Update in NMOSD

Topic review in Neuroimmunology

23 May 2023

Oranuch Chuapakdee, MD

1894 — Devic and his student Gault describing the first anatomopathological findings

Condition termed Devic's disease[2]

1927 — "Relapsing" course described by Beck; "remitting-relapsing form" described by McAlpine in 1938[3]

1999 — MRI used to classify NMO

Initial diagnostic criteria published[3]

2004 — Highly specific autoantibody biomarker (AQP4-ab) for distinguishing NMO from MS[4]

2005 — In 2005, AQP4 was shown to be the antigenic target of AQP4-ab[5]

2006 — Serum AQP4-ab was included into revised NMO diagnostic criteria[6]

2007 — The term NMOSD was introduced to include AQP4-ab seropositivity[7]

2008 — National MS Society (task Force on differential diagnosis in MS) diagnostic criteria for NMO[8]

2011 — Antibodies for MOG were observed[9]

2015 — IPND diagnostic criteria unified the term for disease as NMOSD with stratification by AQP4-ab status[10]

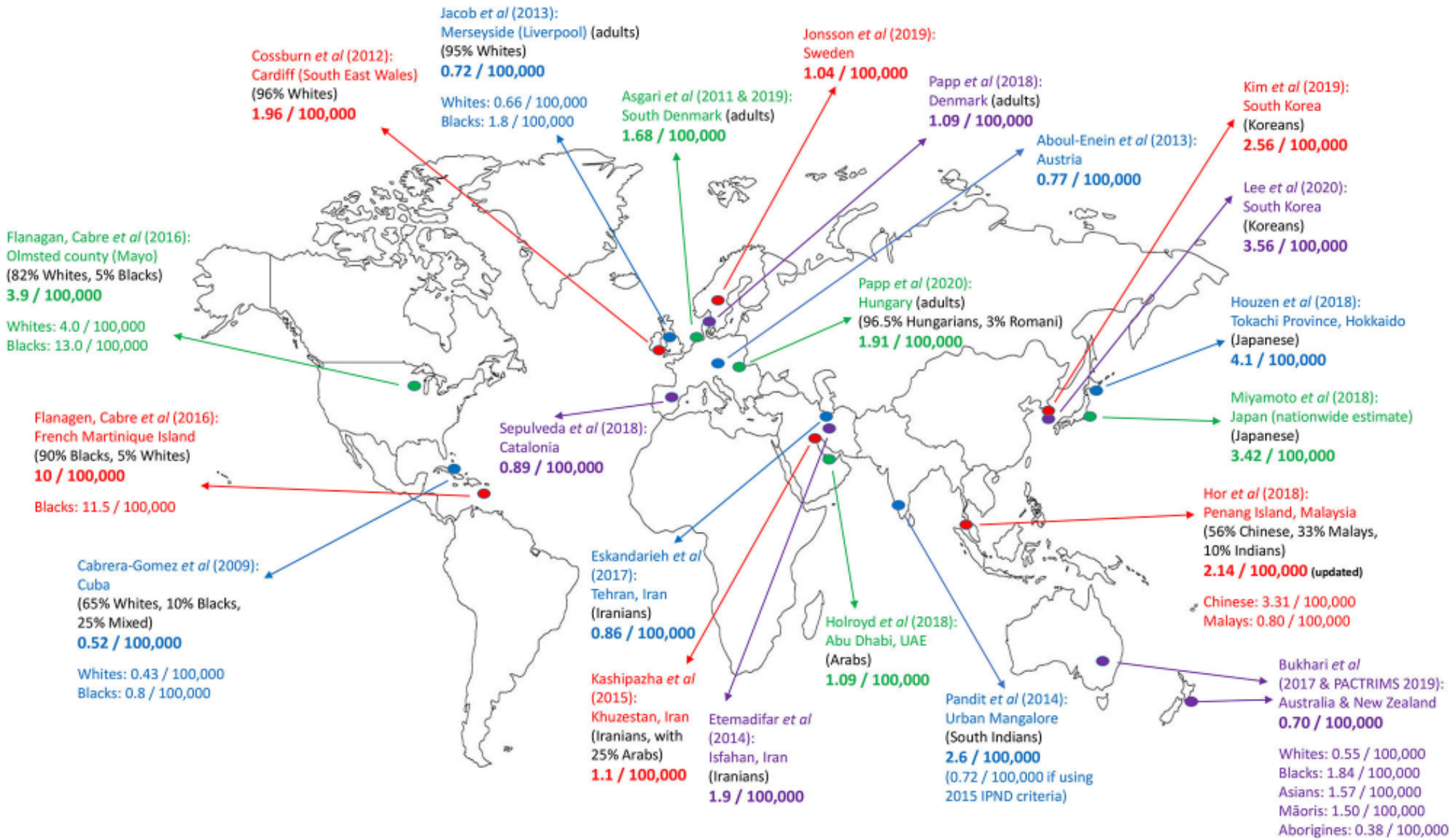
2017 — NMOSD to be considered in any patient being evaluated for MS[11]

2018 — International consensus recommendations on patients in whom MOG-ab should be tested [12]

2019 — The first FDA-approved treatment for NMOSD positive patients[13]

Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021;18(1):208.

World Map Showing Population-Based Studies of NMOSD



Hor JY, Asgari N, Nakashima I, Broadley SA, Leite MI, Kissani N, et al. Epidemiology of Neuromyelitis Optica Spectrum Disorder and Its Prevalence and Incidence Worldwide. Frontiers in Neurology. 2020;11.

NMOSD in Thailand

Epidemiology and Burden of NMOSD, MS, and MOGAD in Thailand: a Population-Based Study

Nanthaya Tisavipat, Pornpong Jitpratoom, Sasitorn Siritho, Naraporn Prayoonwiwat, Metha Apiwattanakul, Natthapon Rattanathamsakul, Jiraporn Jitprapaikulsan

Objective

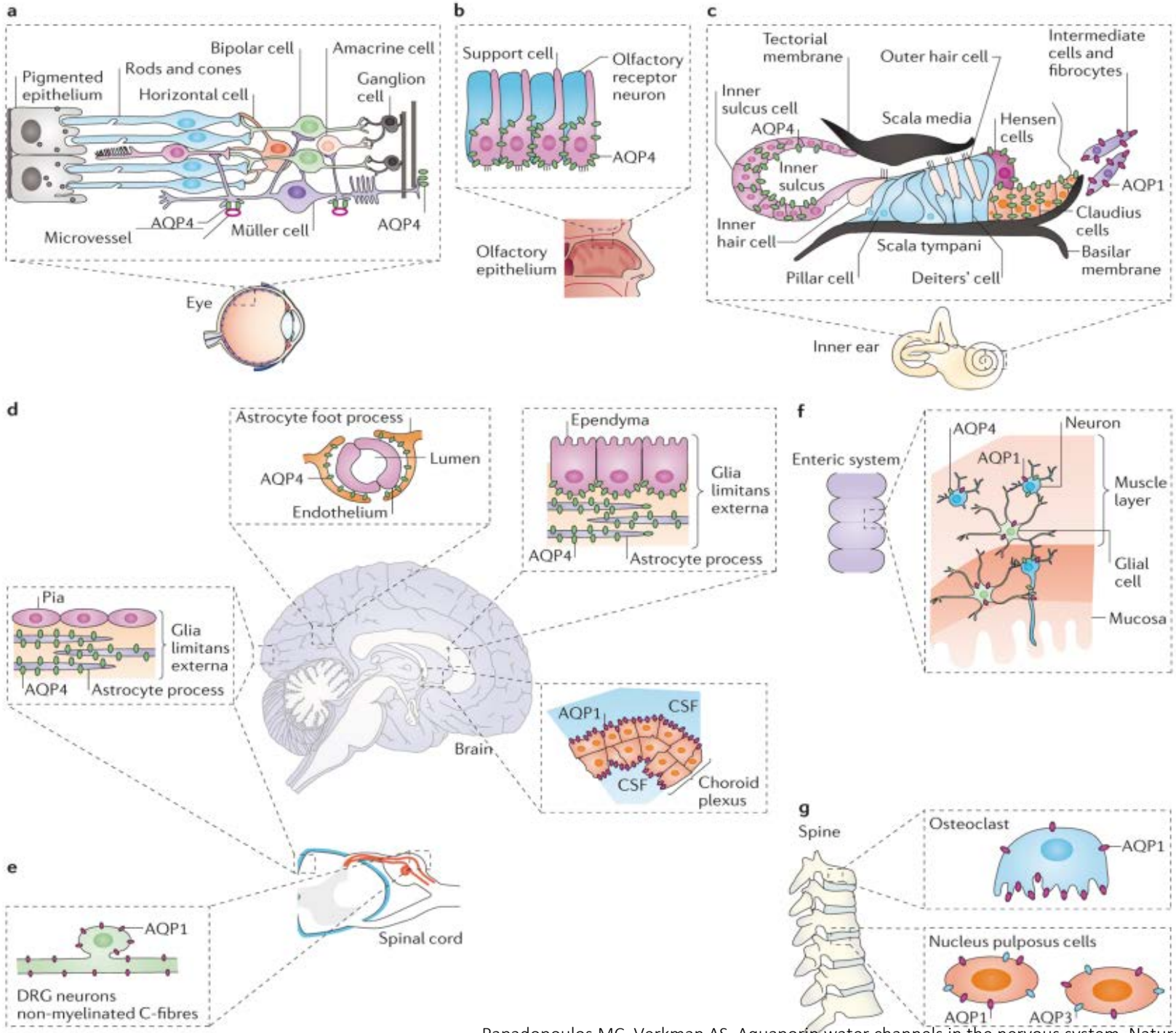
To determine cumulative incidence and point prevalence of neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) in Thailand using population-based data of Chumphon province.

- Population-based study
- Searching for CNSIDD patients at a public secondary care hospital in Chumphon from January 2016 to December 2021 was performed using relevant ICD-10-CMcodes
- NMOSD was the most prevalent CNSIDD (CNS inflammatory demyelinating diseases) in adult Thai population at 3.33 per 100,000 persons (crude prevalence 2.55).

NMOSD

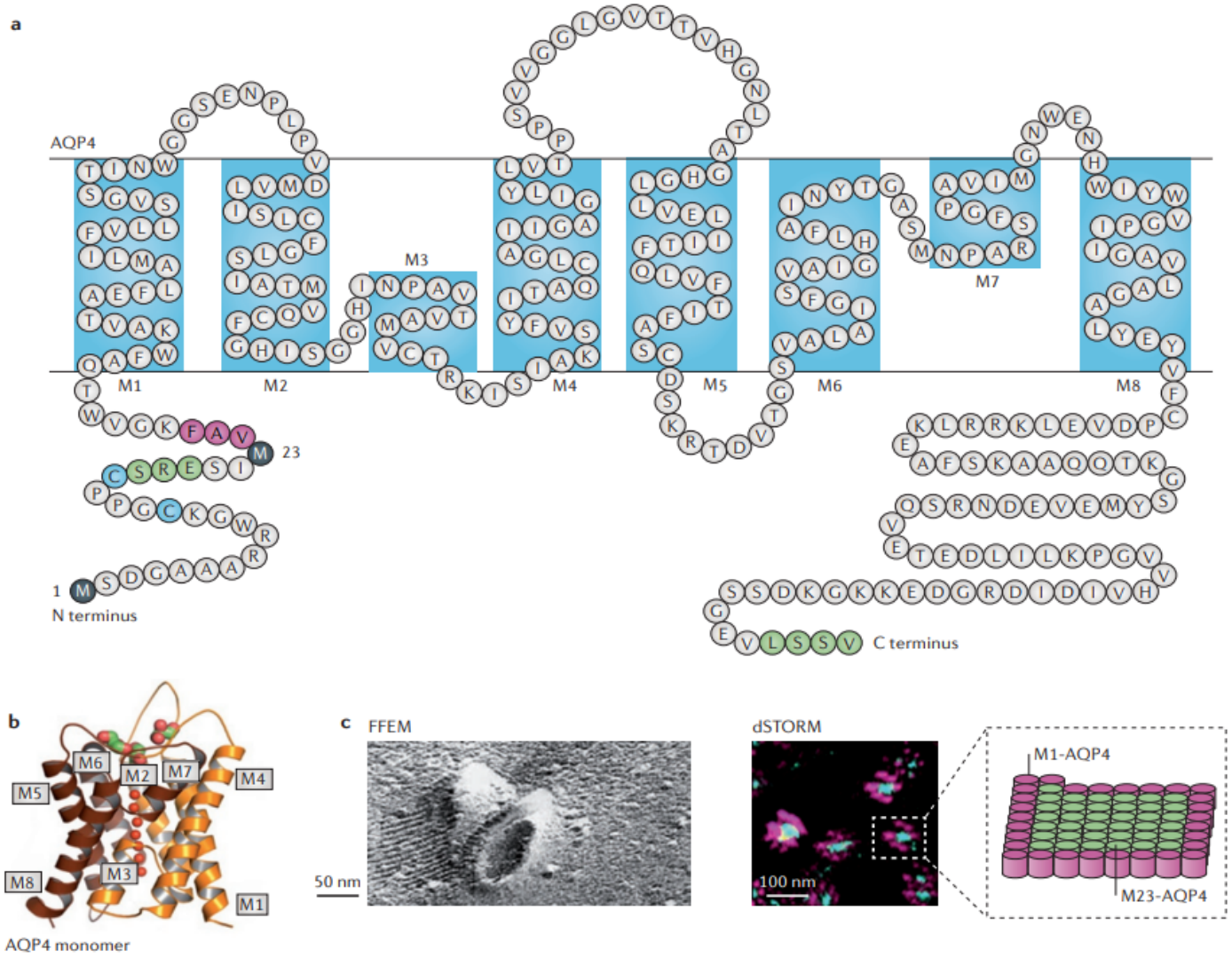
- Autoimmune aquaporinopathy
- East Asians: 3.5/100,000 Whites: 1/100,000 Blacks: range from 1.8 to 10/100,000
- Female : Male ratio = 9 : 1
- The median age of onset is 35–37 years but people of any age can be affected
- Coexisting autoimmune disease :HLA-DR B1*03:01(white), HLA-DPB1*05:01 (Asia)
- AQP4-IgG seropositivity is associated with a high risk of relapse after a first event of longitudinally extensive transverse myelitis4 and in those with single or recurrent optic neuritis
- A relapsing disease.
- Attacks are often severe and lead to disability as a result of cumulative sequelae of relapses

Pittock SJ, Zekeridou A, Weinshenker BG. Hope for patients with neuromyelitis optica spectrum disorders — from mechanisms to trials. Nature Reviews Neurology. 2021;17(12):759-73.



