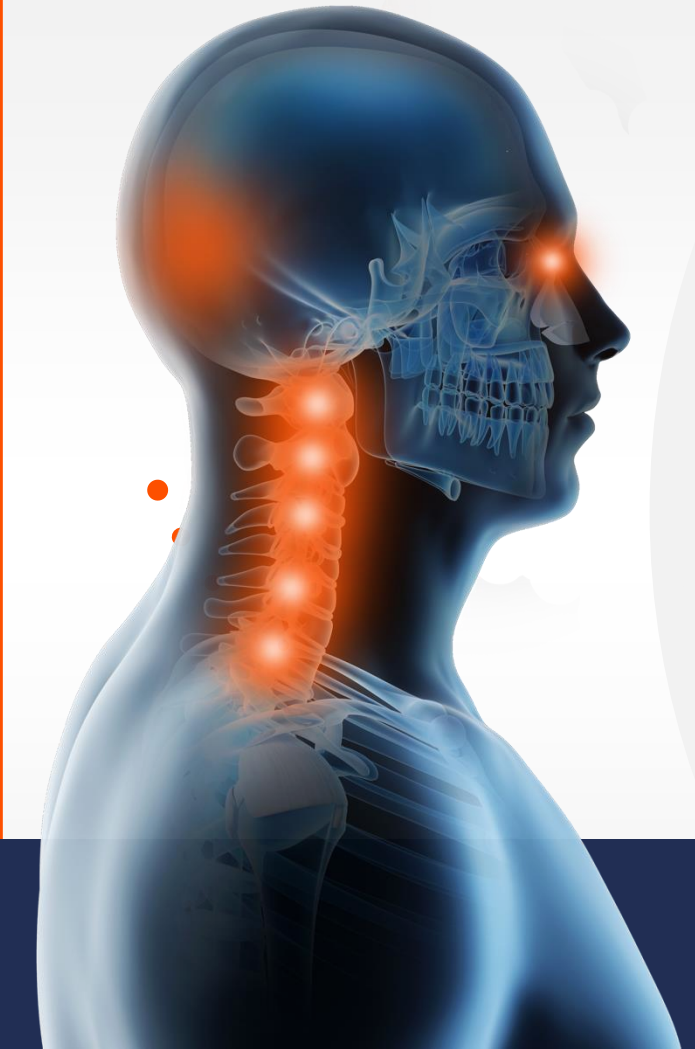

touchSATELLITE SYMPOSIUM

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

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touchSATELLITE SYMPOSIUM at MSVirtual2020

13 September 2020, 08.00–09.00 EDT

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Disclosures

Prof. Kazuo Fujihara	*Consultant/advisory boards:* Alexion Pharmaceuticals, Asahi Kasei, Biogen, Chugai Pharmaceutical Co., Novartis, Mitsubishi Tanable, Takeda, Teijin Limited, Viela Bio
Prof. Jackie Palace	*Grants/research support:* Merck Serono, Myware, Sparks (Great Ormond Street Hospital's Charity); *Consultant/advisory boards:* Amplo, Alexion Pharmaceuticals, Argenx, Blueprint Medicines, Merck, Mitsubishi, Roche, Viela Bio, Vitaccess, UCB
Prof. Sean Pittock	*Grants/personal fees/other:* Alexion Pharmaceuticals, Astellas, Autoimmune Encephalitis Alliance, Grifols, MedImmune, UCB *Patents issued*: Patent # 8,889,102 (Application # 12-678350, Neuromyelitis Optica autoantibodies as a marker for neoplasia); Patent# 9,891,219B2 (Application # 12-573942, Methods for treating Neuromyelitis Optica [NMO] by administration of eculizumab to an individual that is aquaporin-4 (AQP4)-IgG autoantibody positive)

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.

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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

Does early detection reduce the burden of NMOSD?

Prof. Kazuo Fujihara
Department of Multiple Sclerosis Therapeutics,
Fukushima Medical University School of Medicine,
Fukushima, Japan

NMOSD, Neuromyelitis optica spectrum disorder.

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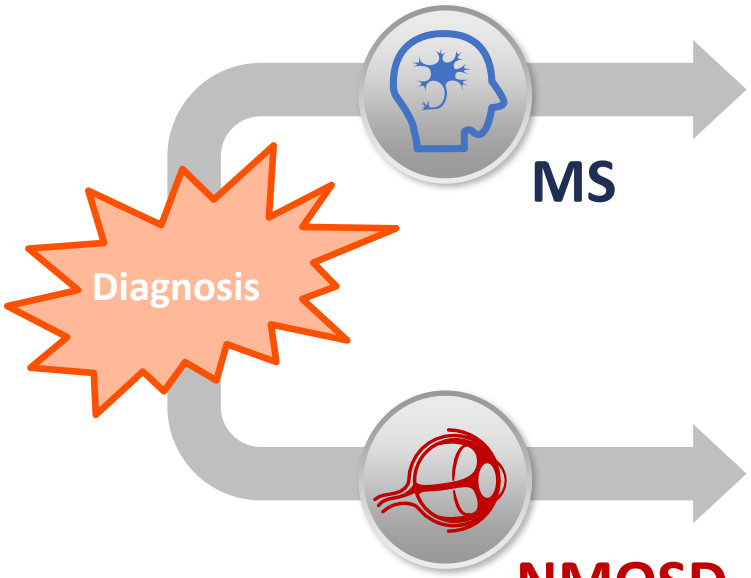
Treatment pathway for MS vs NMOSD



Disease-modifying therapies, including:[1,2]

- Interferon-β, glatiramer acetate, teriflunomide, cladribine, dimethyl fumarate, fingolimod, natalizumab, alemtuzumab, ocrelizumab, etc.

