatient infusion centres, access to home infusion facilities and then obviously cost and insurance coverage. All of these things have to be taken into account Jackie.

Prof. Jackie Palace: We have many, many questions coming through, I'm very grateful to the audience for sending these through. Kazuo, somebody has asked: "Is IL-6 stimulation necessary for plasmablasts to produce AQP4 antibodies?" I don't know whether the knowledge is robust enough to answer that question.

Prof. Kazuo Fujihara: As far as I know, those plasmablasts producing AQP4 antibodies are mainly supported by IL-6 and IL-6 can enhance the production of AQP4 antibodies. So, without IL-6 stimulation the activity of plasmablasts may be much weaker. That's what I know about this.

Prof. Jackie Palace: We've got a couple of questions focusing on TPMT levels. They're either asking whether we monitor enzyme activity and maybe just give a lower dose, whether we would just avoid it altogether, and in fact why are we using it at all. In general practice somebody says they don't even consider it. Sean, what is your opinion?

Prof. Sean Pittock: I think that's a very good question. At the end of the day, in terms of azathioprine's efficacy, obviously, as we've discussed, there's very limited data and only retrospective data. It is one of the traditional drugs that we've used and honestly there are going to be places in the world where patients do

not have access to these three newer drugs that we've discussed. In that situation, I think azathioprine is a good drug to consider. What we do know is that if you are genetically predisposed to having very poor ability to enzymatically breakdown that drug, you're at an increased risk of developing side effects and generally I don't use the drug if the TPMT levels come back low. There are some individuals in rheumatology and many of my colleagues who will start on a very low dose and titrate up, obviously monitoring more carefully for potential toxicity in that disease. The most important thing, as Kazuo pointed out in his talk, is that you really have to monitor the MCV (mean corpuscular volume). In the study that Andrew McKeon did on 100 patients with azathioprine, what he found was that if you don't have a robust increase in MCV, you have a much higher likelihood of relapse. So, if you're going to use the drug, use it at a sufficient dose that allows you to get a robust effect and you can monitor that by measuring the MCV. In my practice I would not use that drug because I don't think it's proven to be of benefit and I think the relapse rate, even if you get your MCV up, is quite high and so I would tend to use one of the newer drugs.

Prof. Kazuo Fujihara: One unique situation in East-Asian populations, including Koreans and Japanese, is that some patients are intolerant to azathioprine in that it causes bone marrow suppression. But in East-Asian populations as far as I know, TPMT genetic variation is quite rare. On the other hand, Korean investigators discovered that the NUDT15 gene variation is associated with intolerance to azathioprine and the result was confirmed in the Japanese population as well. So, for the East-Asian populations maybe their NUDT15 gene variation should be tested to see if there is a higher risk of potential bone marrow suppression as a result of azathioprine treatment.

Prof. Jackie Palace: Thank you. Also, it's probably worthwhile mentioning, and perhaps because there are other genetic reasons why people don't tolerate azathioprine even when the TPMT level is normal, many patients don't tolerate it and it doesn't rule out that they won't have an allergic reaction. There's a question about: "Why does rituximab work, but ocrelizumab doesn't work?" I think that probably ocrelizumab will work. I don't know if Sean or Kazuo have any comment on that?

Prof. Sean Pittock: It will work. I think in the sense that it has essentially the same mechanism of action, there's no reason to think that it wouldn't work.

Prof. Jackie Palace: That's my view as well. Kazuo do you agree with that?

Prof. Kazuo Fujihara: Yes

Prof. Jackie Palace: We have a number of questions about treating young patients or elderly patients—do we have differences in how we choose? We've talked about many other issues, but we haven't talked about the age effects of treating either the young or the elderly. Sean could you talk maybe about any age-related issues regarding children?

Prof. Sean Pittock: Honestly, these studies did not include children. I know there are ongoing studies related to all three trials potentially regarding children, so it's difficult for us to say. What we do know is that there's expansive literature on and experience with the use of eculizumab in children with PNH and haemolytic uraemic syndrome. We have many years of using this drug in children and it's pretty safe. Obviously, you do have this risk of meningococcal infection, but there is that knowledge that it is safe in children, at least in those disorders. We don't have any experience with inebilizumab in children and I'm not aware of any studies of satralizumab in children. So, I think we're just going to have to see and hope that we can get some additional trial data on children so we can make those decisions.

Prof. Kazuo Fujihara: I think there were some patients in satralizumab trial who were adolescents, so there may be some data, but the numbers are quite limited so we have to collect more data for the treatment effects in children.

Prof. Jackie Palace: Now, there are so many questions and I would really like to thank the audience for their great interaction today as well as listening to the presentations. I'd very much like to thank my two colleagues for their fantastic contribution to this symposium. I hope you all feel that this has been a useful, educational experience in the treatment of AQP4-antibody disease mainly, but also briefly covering the other MOG and antibody-negative conditions. I would like to conclude by thanking Alexion for their support and the symposium is CME accredited and has been provided by touchIME and Oakstone Publishing. Please give your feedback to earn your CME credits, could you comment on the online evaluation form, and the link can be found in the supporting materials for this symposium. So again, thank you very much and if we can answer any of your questions via text or email, we will continue to do this, thank you.

Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions. The presenting faculty have been advised by touchIME to ensure that they disclose any such references made to unlabelled or unapproved use. No endorsement by touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in touchIME activities. touchIME accepts no responsibility for errors or omissions.

This content is intended only for healthcare professionals.

Launch date: 16 November 2020

Abbreviations

AQP4, aquaporin-4; C5, complement 5; CD19/20, cluster of differentiation 19/20; CSF, cerebrospinal fluid; DMTs, disease-modifying therapies; IgG, immunoglobulin G; IL, interleukin; MCV, mean corpuscular volume; MOG, myelin oligodendrocyte glycoprotein; MRI, magnetic resonance

imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; PNH, paroxysmal nocturnal haemoglobinuria; Th T helper; TPMT, thiopurine methyl transferase