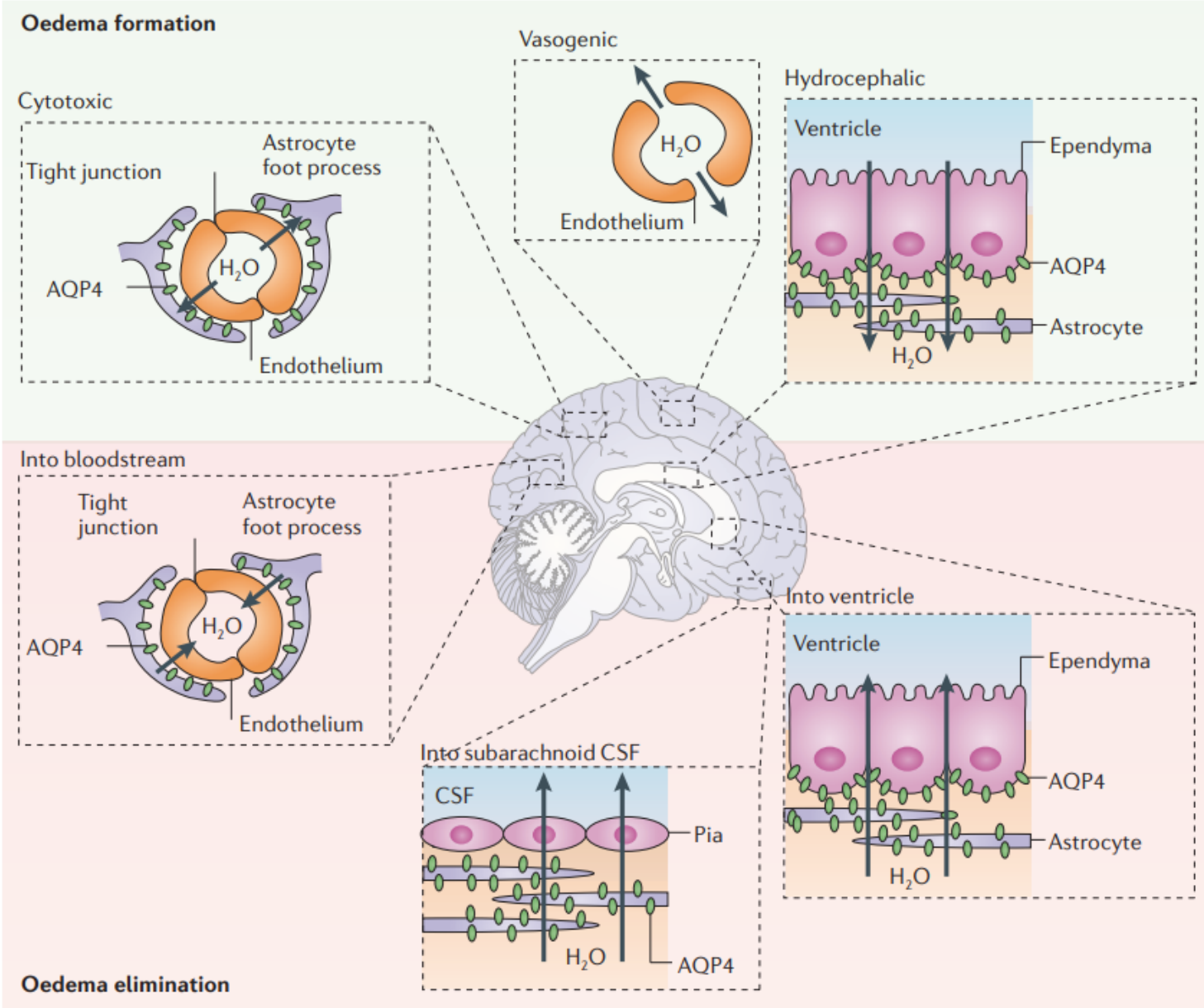
NMOSD

- AQP4 expression is high at the astrocytic foot process
- AQP4 structure
  - 2 isoforms = M1 (complete internalization), M23 (resist internalization)
  - Orthogonal arrays particle (OAP) formed by M23 isoform (only in CNS)
  - OAP for IgG and complement C1Q binding (CDCC)
  - Best assay = M23-isoform
- Antibodies in NMOSD (AQP4-IgG1)
  - Complement activation (CDC) – MAC
  - Activation of effector cells (NK cell) – Ab dependent cell-mediated cytotoxicity (ADCC)
  - Target internalization of the receptor
  - Modification of target function

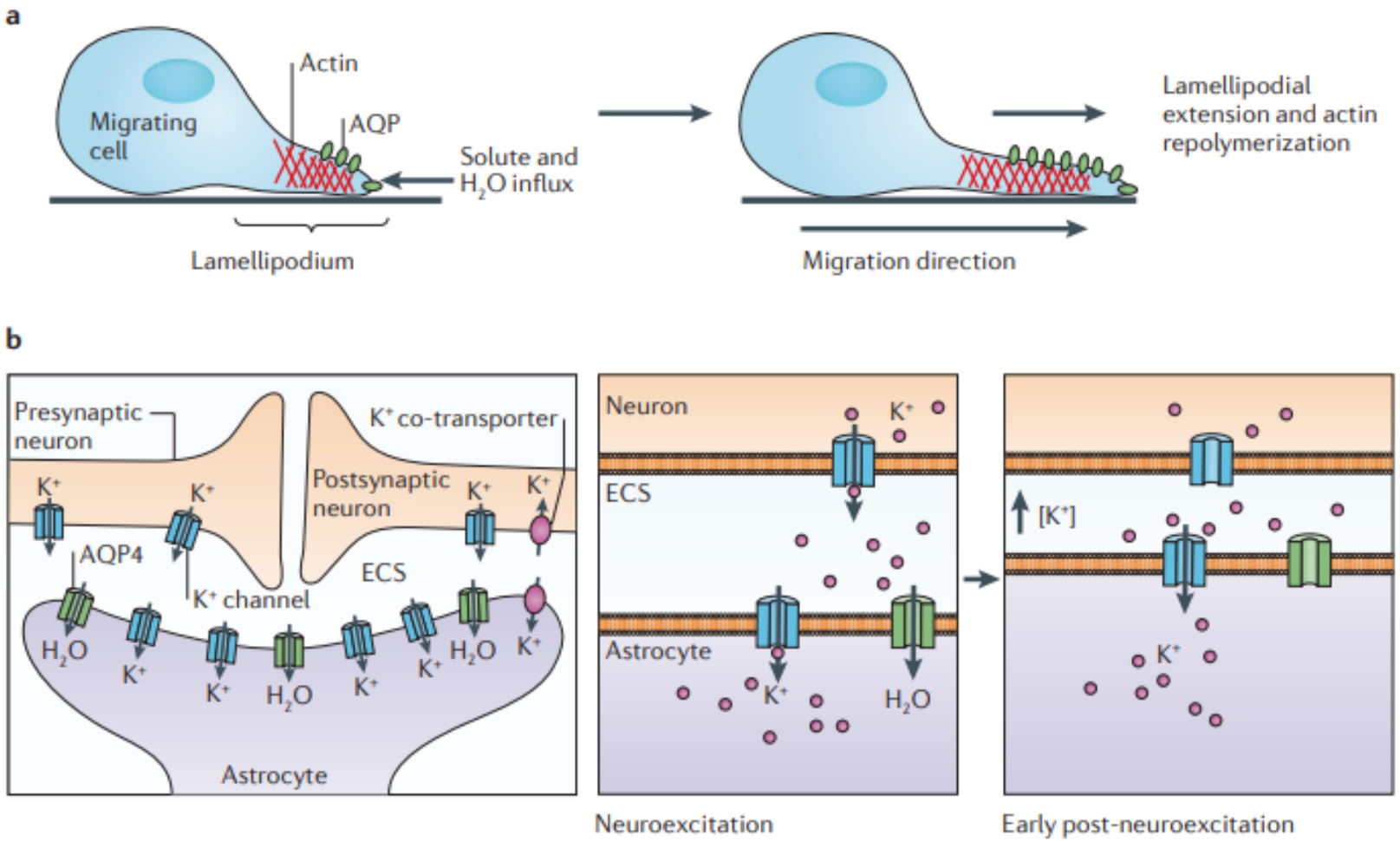


Papadopoulos MC, Verkman AS. Aquaporin water channels in the nervous system. Nature Reviews Neuroscience. 2013;14(4):265-77

- In <u>cytotoxic edema</u>
  - water enters the CNS AQP4 located in **perivascular astrocyte** foot processes.
- In <u>vasogenic edema</u>
  - CNS water entry is AQP4- independent and occurs through intercellular spaces.
- In hydrocephalic edema
  - water enters the brain through AQP4 in ependymal cells **and subependymal astrocytes**.
- <u>Interstitial edema</u>
  - astrocyte foot processes into the bloodstream,
  - subpial astrocyte processes and pial cells into subarachnoid cerebrospinal fluid (CSF)
  - subependymal astrocyte processes and ependyma into ventricle.

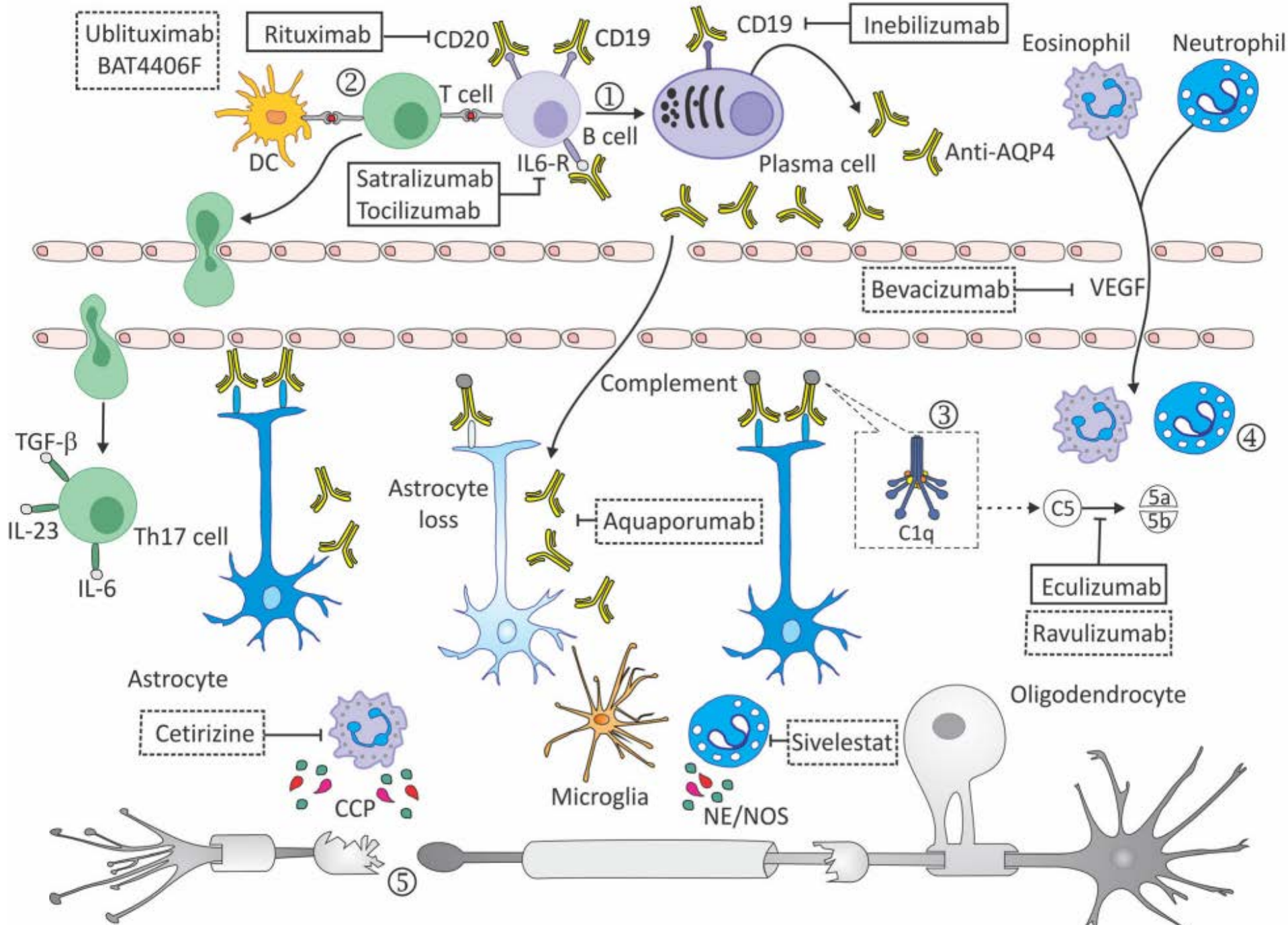


Papadopoulos MC, Verkman AS. Aquaporin water channels in the nervous system. Nature Reviews Neuroscience. 2013;14(4):265-77



- Role of AQP4
  - Astrocyte migration
  - Neuroexcitation outside the synaptic cleft: helping reuptake potassium and water by astrocytes → decrease extracellular space and volume
  - Modulate function of EAAT2 on astrocyte (reuptake glutamate into astrocyte)

Papadopoulos MC, Verkman AS. Aquaporin water channels in the nervous system. Nature Reviews Neuroscience. 2013;14(4):265-77



Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021;18(1):208.

AUTOIMMUNE ASTROCYTOPATHIC DISEASE

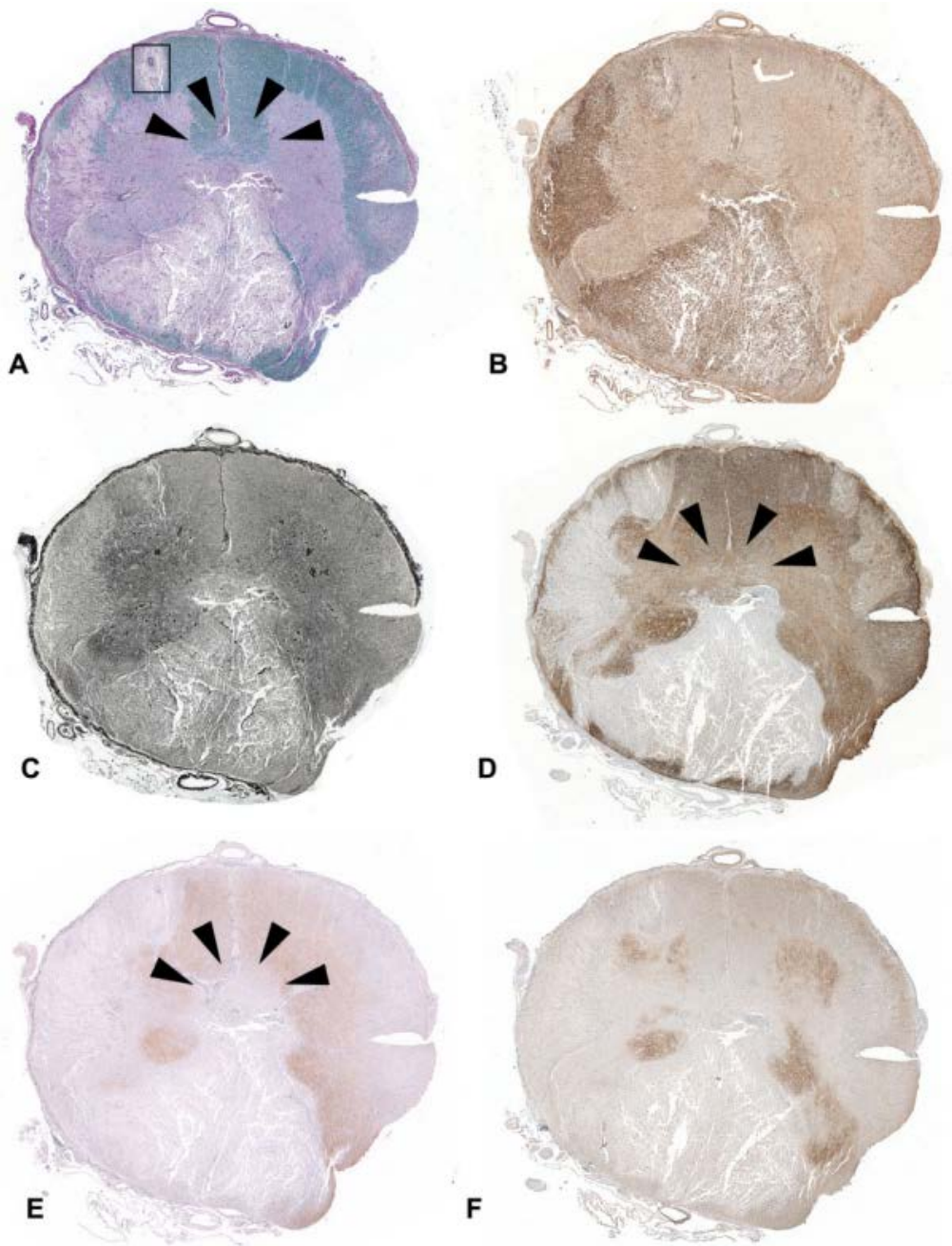
- AQP4-expressing astrocyte is the major target of immune attack and astrocytic destruction

1. Extensive loss of AQP4 and GFAP immunostaining in the CNS lesions
    - In contrast, astrocyte destruction is not seen or minor at best in typical multiple sclerosis.
2. Remarkably high CSF-GFAP levels during relapse
    - CSF GFAP is not elevated at all in typical multiple sclerosis
3. Low myo-inositol/creatinine value in the cervical-cordon H-MRS
    - Myo-inositol detected by 1 H- magnetic resonance spectroscopy reflects proliferation and activity of astrocytes
    - The myo-inositol/creatine ratio is significantly lower in the cervical cord of AQP4-antibody-seropositive NMOSD than in multiple sclerosis
4. Pathogenicity of AQP4-antibody in experimental studies(in vitro and in Vivo)
5. Significantly reduced thickness of Muller cell-rich fovea on OCT
    - foveal change around Muller cell-rich fovea supports a retinal astrocytopathy

Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. *Curr Opin Neurol*. 2019;32(3):385-394