Agents in **red** can exacerbate NMOSD

Acute and **preventive** treatment, including:[3]

- High-dose steroids, plasma exchange
- Azathioprine, mycophenolate mofetil, rituximab, methotrexate

Novel agents

- **Eculizumab**
- **Inebilizumab**
- **Satralizumab**

MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

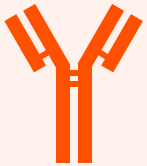
1. Montalban X, et al. *Mult Scler.* 2018;24:96–120. 2. AAN Practice Guideline Recommendations. Available at www.aan.com/Guidelines/home/GuidelineDetail/898 (accessed July 2020).
3. Kessler RA, et al. *Curr Treat Options Neurol.* 2016;18:2.

Diagnosing NMOSD

Core clinical characteristics

- Optic neuritis
- Acute myelitis
- Area postrema syndrome
- Acute brainstem syndrome
- Narcolepsy/acute diencephalic clinical syndrome
- Symptomatic cerebral syndrome

Cell-based aquaporin 4 (AQP4)-IgG test



NMOSD with AQP4-IgG

- 1 core characteristic
- Positive APQ4-IgG test

NMOSD without AQP4-IgG/AQP4-IgG status unknown

- ≥2 different, separated, core characteristics
- Optic neuritis, acute myelitis with LETM, or APS
- Negative/unavailable AQP4-IgG test
- Additional MRI requirements: LETM >3 VS, etc.

APS, area postrema syndrome; AQP4, aquaporin-4; IgG, immunoglobulin G; LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; NMOSD, neuromyelitis optica spectrum disorder; VS, vertebral segments.

Wingerchuk DM, et al. *Neurology.* 2015;85:177–89.

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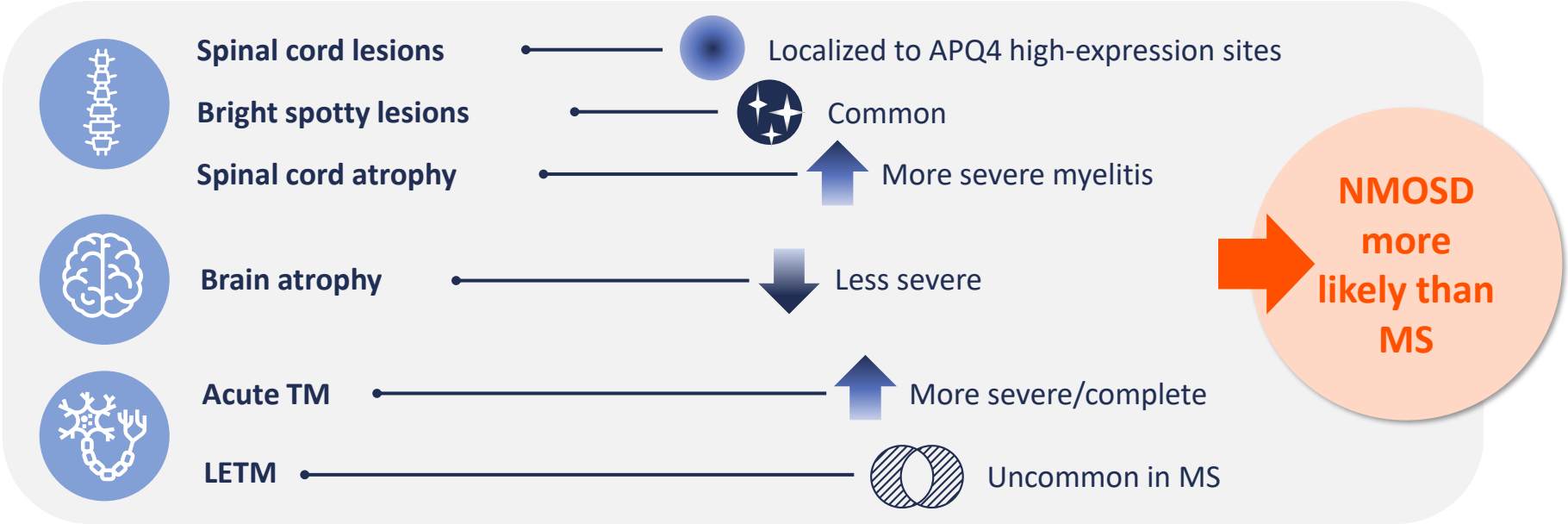
Differentiating NMOSD from MS

Symptom magnitude and disease history can help differentiate NMOSD from MS



- Correct diagnosis is important for therapeutic choice and to reduce treatment failures and long-term disability

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

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Red flags: atypical findings in NMOSD

Clinical/laboratory findings

- Progressive overall clinical course
- <4 hours or >4 weeks to nadir of attack
- Partial transverse myelitis
- CSF oligoclonal bands

Comorbidities

- Suspected sarcoidosis
- Cancer

Imaging characteristics

Brain lesions

- Perpendicular to lateral ventricular surface
- Adjacent to lateral ventricle in inferior temporal lobe
- Juxtacortical with subcortical U-fibres
- Cortical lesions
- Persistent gadolinium enhancement

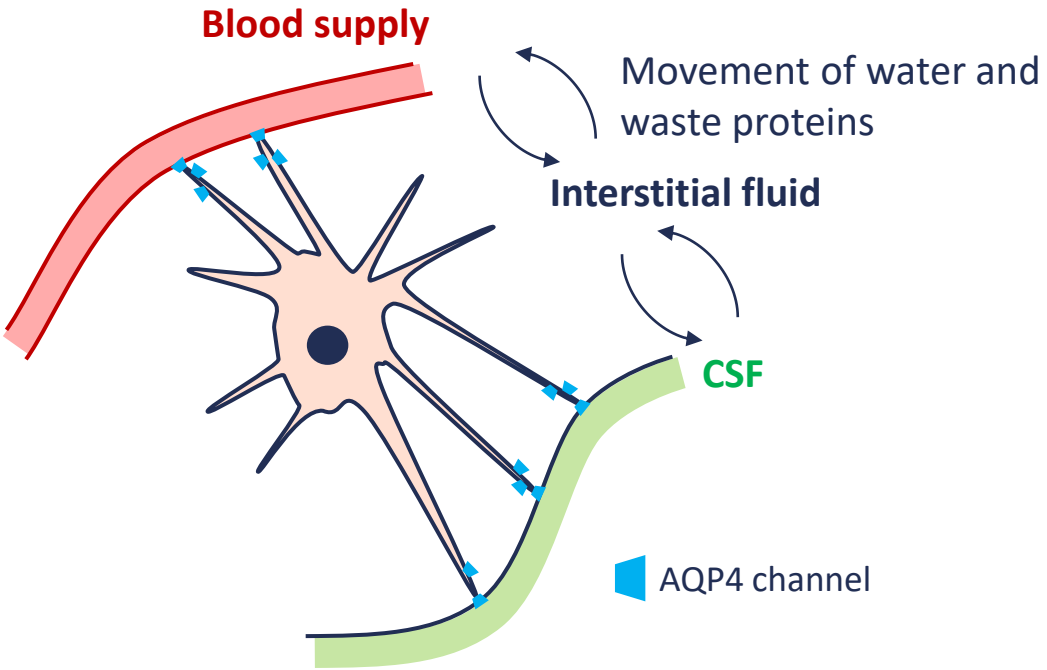
Spinal cord lesions

- <3 complete vertebral segments
- Predominantly in peripheral cord
- Indistinct signal change on T2 sequences

CSF, cerebrospinal fluid; NMOSD, neuromyelitis optica spectrum disorder.

Wingerchuk DM, et al. *Neurology.* 2015;85:177–89.

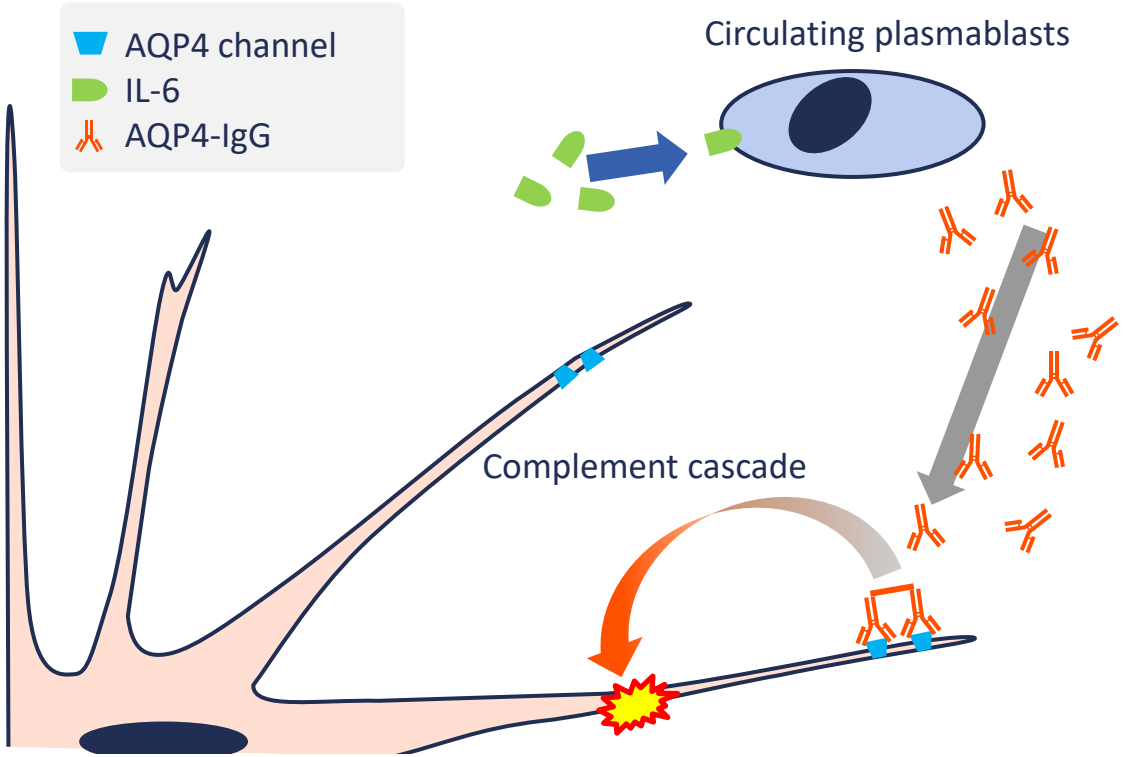
AQP4 in the healthy adult brain[1,2]



- AQP4 is a water channel on astrocyte endfeet
- Maintains water homeostasis
- Helps mediate waste protein clearance
- Target antigen in NMOSD

AQP4, aquaporin-4; CSF, cerebrospinal fluid; NMOSD, neuromyelitis optica spectrum disorder.
1. Desai B, et al. *Neurosurg Focus.* 2016;41:E8. 2. Mader S, Brimberg L. *Cells.* 2019;8:90.