Pathology of NMOSD

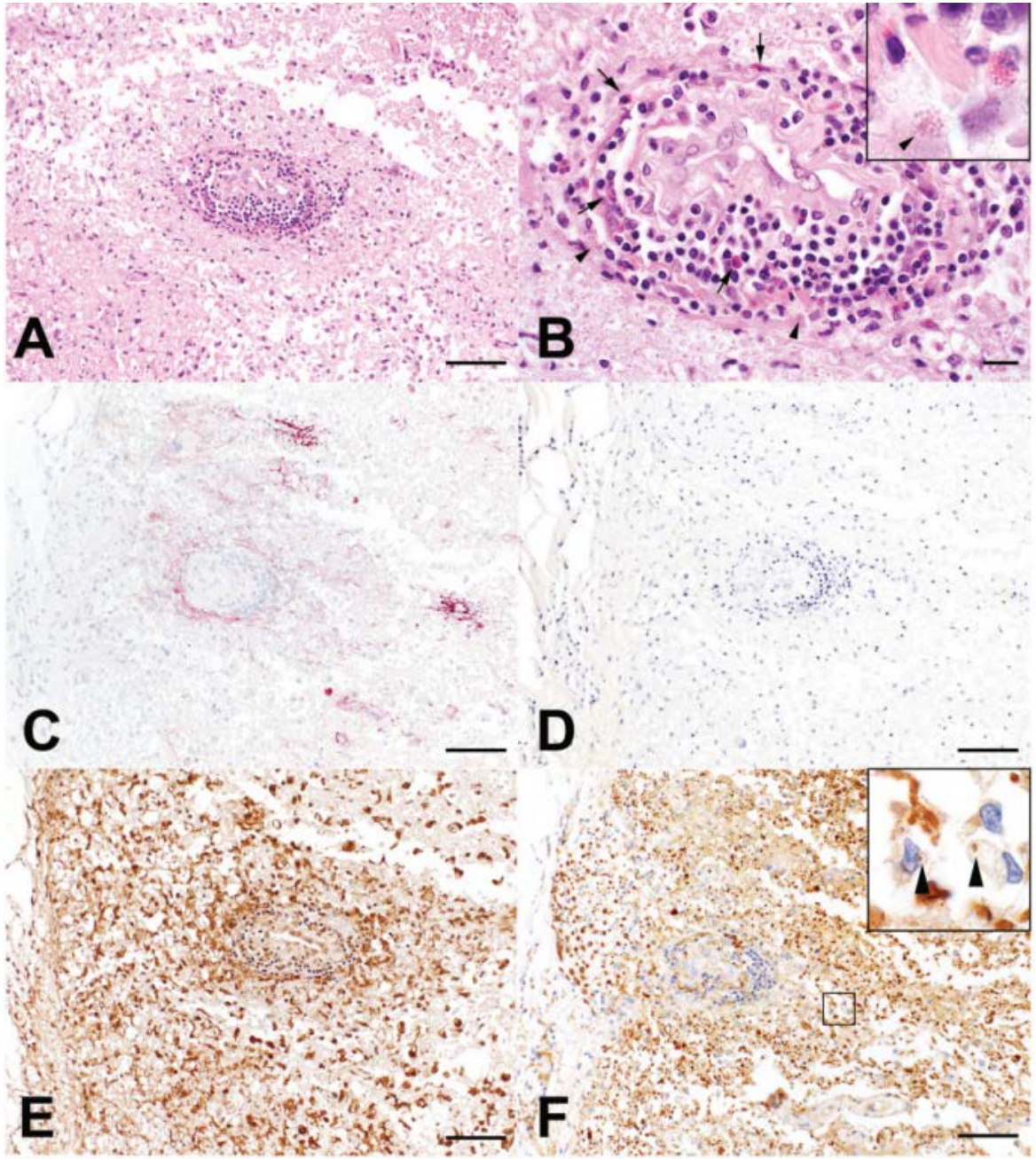
- Demyelination involving both the gray and white matter (LFB/PAS)
- Macrophage/microglia infiltration.
- Severe axonal loss is present in some areas of the lesion (Bielschowsky's staining).
- loss of GFAP, AQP4 receptor and the glutamate transporter, EAAT2



Lucchinetti CF, Guo Y, Popescu BF, Fujihara K, Itoyama Y, Misu T. The pathology of an autoimmune astrocytopathy: lessons learned from neuromyelitis optica. Brain Pathol. 2014;24(1):83-97.

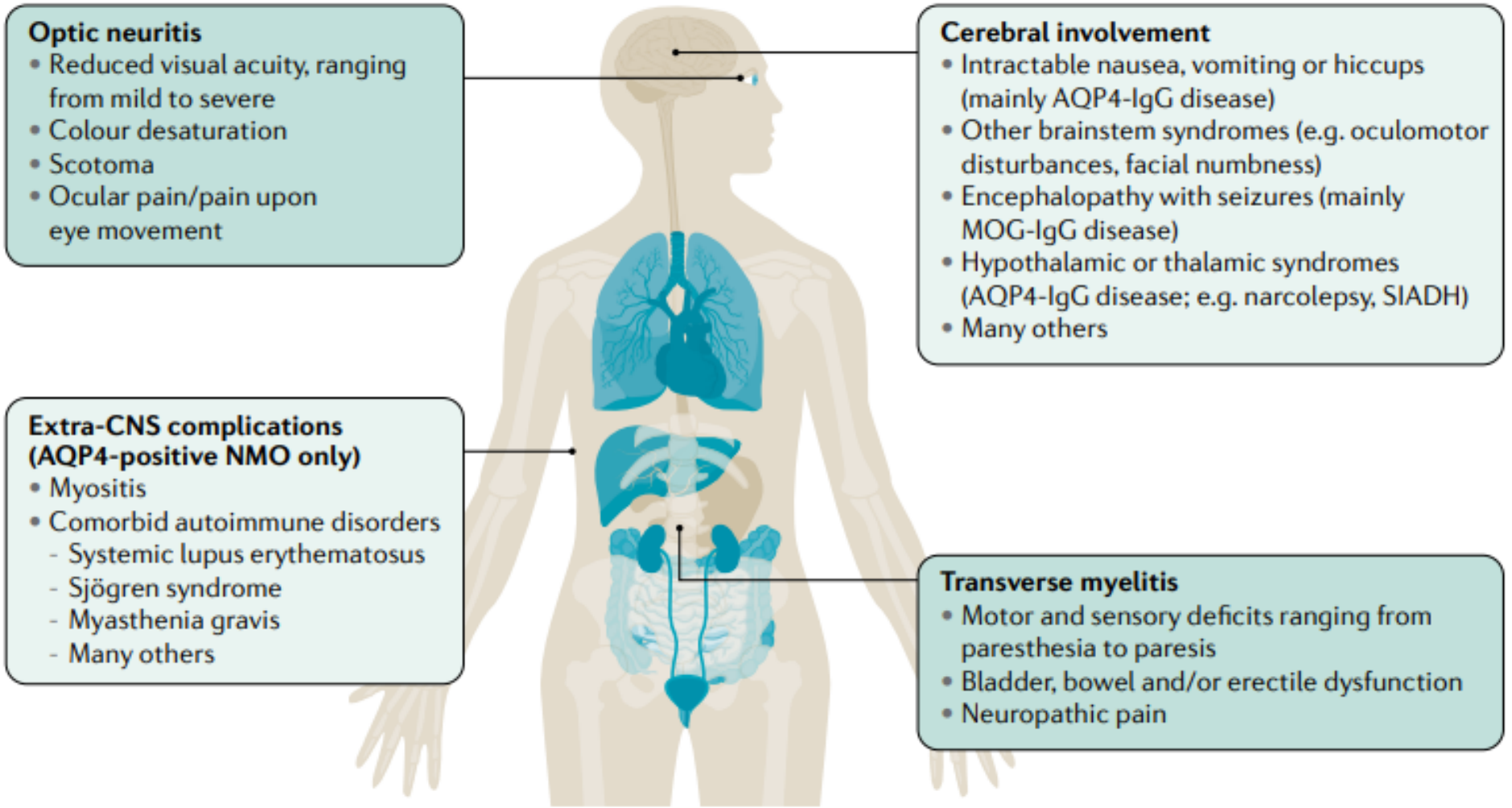
Pathology of NMOSD

- Perivascular complement deposition (Rosette/mesh pattern)
- Lymphocyte and eosinophil perivascular infiltration with degranulation
- Complement deposition at perivascular region
- Active Demyelination
- Myelin laden macrophage



Lucchinetti CF, Guo Y, Popescu BF, Fujihara K, Itoyama Y, Misu T. The pathology of an autoimmune astrocytopathy: lessons learned from neuromyelitis optica. Brain Pathol. 2014;24(1):83-97.

Clinical Manifestation



Jarius S, Paul F, Weinshenker BG, Levy M, Kim HJ, Wildemann B. Neuromyelitis optica. Nature Reviews Disease Primers. 2020;6(1):85.

NMOSD and Rheumatologic Disease

Q1. Is the syndrome-specific biomarker for NMO, aquaporin-4 autoantibodies, present in patients with systemic rheumatologic diseases, and if so, is it confined to the group of patients who have optic neuritis or myelitis?

- Answer. a high proportion of cases of both NMO and NMO associated with rheumatologic diseases had aquaporin-4 autoantibodies and the frequency did not differ between these two groups

Q2. When myelitis occurs in a connective tissues disease, is it clinically, radiologically and pathologically similar to the myelitis seen in neuromyelitis optica?

- Answer. no reported detailed immunopathological analyses of spinal cord lesions in patients with NMOSDs in the context of SS or SLE

DM Wingerchuck. Multiple Sclerosis Journal.2012;18(1):5–10

NMOSD and Rheumatologic Disease

Q3. Do systemic rheumatologic disorders consistently or characteristically precede NMO, or can either one occur first?

- Answer. Not associated

Q4. Is NMO associated only with systemic rheumatologic disease that is associated with vasculitis or potential to produce CNS pathology, or can it be associated with other autoimmune disorders not otherwise associated with CNS tissue damage?

- Answer. Association with other systemic inflammatory diseases not associated with CNS pathology; autoimmune thyroid disease, celiac disease, MG

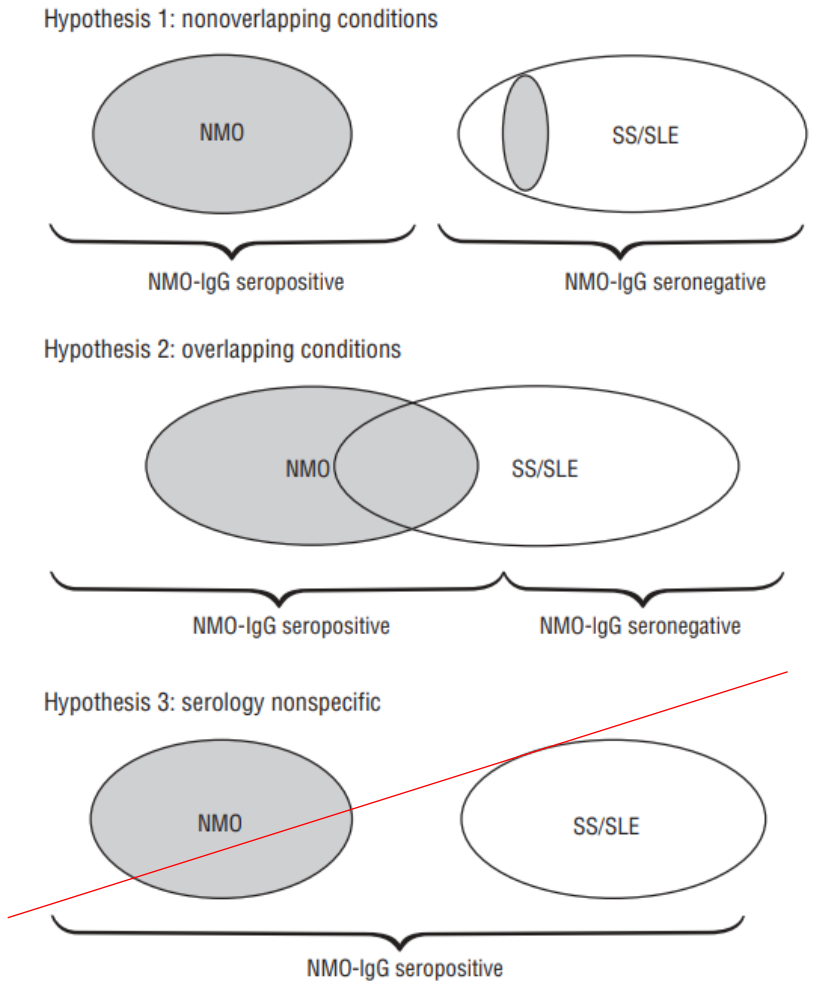
DM Wingerchuck. Multiple Sclerosis Journal.2012;18(1):5–10
Pittock SJ, Lennon VA, de Seze J, Vermersch P, Homburger HA, Wingerchuk DM, et al. Neuromyelitis optica and non organ-specific autoimmunity. Arch Neurol. 2008;65(1):78-83.

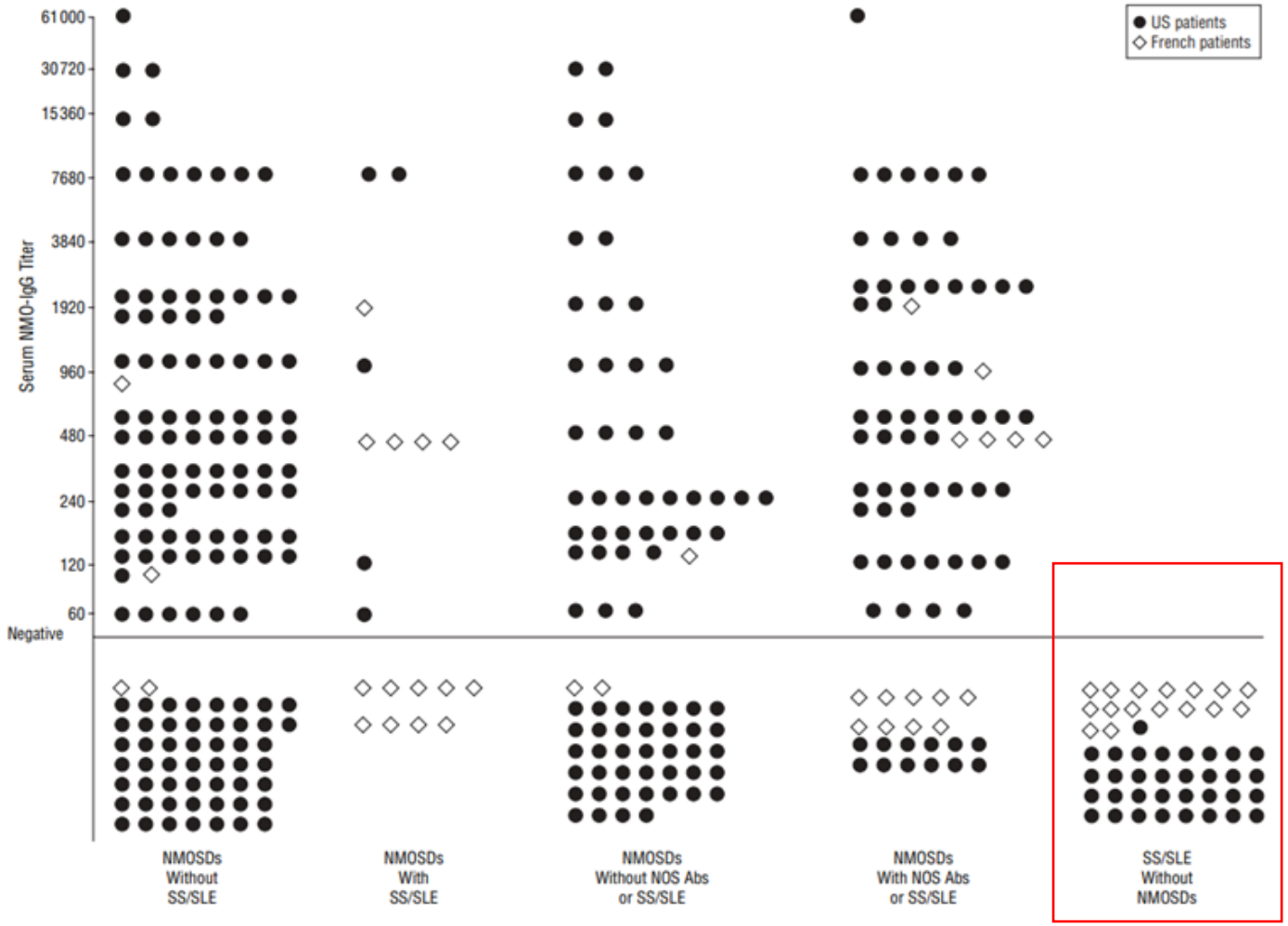
NMOSD and Rheumatologic Disease

- Patient with known rheumatologic disease of ON or LETM, should prompt evaluation for AQP4 antibody
- Patient with rheumatologic disease who develop recurrent episodes LETM/ON with 'signature NMOSD' MRI lesion patterns → very likely to have NMO
- Patients with LETM/ON, without recognized rheumatologic disease who are found to have non-organ-specific autoantibodies (ANA) → more likely to have NMO > lupus myelitis
- The frequent use of immunosuppressive therapy for a previously diagnosed rheumatologic disease may suppress aquaporin-4 antibodies → follow up
- Rheumatologists and neurologists should avoid monoclonal antibody or fusion protein therapies that interfere with tumor necrosis factor-alpha function, including such as infliximab, adalimumab, or etanercept

DM Wingerchuck. Multiple Sclerosis Journal.2012;18(1):5–10

NMOSD and Rheumatologic Disease





Pittock SJ, Lennon VA, de Seze J, Vermersch P, Homburger HA, Wingerchuk DM, et al. Neuromyelitis optica and non organ-specific autoimmunity. Arch Neurol. 2008;65(1):78-83.