Pathogenesis of AQP4-IgG-positive NMOSD[1,2]



- **IL-6 supports plasmablasts to promote AQP4-IgG release**
- **AQP4-IgG binds with AQP4 and activates the complement cascade**
- **Lytic damage to astrocytes and associated inflammation**

AQP4, aquaporin-4; IgG, immunoglobulin G; IL-6, interleukin-6; NMOSD, neuromyelitis optica spectrum disorder.

1. Verkman AS, et al. *Brain Pathol.* 2013;23:684–695. 2. Weinshenker BG, Wingerchuk DM. *Mayo Clin Proc.* 2017;92:663–679.

Other biomarker candidates in NMOSD

Th17-related cytokines[1]

- 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 CSF[3]

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

GFAP and NfL[2]

- 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 microRNAs[4]

- 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 Trans Neurol* 2020; doi: 10.1002/acn3.51094. 4. Chen C, et al. *Front Immunol.* 2020;11:1064.

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
- Fulfils 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. *Neurol Neuroimmunol Neuroinflamm.* 2019;6:e626.

Impact on outcomes and patient QoL

QoL assessment in 193 patients with NMOSD

Most patients had an initial diagnosis other than NMOSD

Strong negative impact on physical health

- Pain
- Bowel/bladder dysfunction

Relatively unimpaired emotional wellbeing

Biggest negative factors were

- Inability to work
- Reduced QoL and sexual function
- Increased pain

Dissatisfaction with

- **Treatment options**
- **Economic burden**

Early diagnosis and detection of NMOSD activity biomarkers should allow for quicker and more accurate treatment selection

NMOSD, neuromyelitis optica spectrum disorder; QoL, quality of life.
Beekman J, et al. *Neurol Neuroimmunol Neuroinflamm.* 2019;6:e580

How do novel therapies work to reduce relapse?

Prof. Sean Pittock

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

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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

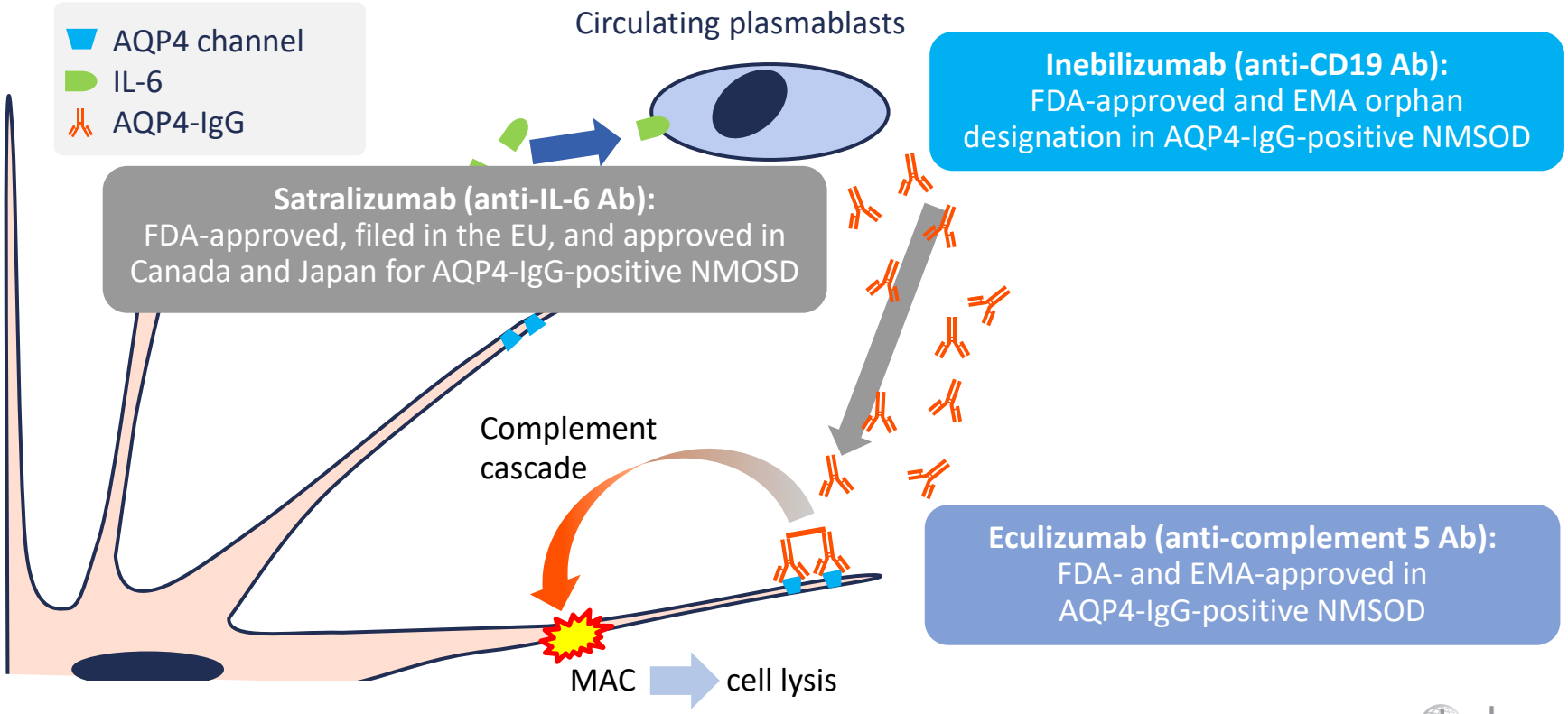
Traditional approach to treatment relied on

- Immunosuppression: steroids, azathioprine, methotrexate and mycophenolate mofetil
- B-cell targeted therapy with rituximab

NMOSD, neuromyelitis optica spectrum disorder.

1. Akaishi T, et al. *Neurol Neuroimmunol Neuroinflamm.* 2020;7:e640. 2. Weinshenker BG, Wingerchuk DM. *Mayo Clin Proc.* 2017;92:663–679.

Novel agents target NMOSD pathophysiology



Ab, antibody; AQP4, aquaporin-4; CD19, cluster of diffentiation-19; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IgG, immunoglobulin G; IL-6, interleukin-6; MAC, membrane attack complex; NMOSD, neuromyelitis optica spectrum disorder.

Selmaj K ,Selmaj I. *Neurol Neurochir Pol.* 2019;53:317–326.

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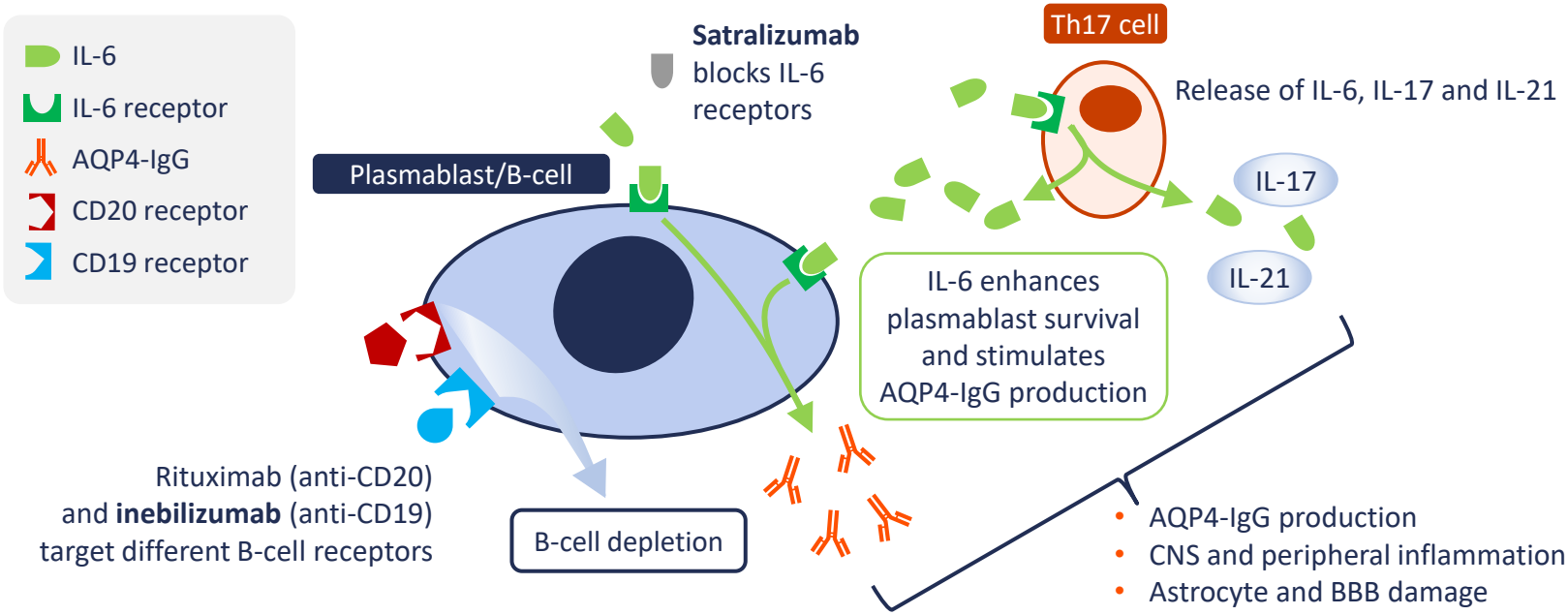
IL-6, plasmablasts and NMOSD pathology[1–3]



- High IL-6 levels are associated with NMOSD relapse and severity of neurological disability[1]

AQP4, aquaporin-4; BBB, blood–brain barrier; CD19/20, cluster of differentiation 19/20; CNS, central nervous system; IgG, immunoglobulin G; IL, interleukin; NMOSD, neuromyelitis optica spectrum disorder; Th, T-helper.

1. Barros PO, et al. *Clin Exp Immunol.* 2015;183:480–9. 2. Chihara N et al, *Proc Natl Acad Sci USA.* 2011;108:3701–6. 3. Uzawa A, et al. *Clin Exp Neuroimmunol.* 2013;4:167–72.