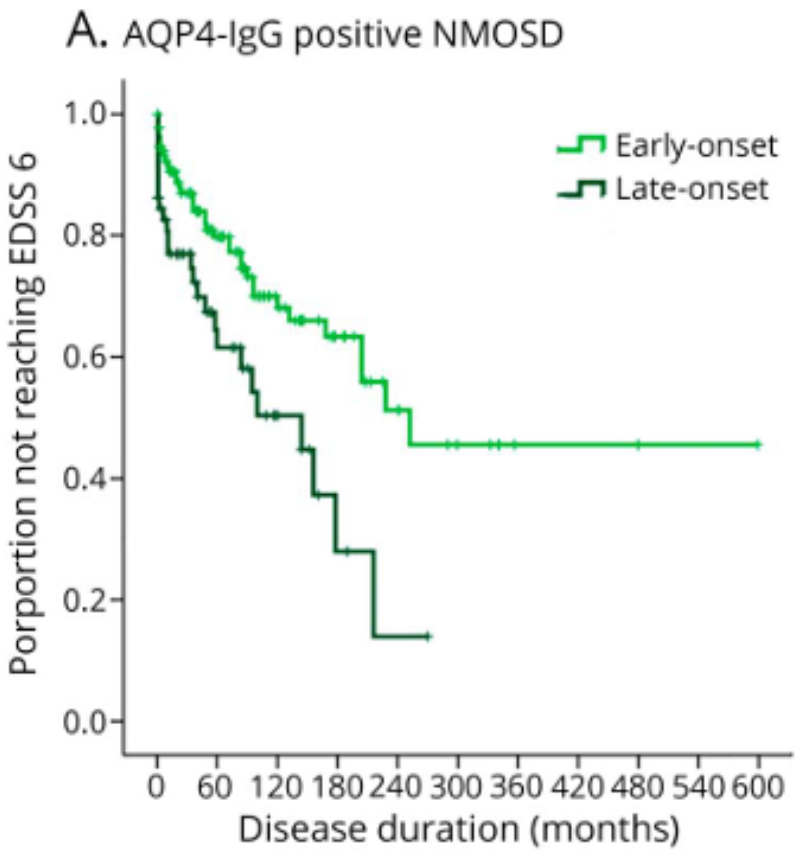
	EO-NMOSD (n = 133)	LO-NMOSD (n = 60)	*p* Value
Female:male (ratio)	122:11 (11:1)	48:12 (4:1)	0.037
White ethnicity, n (%)	107 (80)	56 (93)	0.030
Age at onset, y, median, range	32 (10–49)	59 (50–84)	N/A
Coexisting autoimmune diseases, n (%)	25 (19)	20 (33)	0.049
Onset attack type, n (%)			
Optic neuritis	56 (42)	22 (37)	
Myelitis	50 (38)	28 (47)	0.488
Simultaneous[a] optic neuritis + myelitis	16 (12)	4 (7)	
Brainstem/brain	11 (8)	6 (10)	
EDSS score after first attack, median (range)	3.0 (1.0–8.0)	4.0 (1.0–8.5)	0.012
Monophasic course, n (%)	11 (8)	17 (29)	<0.001
Chronic treatment, n (%)	111 (85)	40 (69)	0.016
Follow-up, y, median (range)	7.1 (0.3–50.0)	4.5 (0.2–22.4)	0.011
Annualized relapse rate, mean (SD)	1.6 (3.6)	1.4 (2.3)	0.261
Time to first relapse, mo, median (95% CI)	9.5 (5.3–13.8)	19.5 (4.6–34.3)	0.106
Disability:			
Outcome reached at last follow-up			
Last EDSS score, median (range)	3.0 (0–9.0)	4.8 (1.0–9.5)	0.007
EDSS score ≥6.0, n (%)	40 (30)	26 (46)	0.045
EDSS score ≥8.0, n (%)	13 (10)	10 (18)	0.146
Visual acuity[b] ≤20/100, n (%)	31/107 (28)	15/35 (43)	0.148
Concomitant neoplasia, n (%)	2 (2)	8 (13)	0.004
Paraneoplastic NMOSD[17]	1 (0.8)	4 (7)	0.033
Patients who died, n (%)	7 (5)	6 (10)	0.366

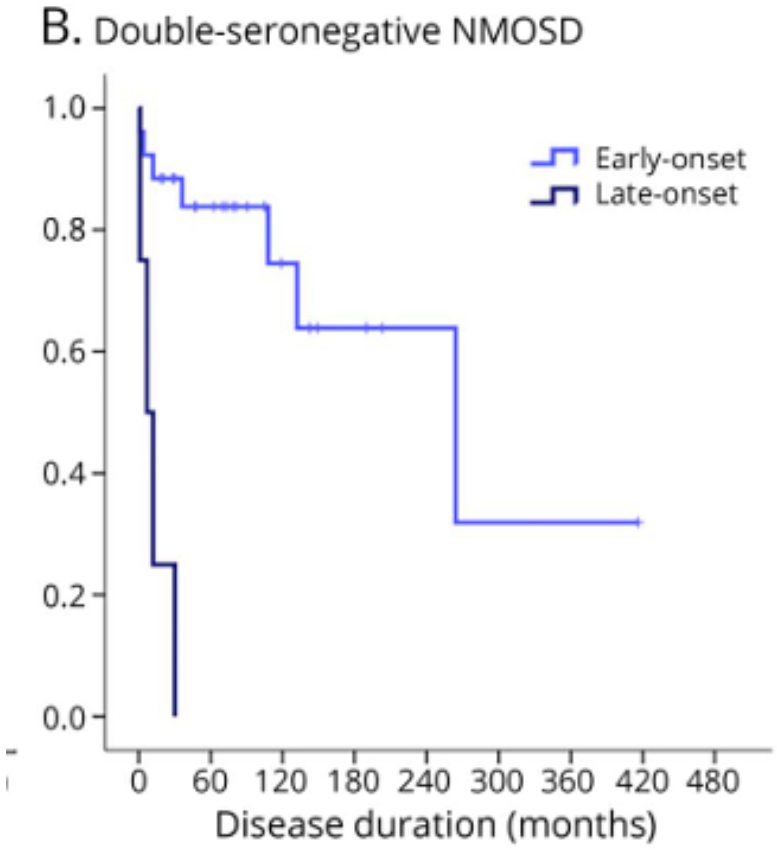
Late Onset NMOSD

- Disease onset ≥ 50years
- Type and frequency of initial attack not difference from early onset
- 31% of AQP4 positive NMOSD patient had LO- NMOSD
- Lower female : male ratio (11.1 vs 4.1)
- Coexisting autoimmune
- Higher EDSS after first attack and last follow up
- 7% diagnosed with paraneoplastic NMOSD
- Predictor of disability
  - Higher EDSS after first attack
  - ARR

Sepulveda M, Delgado-García G, Blanco Y, Sola-Valls N, Martinez-Lapiscina EH, Armangué T, et al. Late-onset neuromyelitis optica spectrum disorder: The importance of autoantibody serostatus. Neurol Neuroimmunol Neuroinflamm. 2019;6(6).

Late Onset NMOSD





A. AQP4 positive NMOSD

- 38% LO-NMOSD were expected to use a cane, at 60 months (5 years) after onset

B. Double seronegative NMOSD

- 100% LO-NMOSD were expected to use a cane, at 60 months (5 years) after onset

Sepulveda M, Delgado-García G, Blanco Y, Sola-Valls N, Martinez-Lapiscina EH, Armangué T, et al. Late-onset neuromyelitis optica spectrum disorder: The importance of autoantibody serostatus. Neurol Neuroimmunol Neuroinflamm. 2019;6(6).

NMOSD Diagnostic Criteria: Wingerchuck 2015

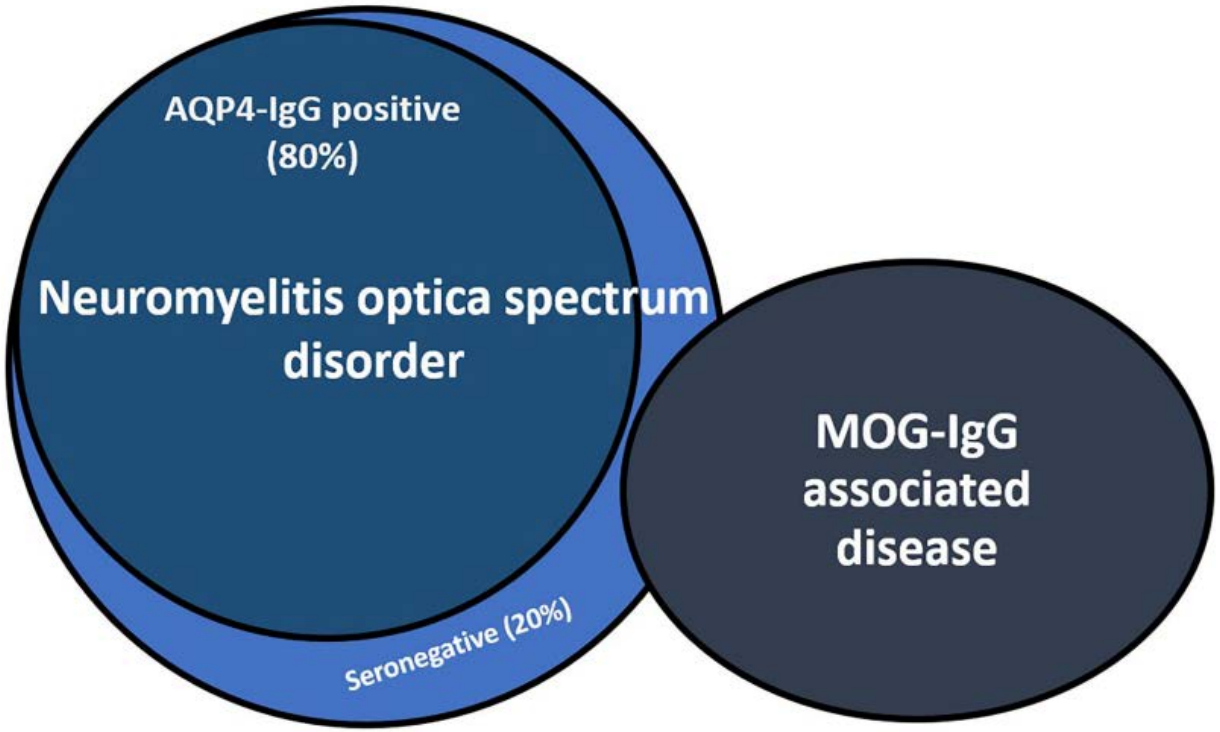
Seropositive	Seronegative ("double negative")
≥ 1 of 6 core clinical criteria	≥ 2 of 6 core clinical criteria attributable to ≥ 1 relapses
	≥ 1 core criterion must be either of – optic neuritis – acute myelitis as defined by LETM – area postrema syndrome (e.g., singultus not otherwise explained nausea)
	Dissemination in space must be met (≥ 2 core clinical criteria)—additional MR criteria should be met, if applicable
Positive AQP4-IgG status	Negative test for AQP4-IgG with the best available test
Exclusion of alternative diagnoses	Exclusion of alternative diagnoses

LETM longitudinally extensive transverse myelitis, *AQP4-IgG* aquaporin-4 immunoglobulin G, *MR* magnetic resonance

Core criteria	MRI additional criteria
Optic neuritis	*Acute optic neuritis:* requires a) unremarkable cranial MRI or nonspecific white matter changes or b) T2 hyperintense lesions or gadolinium-enhancing lesion of at least half of the optic nerve or chiasm
Acute myelitis	*Acute myelitis:* requires lesion intramedullary over three vertebral segments or atrophy extending over three vertebral segments in patients with history of acute myelitis
Area postrema syndrome: episode of otherwise unexplained singultus, nausea, or vomiting	*Area postrema syndrome:* requires a lesion located dorsally in the medulla oblongata or in the area postrema
Acute brainstem syndrome	*Acute brainstem syndrome:* requires a periependymal brainstem lesion
Symptomatic narcolepsy or acute diencephalic syndrome with NMOSD-typical diencephalic changes on MRI	–
Symptomatic cerebral symptoms in combination with MRI lesions typical for NMOSD	–

Ponleitner M, Rommer PS. Treatment of neuromyelitis optica spectrum disorder: revisiting the complement system and other aspects of pathogenesis. Wiener Medizinische Wochenschrift. 2022.

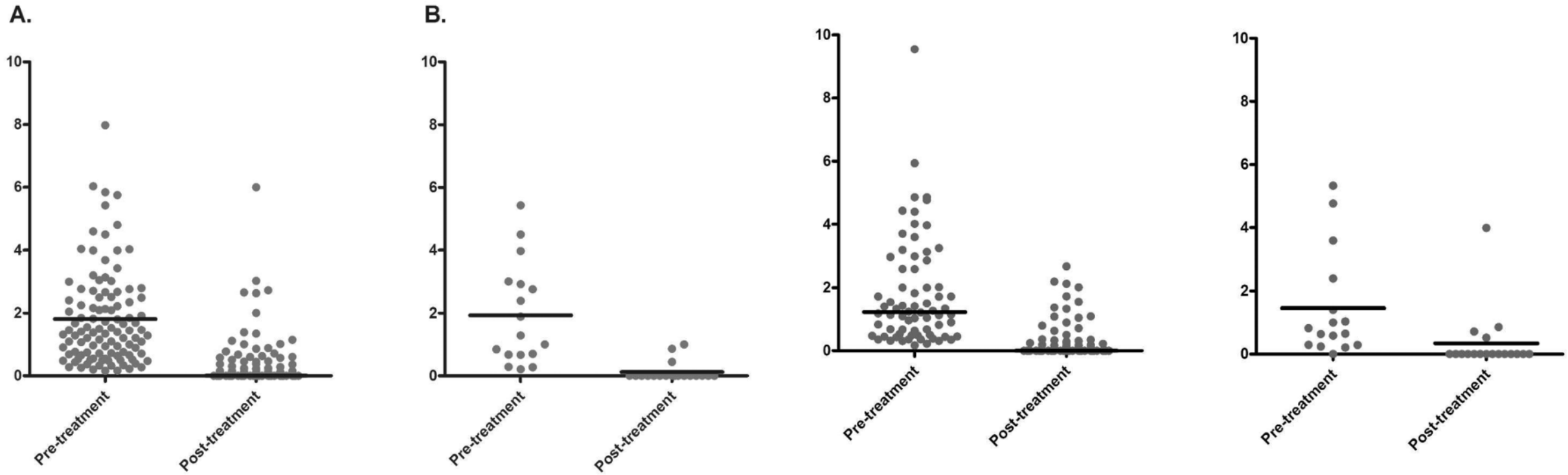
Seronegative NMOSD



- The female to male ratio was 1:1 in seronegative and 9:1 in seropositive
- Caucasian ethnicity (100 vs. 73.6%)
- Opticomyelitis at onset (27 vs. 6%)
- Less frequent severe visual impairment (12 vs. 54%)
- Simultaneous optic neuritis and transverse myelitis as onset attack type (within 30 days of each other) (32 % VS 3.6%)
- Relapse rate, disability outcome and other clinical characteristics did not differ significantly

Fujihara K. Neuromyelitis optica spectrum disorders: still evolving and broadening. *Curr Opin Neurol*. 2019;32(3):385-394
Dinoto A, Sechi E, Flanagan EP, Ferrari S, Solla P, Mariotto S, et al. Serum and Cerebrospinal Fluid Biomarkers in Neuromyelitis Optica Spectrum Disorder and Myelin Oligodendrocyte Glycoprotein Associated Disease. Front Neurol. 2022;13:866824.

Serostatus



- Multicenter retrospective analysis of 245 patients with NMOSD (seropositive and seronegative)
- In Rituximab ARR declined to 0.32 (seropositive; $p<0.0001$) and 0.12 (seronegative; $p=0.0001$).
- In mycophenolate mofetil, ARR declined to o 0.29 (seropositive; $p<0.0001$) and 0.30 (seronegative; $p<0.005$).
- Treatment was effective regardless of serostatus

Mealy MA, Kim SH, Schmidt F, López R, Jimenez Arango JA, Paul F, et al. Aquaporin-4 serostatus does not predict response to immunotherapy in neuromyelitis optica spectrum disorders. Mult Scler. 2018;24(13):1737-42.