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Novel agents: clinical trials

Eculizumab: PREVENT study (NCT01892345)[1]

N=143 adults with **AQP4-IgG+** NMOSD
- ≥2 attacks/last 12 mo, or ≥3 attacks/last 24 mo with ≥1/last 12 mo
- EDSS ≤7

Eculizumab (n=96)
900 mg IV Q1W x4, then 1200 mg iv Q2W

Placebo (n=47)

Stable-dose immunosuppressive therapies allowed *except* rituximab and mitoxantrone during last 3 months before study

Inebilizumab: N-MOmentum (NCT02200770)[2]

N=230 adults with **AQP4-IgG±** NMOSD
- ≥1 attacks/last 12 mo, or ≥2 attacks/last 24 mo requiring rescue therapy
- EDSS ≤8

Inebilizumab (n=174)
300 mg IV Q2W

Placebo (n=56)

Inebilizumab at extension phase or at relapse

Prophylactic corticosteroid support during Days 1–21, but no other immunosuppressive therapy during randomized phase

Satralizumab: SAkuraSky (NCT02028884)[3] and SAkuraStar (NCT02073279)[4]

N=83 adults with **AQP4-IgG±** NMOSD[3]
- ≥1 attacks/last 12 mo, and ≥2 attacks/last 24 mo
- EDSS ≤6.5

Satralizumab (n=41) + stable immunosuppression
120 mg SC W0, 2, 4 then Q4W

Placebo (n=42) + stable immunosuppression

N=95 adults with **AQP4-IgG±** NMOSD[4]
- ≥1 attacks/last 12 mo
- EDSS ≤6.5

Satralizumab (n=63)
120 mg SC W0, 2, 4 then Q4W

Placebo (n=32)

Satralizumab at extension phase or at relapse

AQP4, aquaporin-4; AQP4±, AQP4 seronegative patients allowed if meeting 2006 Wingerchuk criteria for neuromyelitis optica; EDSS, expanded disability status scale; IV, intravenous; mo, months; SC, subcutaneous; Q2/4W, every 2/4 weeks; W, week.

1. Pittock SJ, et al. *N Engl J Med.* 2019;381:614–25. 2. Cree BAC, et al. *Lancet*. 2019;394:1352–63. 3. Yamamura T, et al. *New Engl J Med.* 2019;381:2114–24. 4.Traboulsee A. ECTRIMS Online Library. 2019; 278963:P603.

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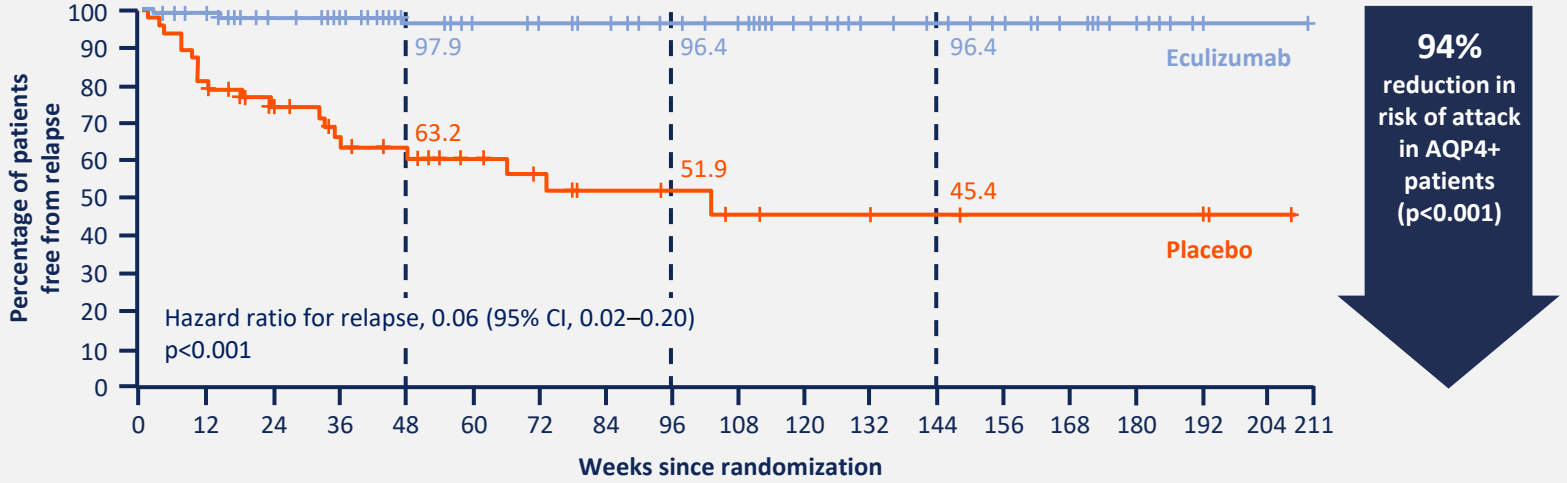
Eculizumab: effect on relapse