Novel Marker for NMOSD

Cytokines

- Cytokine signature may aid in distinguishing MS from NMOSD and MOGAD. The latter are characterized by a predominat Th2 and Th17 involvement.

- CSF IL-6 may be a short term prognistic biomarker in AQP4-IgG NMOSD.

- Whilst cytokines are unable to differentiate MOGAD and NMOSD, HERV-w is able to discriminate between these two conditions.

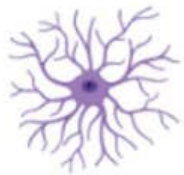
Antibody titers

- Monitoring antibody titers may be an useful MOGAD, but not in AQP4-IgG NMOSD.

- Seronegative conversion or lowering titers are associated with monophasic disease course in MOGAD.

- CSF testing for MOG-IgG is useful in seronegative cases, for diagnostic purposes.

Markers of neuronal and astroglial damage



- The improvement in assays have allowed the detection of these biomarker in sera, deeply reshaping their use in clinical practice.

- GFAP is the most promising biomarker in NMOSD and it is associated with disability and relapses, and it may predict treatment response.

- The role of other biomarkers (NfL, NfH, S100B, tau) in NMOSD and MOGAD still requires evidence and should be aim of further studies.

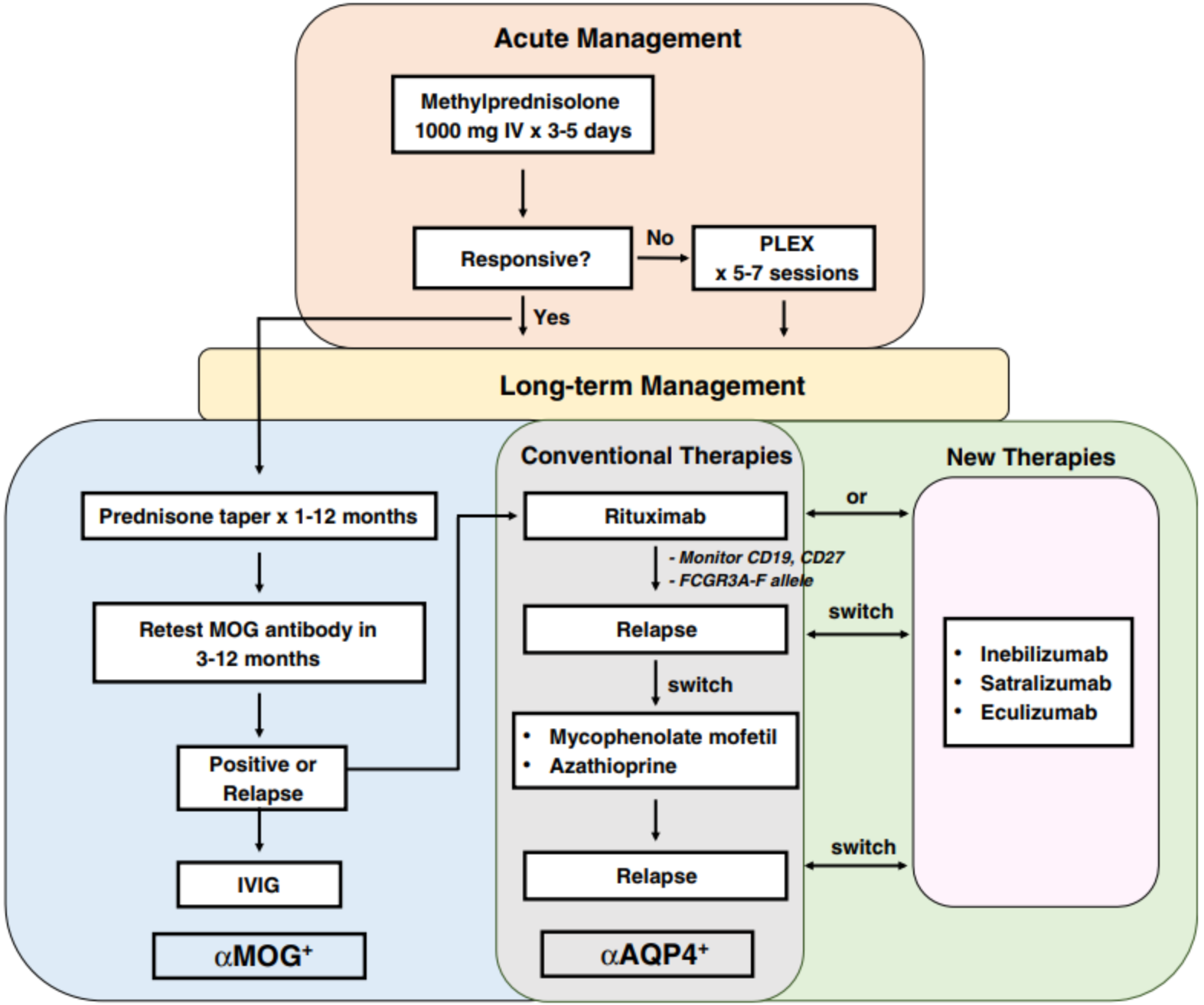
Complement factors

- Complement factors may help to distinguish MS from NMOSD and MOGAD, and may be associated with clinical features, however evidence is still uncompelling.

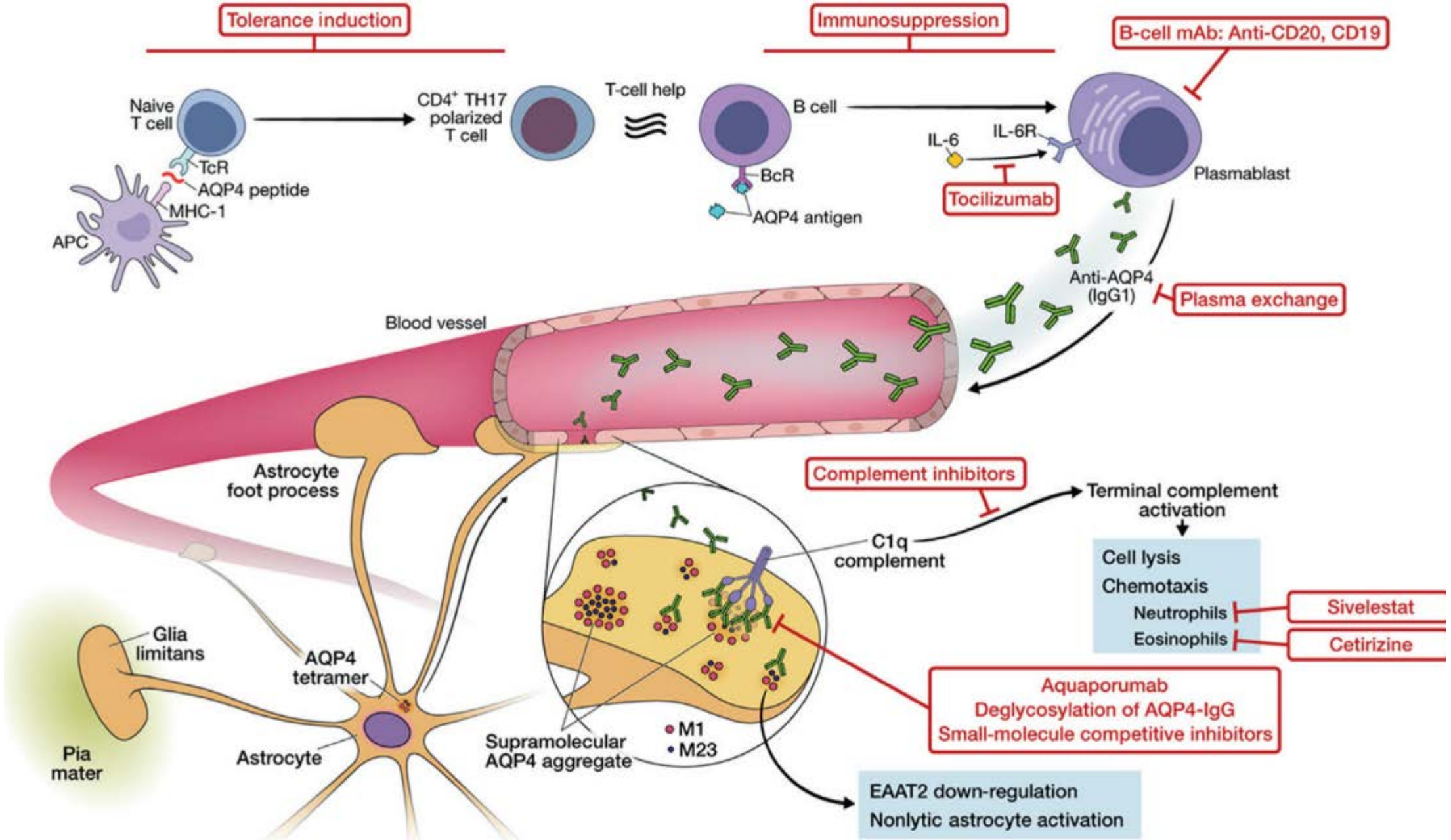
- Despite the lack of a clear role as biomarker, complement has paramount importance in terms of pathogenesis and treatment of these conditions.

- Evidence does not support monitoring in AQP4-IgG in NMOSD
- Complement proteins support the use of complement-directed therapies, but their role as biomarkers has yet to be defined
- Evidence does not support monitoring in AQP4-IgG in NMOSD
- Serum levels of GFAP have a strong association with AQP4-IgG NMOSD disease course

Dinoto A, Sechi E, Flanagan EP, Ferrari S, Solla P, Mariotto S, et al. Serum and Cerebrospinal Fluid Biomarkers in Neuromyelitis Optica Spectrum Disorder and Myelin Oligodendrocyte Glycoprotein Associated Disease. Front Neurol. 2022;13:866824.



Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021;18(1):208.



Weinshenker BG, Wingerchuk DM. Neuromyelitis Spectrum Disorders. Mayo Clinic Proceedings. 2017;92(4):663-79

Pathogenic step	Treatment strategy	Treatment	Current status
T-cell activation	Immunosuppression	Various (corticosteroids, azathioprine, mycophenolate)	Current maintstay of therapy
	Immune tolerance	Various (vaccination to antigen, autoreactive T cells or dendritic cells; oral tolerization; induction of Treg or Breg cells)	In development
TH17 polarization	mAb to cytokines involved in TH17 polarization or to TH17 surface markers	Various	In development
B cell/plasmablast	Anti–B-cell mAb	Anti–CD20 mAb (rituximab)	Current mainstay of therapy
		Anti–CD19 mAb	Phase 3 clinical trial
	Inhibition of B-cell survival	Anti–IL-6 receptor mAb: tocilizumab	Phase I clinical trials
		SA237	Phase 3 clinical trials
Blood-brain barrier permeability	Vascular endothelial growth factor inhibition	Bevacizumab	Phase I clinical trial
AQP4-IgG	Bulk removal	Plasma exchange	Current mainstay of therapy
	Protective inactive AQP4-reactive antibody or generation thereof	Generation of human anti–AQP4 mAb with Fc modifications incapable of complement activation or cell-mediated cytotoxicity	Preclinical work in tissue slice and animal models
Complement-mediated cyototoxicity	Inhibition of complement pathways	Eculizumab	Phase I trial completed; phase 3 study in progress
		C1 esterase inhibitor	Phase I trial completed
Neutrophil cytotoxicity	Inhibition of neutrophil function/products	Sivelestat	Preclinical work in tissue slice and animal models
Eosinophil cytotoxicity	Inhibition of eosinophil function/products	Cetirizine	Preclinical work and phase I clinical trial

Weinshenker BG, Wingerchuk DM. Neuromyelitis Spectrum Disorders. Mayo Clinic Proceedings. 2017;92(4):663-79

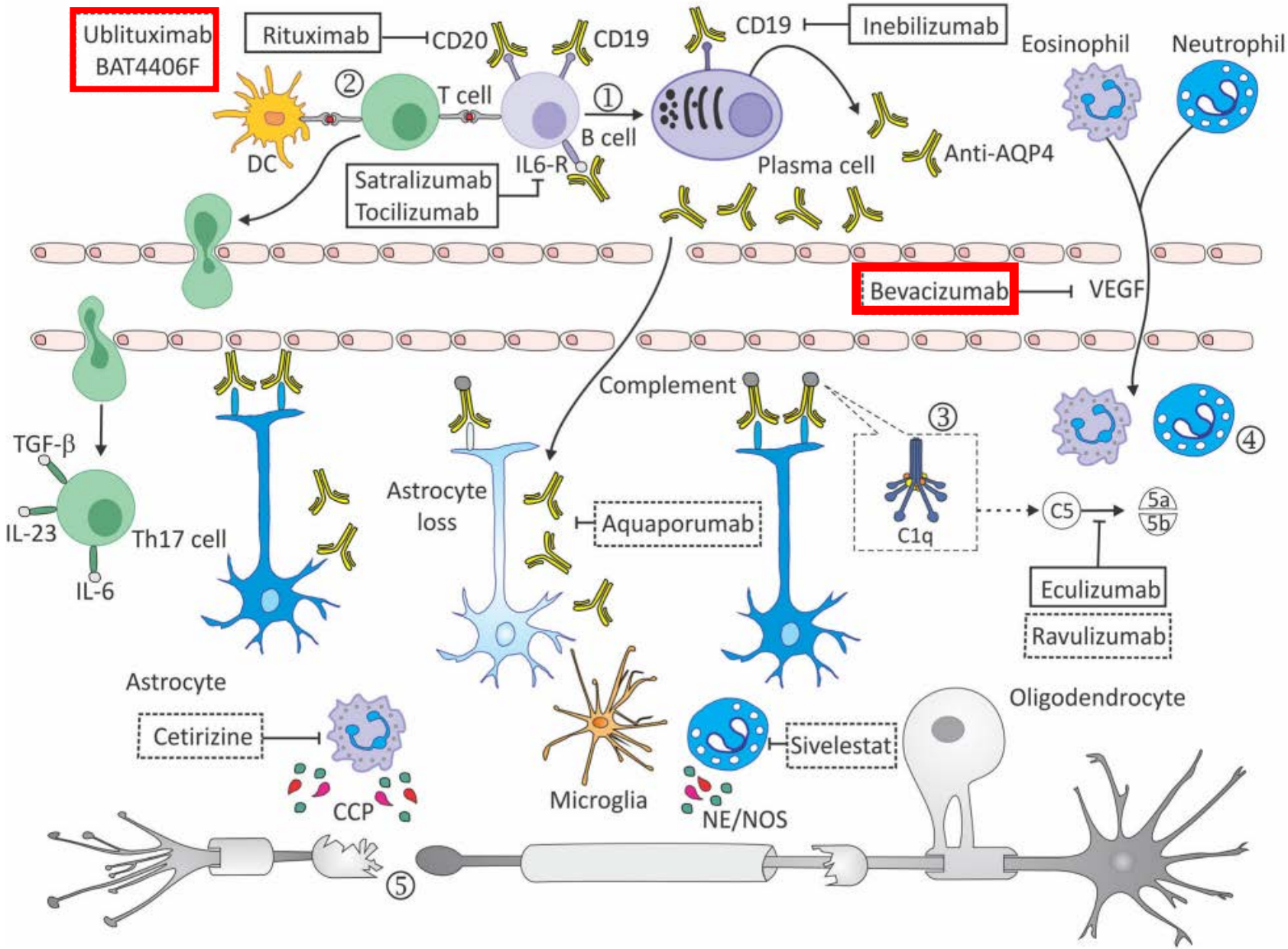
Drug	Target dose	Route	Pretreatment tests and monitoring	Adverse effects	Comment
First-line therapies					
Azathioprine	2.5-3.0 mg/kg daily	Oral	Pretreatment: Avoid if TMPT deficient. CBC with differential and LFTs During treatment: Monthly CBC and LFTs for 6 mo, then twice yearly. Reduce dose if WBC $<3.0 \times 10^9$/L or ANC $<1.0 \times 10^9$/L	Gastrointestinal symptoms, hypersensitivity reaction, excessive bone marrow suppression, hepatotoxicity, malignancy (long-term use), particularly lymphoma	Latency to full biological effect is 4-6 mo; therefore, immunosuppressive bridge required, typically with oral prednisone (see entry for prednisone in this Table). Drug effect can be demonstrated through increase of MCV by >5 points from baseline
Mycophenolate mofetil	750-1500 mg twice a day	Oral	Pretreatment: CBC with differential and LFTs. During treatment: Monthly CBC and LFTs for 6 mo, then twice yearly. Reduce dose if WBC $<3.0 \times 10^9$/L or ANC $<1.0 \times 10^9$ /L.	Gastrointestinal symptoms, excessive bone marrow suppression, teratogenicity	Latency to full biological effect is 4-6 mo; therefore, immunosuppressive bridge required, typically with oral prednisone (see below)
Prednisone	30-60 mg/d initial dose	Oral	Pretreatment: Fasting blood sugar During treatment: Periodic check of fasting blood sugar, electrolytes, blood pressure	Hyperglycemia, hypertension, gastric irritation, fluid retention/weight gain	Stable dose of at least 30 mg/d used until azathioprine or mycophenolate fully effective; then taper gradually over 6 mo
Rituximab	Typical course: 1000 mg given twice, 14 d apart. Each 2-treatment course may be administered (1) every 6 mo or (2) based on reemergence of $CD19^+$ B cells	IV	Pretreatment: CBC with differential, LFTs, hepatitis B serology During treatment: CBC with differential, LFTs before each course. Monthly flow cytometry for $CD19^+$ cells if redosing based on cell depletion. Check immunoglobulins annually	Infusion reactions, hepatitis B reactivation, skin reactions	With first course, consider use of oral prednisone, 30 mg/d, starting before treatment and continuing until 2-4 wk after second infusion. To plan retreatment based on B-cell depletion, monitor $CD19^+$ counts with flow cytometry monthly. Initiate next course when $CD19^+$ count $\geq$1% of total lymphocytes

Weinshenker BG, Wingerchuk DM. Neuromyelitis Spectrum Disorders. Mayo Clinic Proceedings. 2017;92(4):663-79

Update Treatment of NMOSD

- Acute treatment
  - IVMP
  - PLEX 1-1.5 plasma volume (Replacement fluid 50-55 ml/kg/cycle, albumin)
  - IVIG
- Long-term treatment
    - FDA-approved treatment for AQP4 – IgG positive
    - Eculizumab (Soliris®)
    - Satralizumab (Ensyprng®)
    - Inebilizumab (Uplinza®)
  - Not FDA approved
    - Rituximab
    - Azathioprine, Mycophenolate Mofetil, Rituximab, Tocilizumab

Acute treatment future era



Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021;18(1):208.