PREVENT study

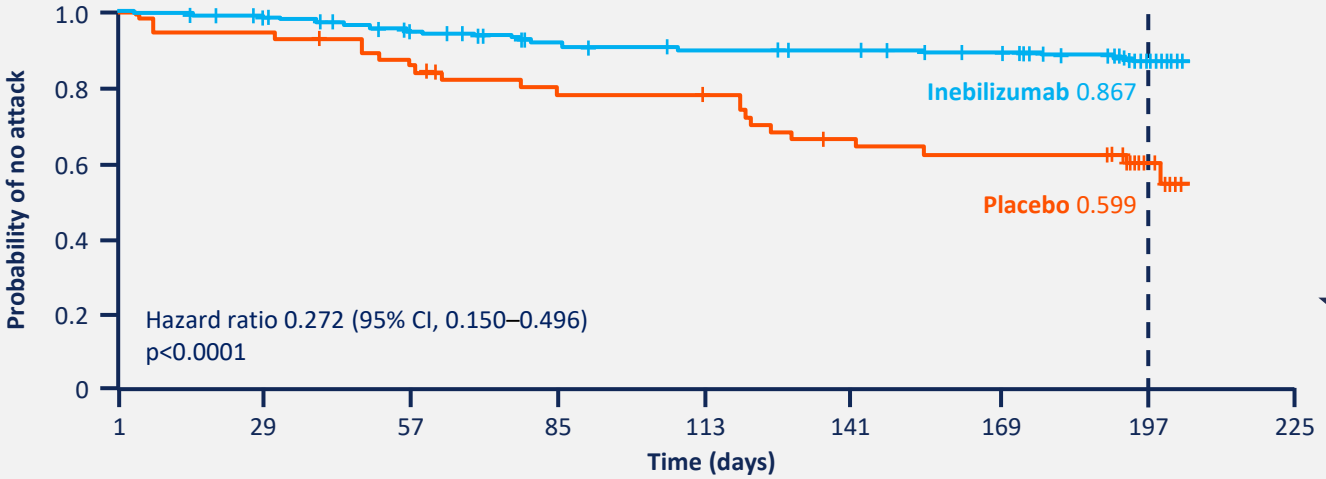


- In 21 patients receiving eculizumab without concomitant immunosuppression, there were no relapses at 144 weeks vs 7/13 patients receiving placebo only

AQP4+, aquaporin-4-positive; CI, confidence interval.
Figure reproduced with permission from Pittock SJ, et al. *N Engl J Med.* 2019;381:614–25.

Inebilizumab: effect on relapse

N-MOmentum study



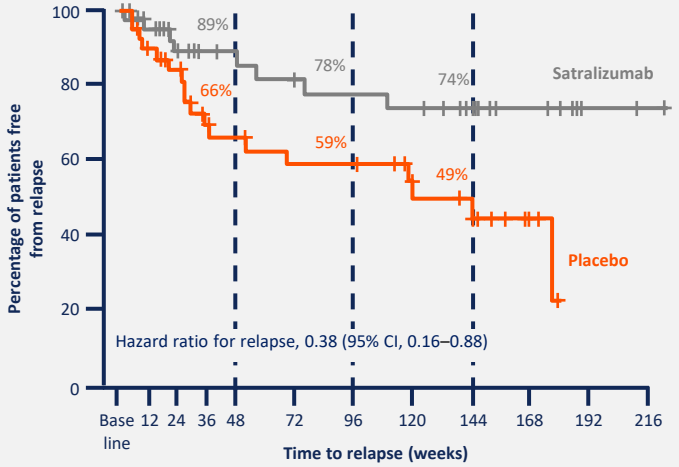
77% reduction in risk of attack in AQP4+ patients (p<0.0001)

- Significant B-cell depletion in circulating CD20 B-cells after day 8 at all time points with inebilizumab vs placebo (p<0.0001)

AQP4+, aquaporin-4-positive; CI, confidence interval.
Figure reproduced with permission from Cree BAC, et al. *Lancet*. 2019;94:1352–63.

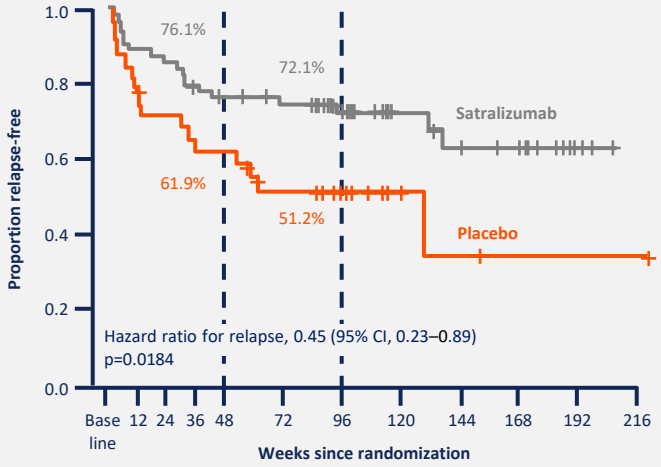
Satralizumab: effect on relapse

SAkuraSky study[1]



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

SAkuraStar study[2]



- 55% reduction in relapse vs placebo

Pooled analysis[3]

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. Traboulsee A. ECTRIMS Online Library. 2019; 278963:P603. 3. Haskova Z, et al. *Invest Ophthalmol Vis Sci.* 2020;61:3173.

Novel agents: safety

Eculizumab: PREVENT study[1]

Most common AEs	Eculizumab (n=96), n (%)	Placebo (n=47), n (%)
Upper RTI	28 (29)	6 (13)
Headache	22 (23)	11 (23)
Nasopharyngitis	20 (21)	9 (19)
Nausea	16 (17)	12 (26)
UTI	13 (14)	10 (21)
Limb pain	11 (11)	10 (21)

- 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

Inebilizumab: N-MOmentum study[2]

Most common AEs	Inebilizumab (n=174), n (%)	Placebo (n=56), n (%)
UTI	20 (11)	5 (9)
Arthralgia	17 (10)	2 (4)
IRR	16 (9)	6 (11)
Back pain	13 (7)	2 (4)
Headache	13 (7)	4 (7)
Nasopharyngitis	13 (7)	6 (11)

- 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)

Satralizumab: SAkuraSky study[3]

Most common AEs	Satralizumab (n=41), n (%)	Placebo (n=42), n (%)
Nasopharyngitis	10 (24)	7 (17)
Upper RTI	10 (24)	6 (14)
Headache	10 (24)	4 (10)
UTI	7 (17)	7 (17)
Constipation	2 (5)	7 (17)

- SAEs: 17% (satralizumab) vs 21% (placebo)
- No deaths or anaphylactic reactions
- 8 discontinuations due to AEs (3 satralizumab and 5 placebo 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. Pittock SJ, et al. *N Engl J Med.* 2019;381:614–25. 2. Cree BAC, et al. *Lancet.* 2019;94:1352–63. 3. Yamamura T, et al. *New Engl J Med.* 2019;381:2114–24.