Acute treatment: future era

Drug/Dose/Route of administration	
Bevacizumab [90] intravenous infusion 10 mg/kg intravenous infusion at onset of exacerbation and, if needed, a second time during the plasma exchange phase	Bevacizumab directly binds vascular endothelial growth factor (VEGF) to inhibit angiogenesis
Ublituximab [91, 92] Intravenous 450 mg once on day 1, plus steroids 1000 mg intravenously daily on days 1–5	Ublituximab is a monoclonal antibody that specifically binds to the transmembrane antigen CD20. Binding induces an immune response that causes lysis of B cells.
NPB-01 (NCT01845584) Intravenous immunoglobulin 400 mg/kg/day for five consecutive days	IgG can inactivate auto-reactive T-cells by competing for, and interrupting their interaction with, antigen presenting cells [87, 88].
HBM 9161 (NCT04227470) injection, 340 mg or 680 mg weekly administered subcutaneously for a period of 4 weeks.	HBM9161(HL161BKN) is a human monoclonal antibody. HBM9161 targets FcRn by blocking the FcRn IgG-Fc binding site and accelerating the degradation of IgG, reducing total IgG level in blood (including pathological IgG). The serum AQP4-IgG associated with NMOSD is a pathological IgG, so the combination of standard of care which is intravenous methylprednisolone with HBM9161 is expected to rapidly reduce AQP4-IgG levels.

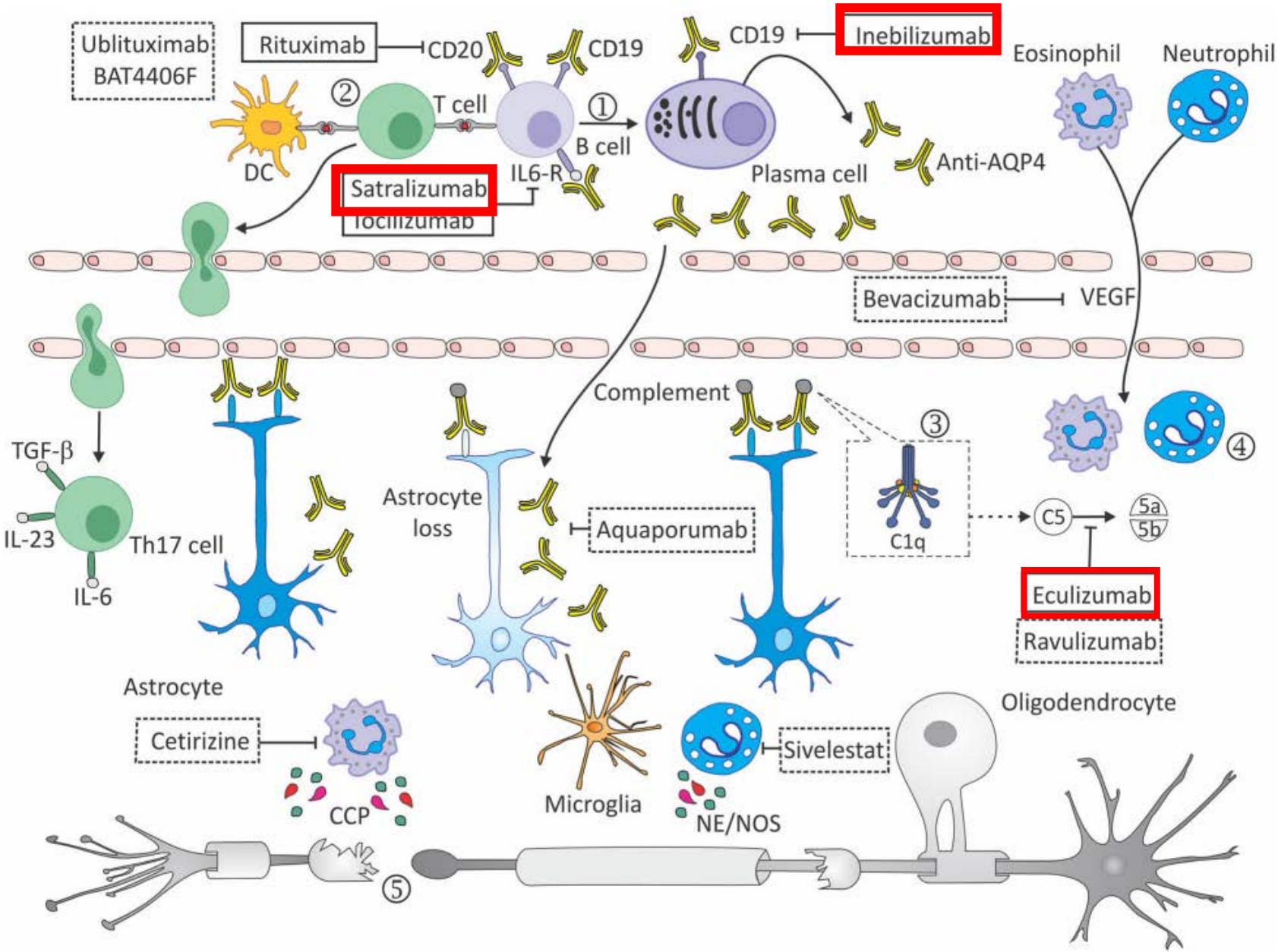
Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021;18(1):208.

Acute treatment: future era

Drug	Study design	Study phase / ClinicalTrials.gov Identifier(status 01/ 2021)	Number of patients (randomization)	NMOSD serostatus	Follow-up	Disability (EDSS stabilization or improvement)	Safety concerns
Bevacizumab	Single-center, Open Label Trial (USA)	Phase 1 add-on therapy (completed) NCT01777412	10	AQP4-ab + (n = 6) and – (n = 4)	91 days after admission	at baseline: 3.5 (2–7) at FU: 3 (1.75–6.5)	UTI that required hospitalization and improved with specific Tx
Ublituximab	Single-center, Open Label Trial (USA)	Phase 1 add-on therapy (completed) NCT02276963	6 (5 completed the study)	AQP4-ab +	90 days after admission	at baseline: 6.5 (5.25-7.5) at FU (n = 3): 4 (2–8)	Leukopenia (n = 1) headache and body ache (n = 3)
NPB-01	Single-center, Open Label Trial (Japan)	Phase 2 add-on therapy (completed) NCT01845584	7	AQP4-ab +	Time frame: 29 days	NA	NA
HBM 9161	Non-randomized, open label, dose exploration study (China)	Phase 3 study (Active, recruiting) NCT04227470	12 (estimated enrollment)	AQP4-ab +	Time frame: 189 days	NA	NA
Immunoadsorption or Plasma Exchange	Prospective, Multicenter, Single-blind, Randomized study (China)	Phase 2 study (not yet recruiting) NCT04064944	144 (estimated enrollment)	AQP4-ab +	Time frame: 4 weeks after the last treatment	NA	NA

Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021;18(1):208.

Long-term Treatment FDA Approved



Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021;18(1):208.

Rituximab- RIN-1

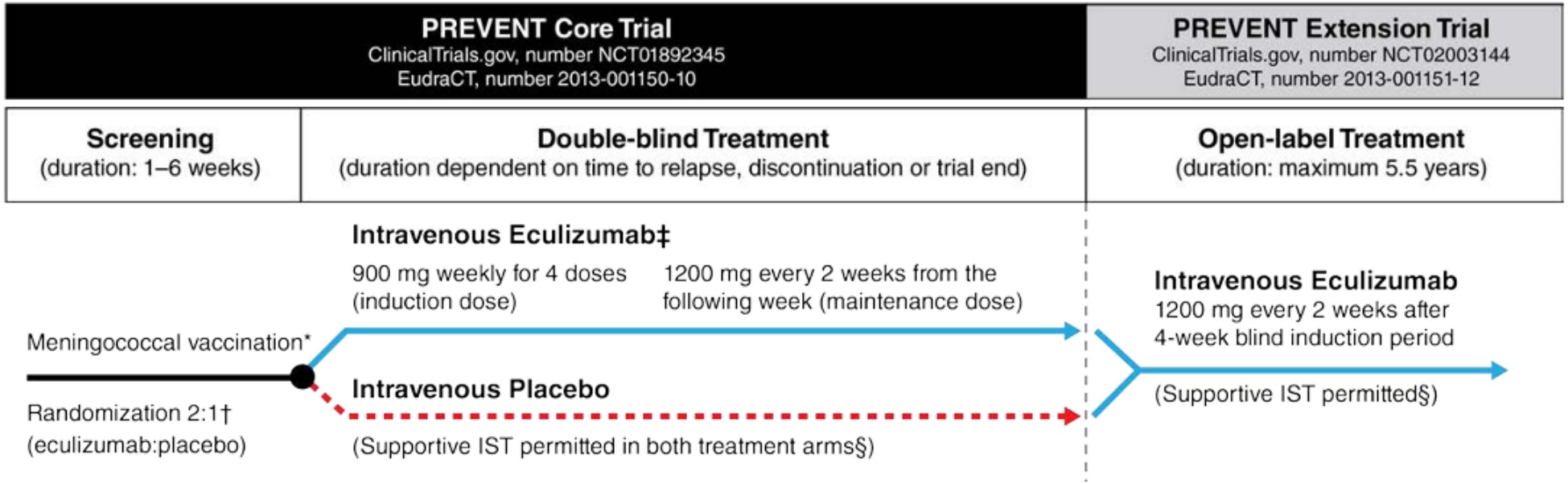
- a multicenter, 1:1 randomized, double-blind, placebo-controlled clinical trial of rituximab for AQP4-IgG+ NMOSD
- Eight hospitals in Japan (72 weeks)
- N = 38
- 375mg/m2 of rituximab weekly for 4 weeks followed by two 1,000 mg infusions 2 weeks apart at 6-monthly intervals
- All patients received a fixed dose of oral steroids (5–30mg of prednisolone) for 8 weeks from randomization and reduced by 10% at each visit to 2 mg daily
- Primary endpoint: time to first relapse
    - 37% on placebo relapse vs 0 % on rituximab
- Adverse event: no PML report, infusion reaction, risk hypogammaglobulinemia

Pittock SJ, Zekeridou A, Weinshenker BG. Hope for patients with neuromyelitis optica spectrum disorders — from mechanisms to trials. Nature Reviews Neurology. 2021;17(12):759-73.

Eculizumab - PREVENT

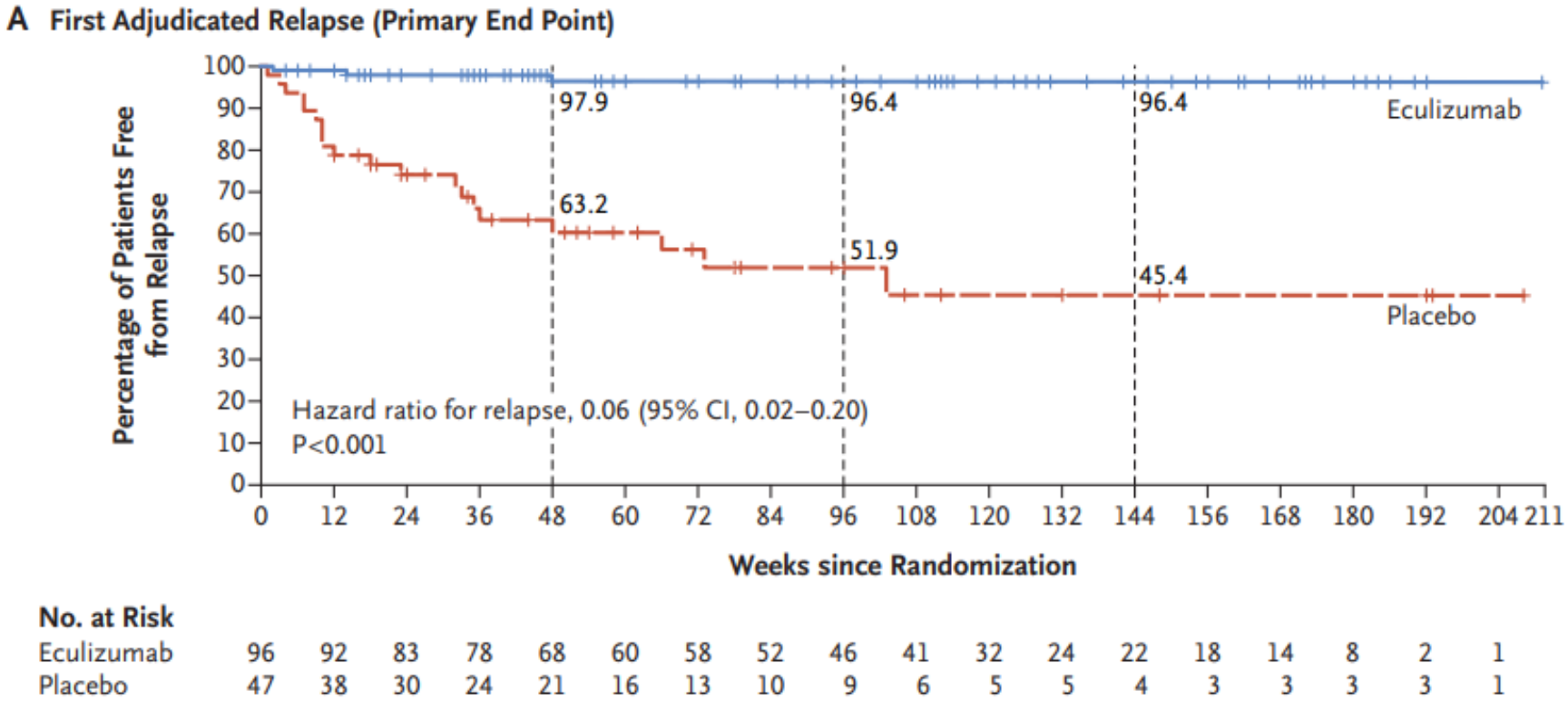
- Approved for atypical HUS
- **First FDA-approved therapy for AQP4 positive NMOSD (2019)**- US, EU, Japan
- Inhibit C5 cleavage to C5a and C5b → prevent MAC formation

- Phase 3, randomized, double-blind, placebo-controlled, time-to-event trial
- April 2014 – October 2017
- Primary endpoint = first adjudicated relapse
- Secondary endpoint = ARR, QOL, EDSS
- SE: meningococcal infection*, encapsulated bacteria



Pittock SJ, Berthele A, Fujihara K, Kim HJ, Levy M, Palace J, et al. Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. New England Journal of Medicine. 2019;381(7):614-25

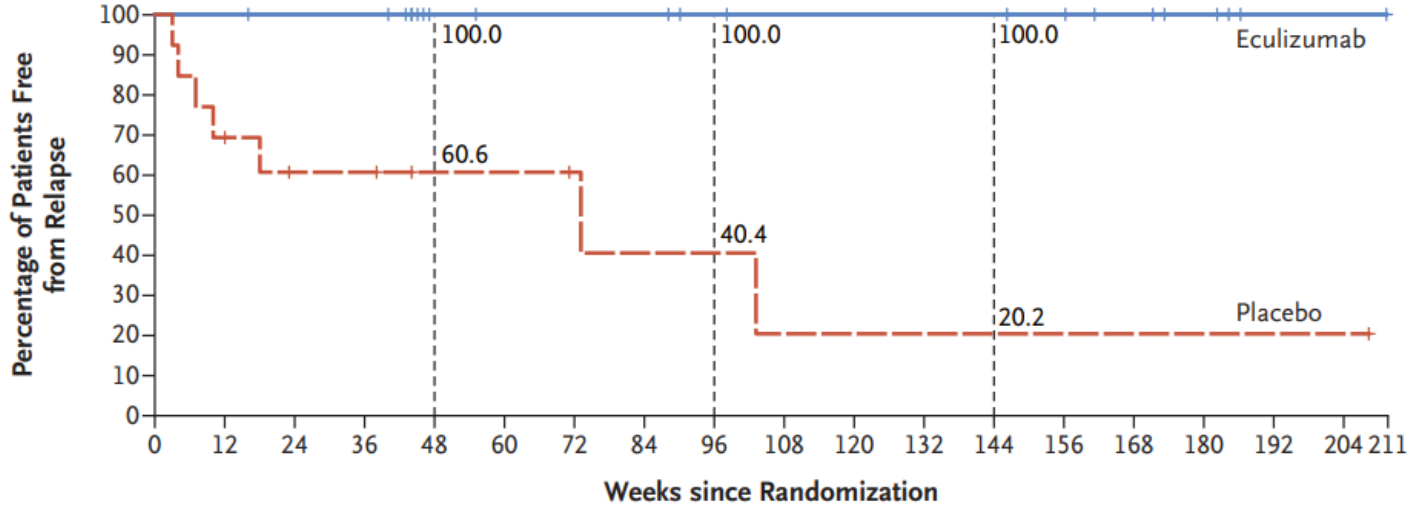
Eculizumab - PREVENT



- Eculizumab reduce percentage of patients who have relapse 94%, and reduce ARR 96% (Compare to placebo)
- EDSS reduced but not significant compare to placebo
- Included only AQP4-IgG positive patients

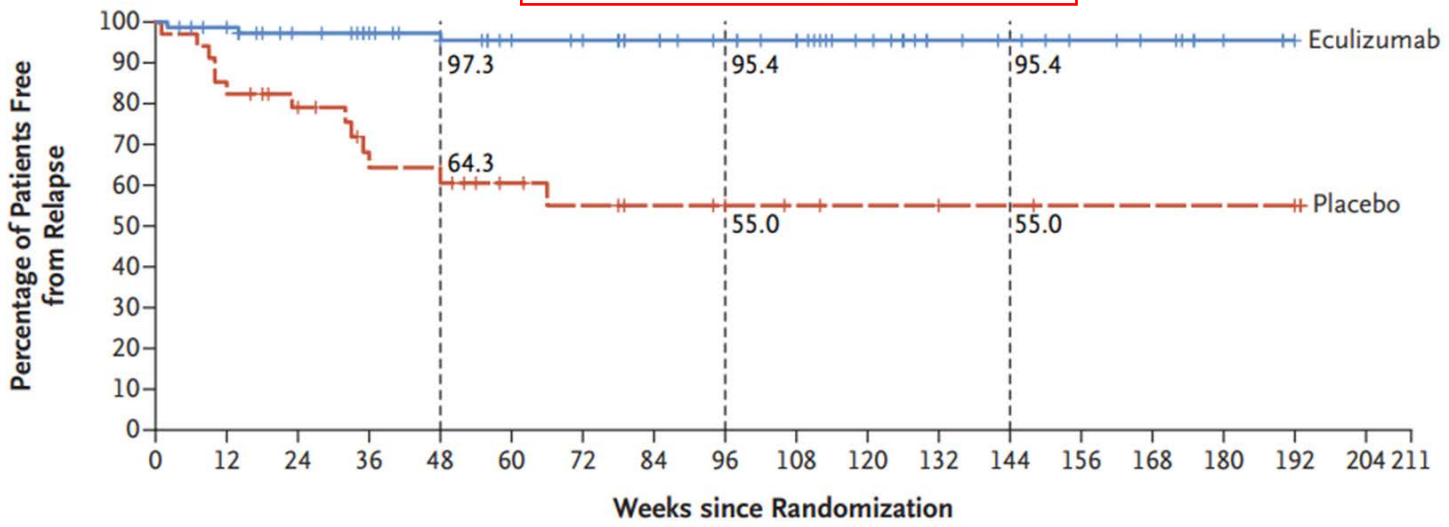
Pittock SJ, Berthele A, Fujihara K, Kim HJ, Levy M, Palace J, et al. Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. New England Journal of Medicine. 2019;381(7):614-25

B First Adjudicated Relapse in Patients Not Receiving Concomitant Immunosuppressive Therapy



No. at Risk																		
Eculizumab	21	21	20	20	14	13	13	13	11	9	9	9	9	8	6	4	1	1
Placebo	13	9	6	6	4	4	3	2	2	1	1	1	1	1	1	1	1	1

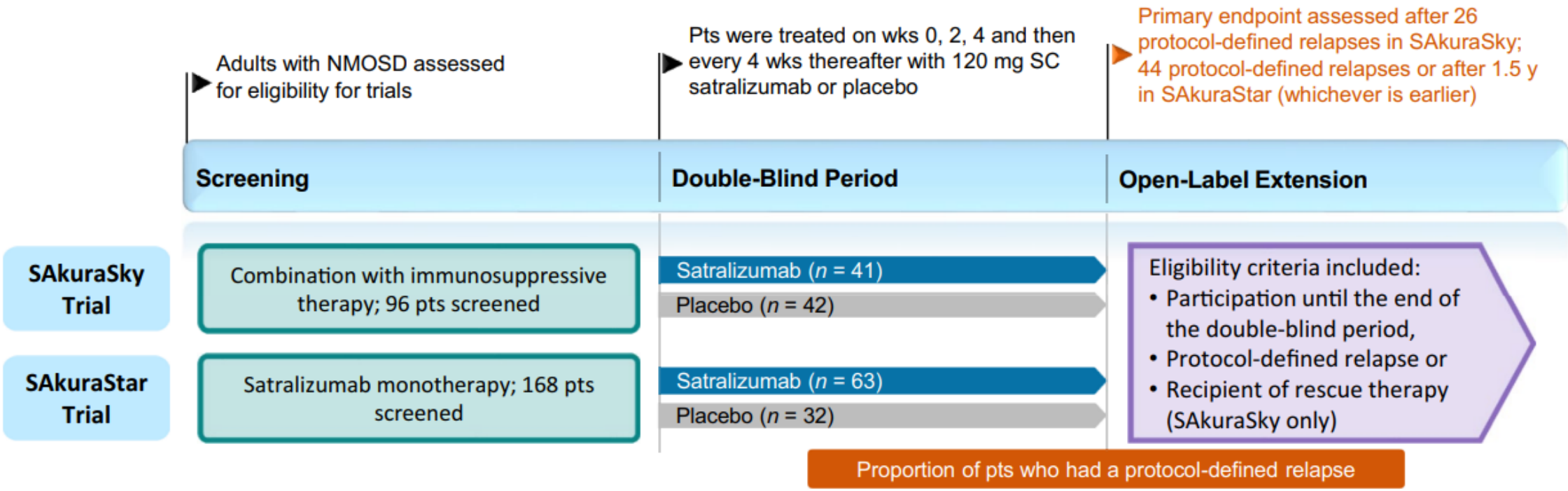
C First Adjudicated Relapse in Patients Receiving Concomitant Immunosuppressive Therapy



No. at Risk																		
Eculizumab	75	71	63	58	54	47	45	39	35	32	23	15	13	10	8	4	1	
Placebo	34	29	24	18	17	12	10	8	7	5	4	4	3	2	2	2	2	

Pittock SJ, Berthele A, Fujihara K, Kim HJ, Levy M, Palace J, et al. Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. New England Journal of Medicine. 2019;381(7):614-25

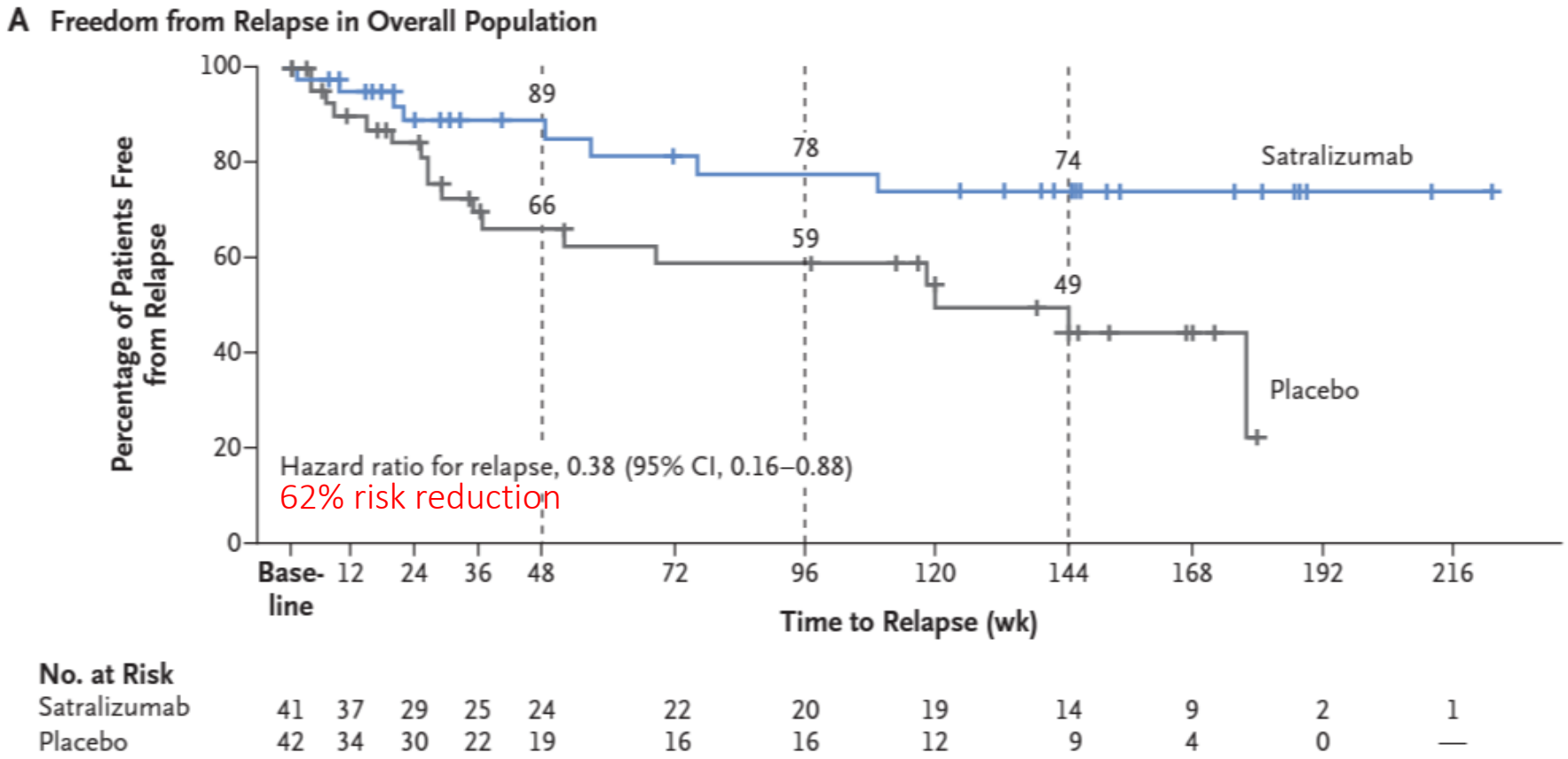
Satralizumab



- Humanized IgG2 targets IL-6 receptor → block IL-6 receptor → decrease B-cell proliferation
- Enhancement design to dissociate from Ag in pH-dependent manner to release into blood stream and bind to Ag again → prolong half life
- **Included seronegative and seropositive NMOSD**

Yamamura T, Kleiter I, Fujihara K, Palace J, Greenberg B, Zakrzewska-Pniewska B, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381(22):2114-24.

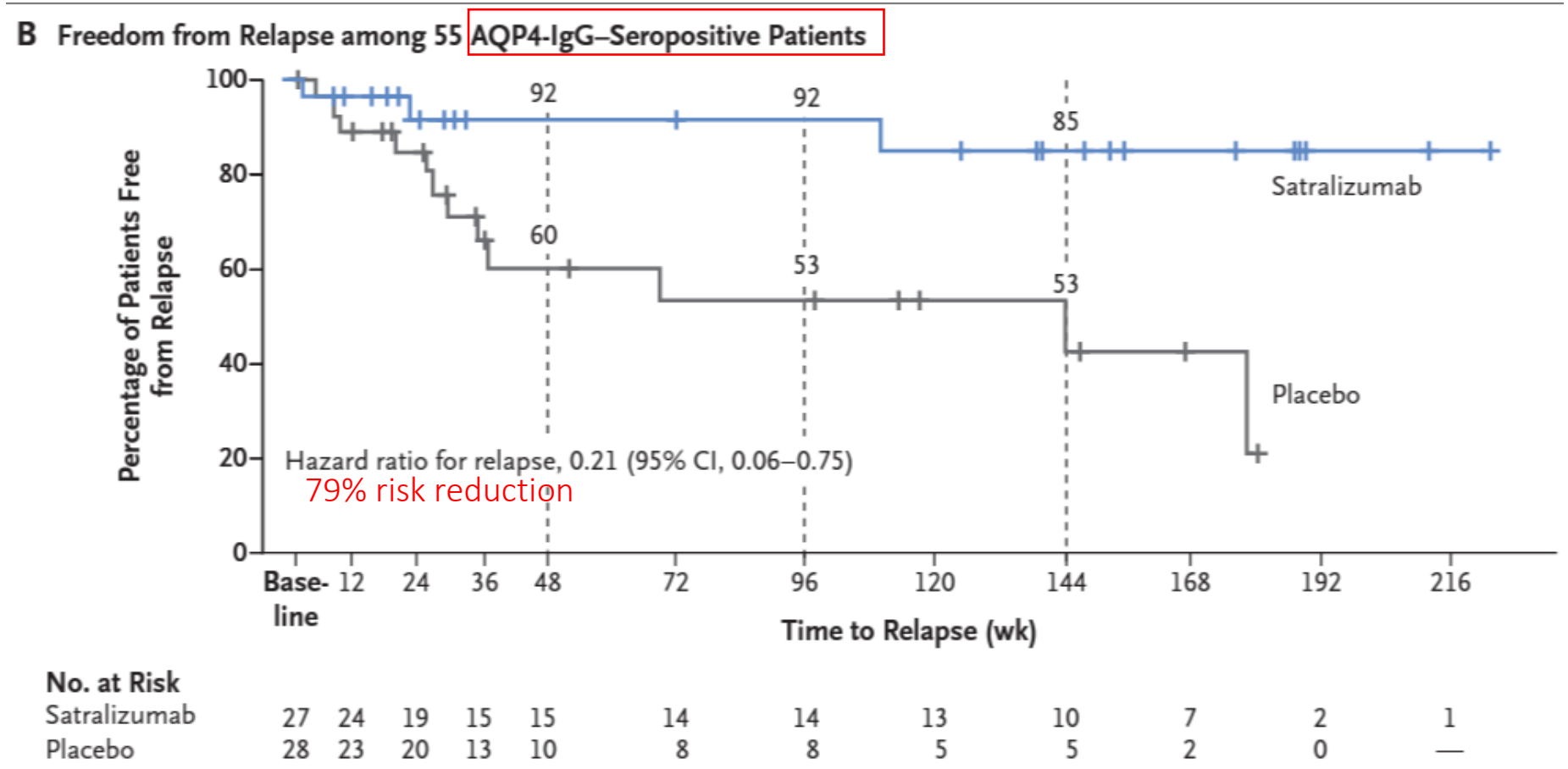
Satralizumab - SAkuraSky



- Phase III, randomized double-blind, placebo-controlled, time to event trial
- 44 sites, 13 countries
- Primary endpoint = adjudicated relapse