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

Prof. Jackie Palace

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

NMOSD, Neuromyelitis optica spectrum disorder.

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Case: female with AQP4-IgG-positive NMOSD

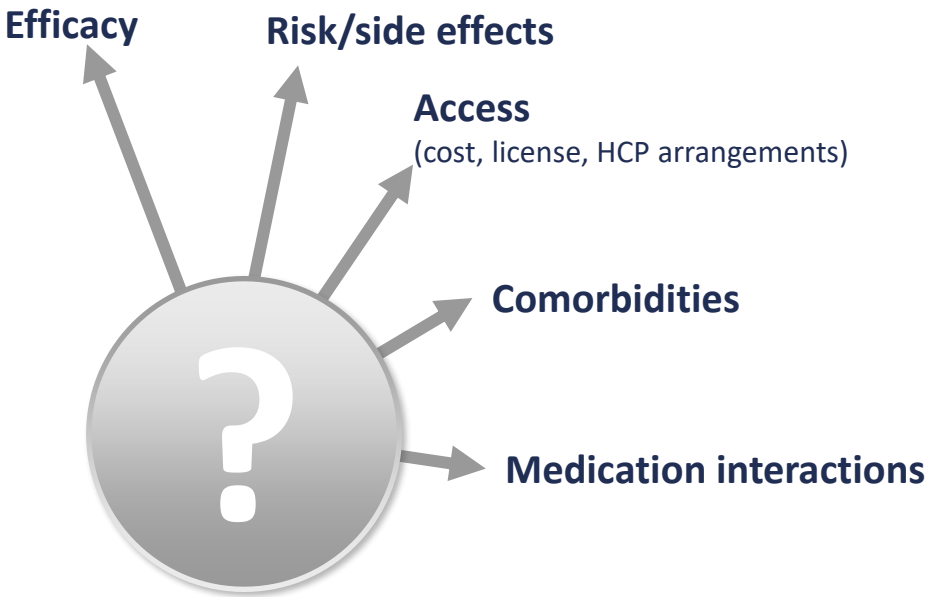
- 35-year-old woman in full-time employment
- 2 school-age children
- Onset attack of transverse myelitis 12 months ago
- Positive serum AQP4 antibodies
- TPMT levels low

- 90% recovery with 5 days IV MPred
- On prednisolone 10 mg OD maintenance, relapse-free since onset
- She feels that the prednisolone is making her anxious and wants to discontinue it

AQP4, aquaporin-4; IgG, immunoglobulin G; IV, intravenous; MPred, methylprednisolone; NMOSD, neuromyelitis optica spectrum disorder; OD, once daily; TPMT, thiopurine methyltransferase.

Case: female with AQP4-IgG-positive NMOSD

Medical considerations for management



Armamentarium

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

AQP4, aquaporin-4; DMTs, disease-modifying drugs; HCP, healthcare provider; IgG, immunoglobulin G; MS, multiple sclerosis; MTX, methotrexate; NMOSD, neuromyelitis optica spectrum disorder.

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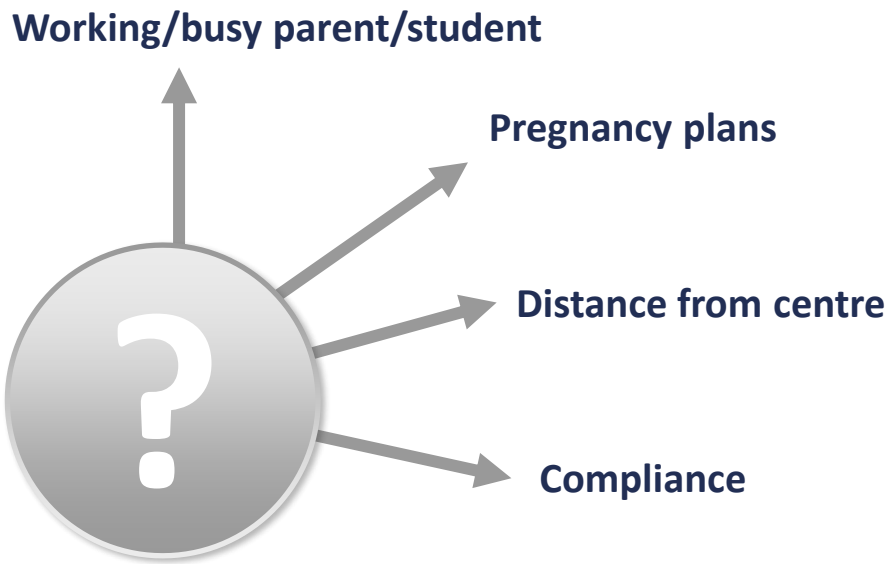
Case: female with AQP4-IgG-positive NMOSD

Patient lifestyle considerations for management



Armamentarium

- Prednisolone
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- **Eculizumab**
- **Inebilizumab**
- **Satralizumab**

AQP4, aquaporin-4; DMTs, disease-modifying drugs; IgG, immunoglobulin G; MS, multiple sclerosis; MTX, methotrexate; NMOSD, neuromyelitis optica spectrum disorder.

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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.