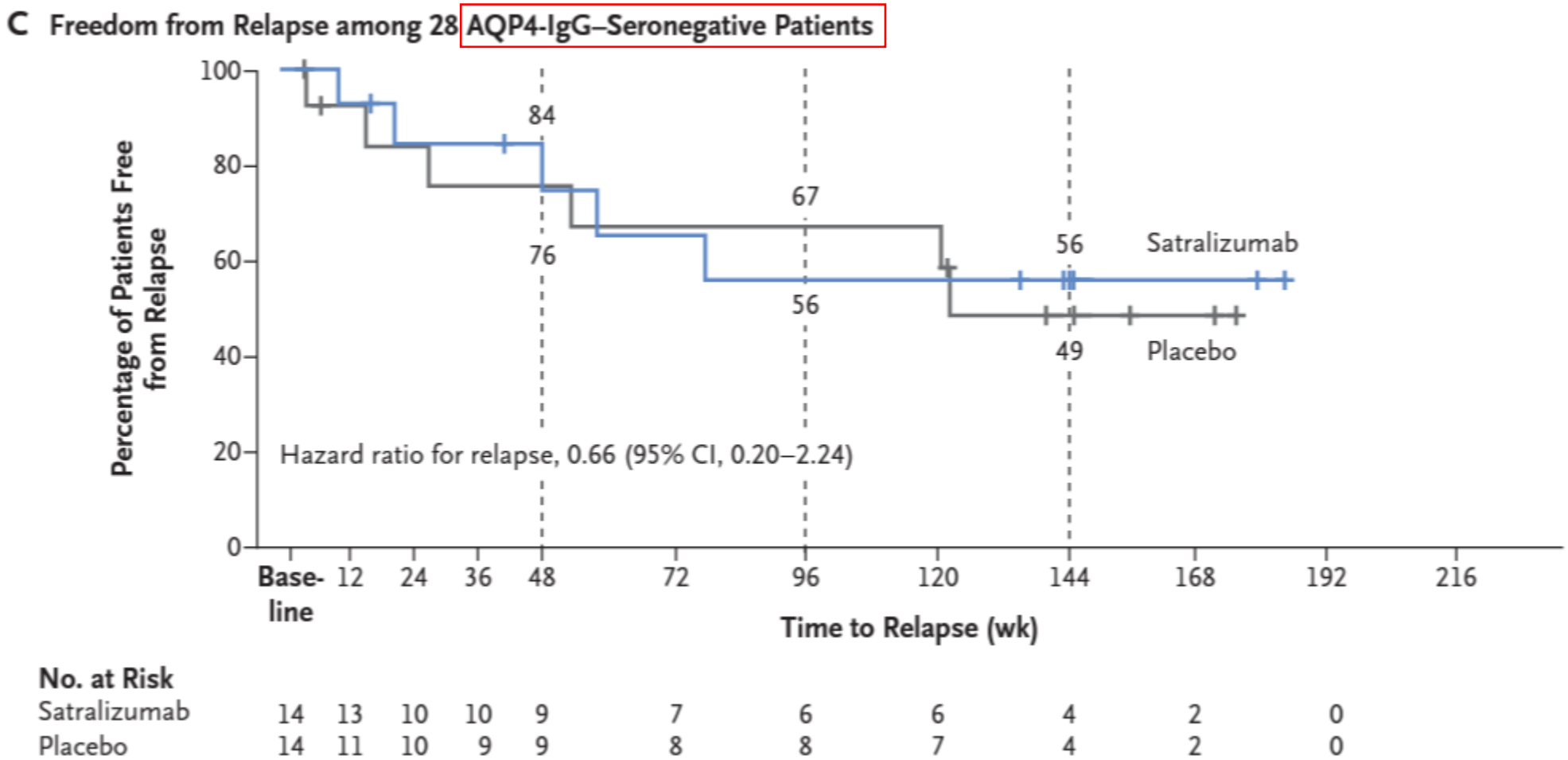
Yamamura T, Kleiter I, Fujihara K, Palace J, Greenberg B, Zakrzewska-Pniewska B, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381(22):2114-24.

Satralizumab - SAkuraSky



Yamamura T, Kleiter I, Fujihara K, Palace J, Greenberg B, Zakrzewska-Pniewska B, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381(22):2114-24.

Satralizumab - SAkuraSky



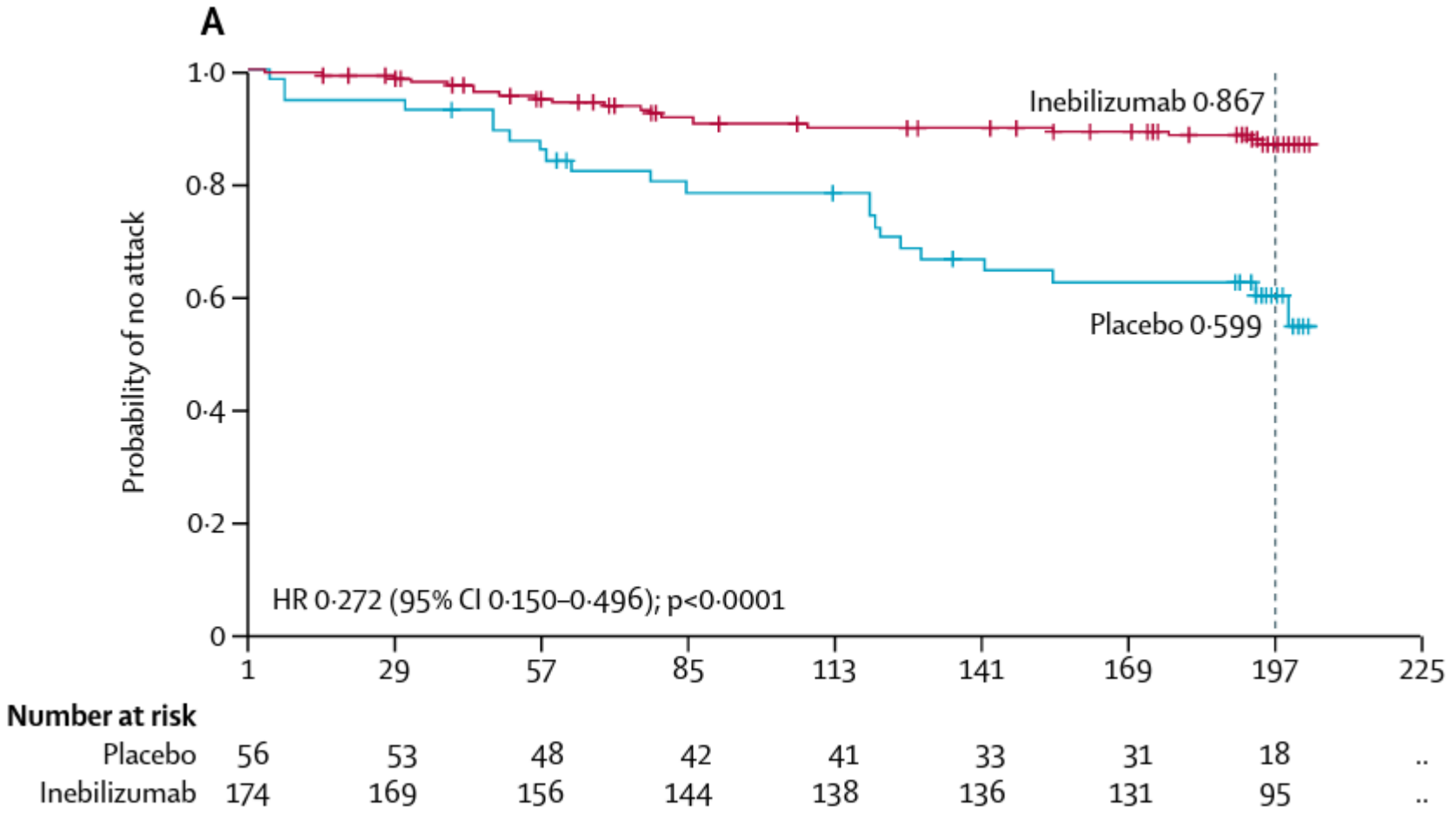
Yamamura T, Kleiter I, Fujihara K, Palace J, Greenberg B, Zakrzewska-Pniewska B, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381(22):2114-24.

Inebilizumab N-Momentum

- Humanized, affinity-optimized, afucosylated IgG1 kappa mAB
- Target B cell surface CD19 at pro-B-cell and pre-B-cell
- Double-blind, randomized placebo-controlled phase II/III with an open-label extension period
- 99 sites, 24 countries, Randomized 3: 1 (drug: placebo), 293 patients
- Dose: 300 mg IV d1 and d15 q 6 months
- All participant received prednisolone 20 mg/day, day 1-14 then tapered to day 21 (prevent an attack during the induction period)
- Primary endpoint = time (days) to the onset of NMOSD attack
- Secondary endpoint = Worsening EDSS from baseline, change from baseline in low-contrast VA binocular score, the cumulative number of active MRI lesions, number of NMOSD-related hospitalization

Cree BAC, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk DM, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet. 2019;394(10206):1352-63

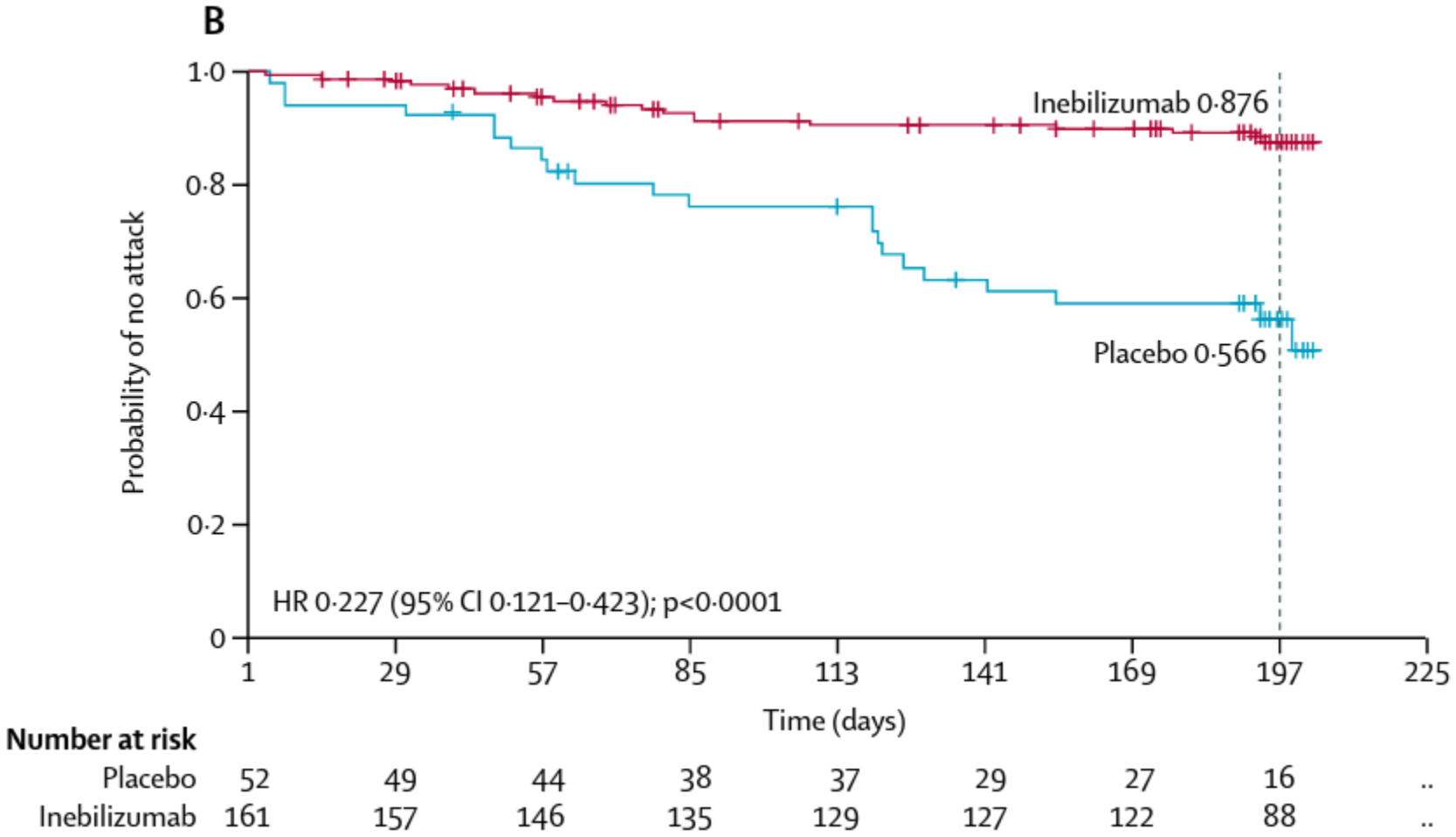
Inebilizumab N-MOmentum



- Overall population
- NMOSD attacks
- Inebilizumab 21/174 (12.1 %)
- Placebo 22/58 (39.3%)
- 73 % risk reduction
- HR 0.272 (p < 0.0001)
- NNT at day 197 = 3.73

Cree BAC, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk DM, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet. 2019;394(10206):1352-63

Inebilizumab N-MOmentum



- **AQP4- IgG seropositive population**
- NMOSD attacks
- Inebilizumab 18/161 (11.2%)
- Placebo 2/52 (42.3%)
- 77 % risk reduction
- HR 0.227 ($p < 0.0001$)
- NNT at day 197 = 3.23

Cree BAC, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk DM, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet. 2019;394(10206):1352-63

Inebilizumab N-MOmentum

- Pharmacodynamic effect on CD20 was observed within 4 weeks
- 3% found anti – inebiizumab, but no effect on pharmacokinetic and dynamic
- Side effects
  - Similar frequency of adverse events as placebo
  - Infusion- related reaction , UTI, arthralgia, back pain, headache, eye pain
  - Serious side effect (1%)
    - Atypical pneumonia, 3rd degree burn, acute cholangitis, acute cholecystitis, LFT elevated

Cree BAC, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk DM, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet. 2019;394(10206):1352-63

	PREVENT (eculizumab)[15]	SAkuraSky[17] and SAkuraStar[16] (satralizumab)	N-Momentum (inebilizumab)[37]
Immunological target	Complement component 5	Interleukin-6 receptor	CD19 B-cell marker
Trial design*	Phase 3 trial of eculizumab with immunosuppressive therapy *vs* placebo with immunosuppressive therapy	Phase 3 trials of satralizumab with immunosuppressive therapy *vs* placebo with immunosuppressive therapy (SAkuraSky) or satralizumab alone *vs* placebo alone (SAkuraStar)	Phase 2/3 trial of inebilizumab *vs* placebo
Background immunotherapy	Background immunotherapy was permitted	SAkuraSky: background therapy was necessary SAkuraStar: no background immunotherapy	No background immunotherapy
Aquaporin-4 serostatus	Aquaporin-4-IgG seropositive only	Aquaporin-4-IgG seropositive or seronegative	Aquaporin-4-IgG seropositive or seronegative
Relapse history	At least two relapses in previous year, or at least three relapses in previous 2 years with at least one in previous year	SAkuraSky: at least two relapses in previous 2 years and at least one relapse in previous year; SAkuraStar: at least one relapse in previous year	At least two relapses in previous 2 years and at least one relapse in previous year
Previous rituximab	Yes, but not within 3 months before baseline	Yes, but not within 6 months before baseline	Yes, but not within 6 months before baseline or B cells below lower limit of normal†
Primary endpoint	Time to event (relapse)	Time to event (relapse)	Time to event (relapse)
Event (relapse) definition	New or worsening symptoms persisting for 24 h not attributable to another cause; relapses were classified as minor or major using Opticospinal Impairment Score	New or worsening symptoms persisting for 24 h and meeting any one of four EDSS or Functional System Score thresholds	Report of neurological symptoms attributable to NMOSD, meeting a set of criteria specific for the area of involvement (eg, optic neuritis, transverse neuritis, brain)
Adjudication committee for assessment of primary outcome	Not in original design; protocol amended after enrollment of 88 patients; 21 relapses occurred before amendment	Yes	Yes
Secondary endpoints	ARR, EDSS, modified Rankin Scale, Hauser Ambulation Index, EQ-5D-3L	Pain (VAS), fatigue (FACIT), SF-36, EQ-5D, timed 25-foot walk, percentage of relapse-free patients, ARR, modified Rankin Scale, Zarit Burden Interview, EDSS, visual acuity	EDSS, incidence of new MRI lesions, disease-related admissions to hospital, visual acuity
EDSS at baseline	≤7·0	≤6·5	≤8·0
Maintenance	Intravenous every 2 weeks	Subcutaneous every 4 weeks	Intravenous every 6 months
Age	≥18 years	12–74 years	≥18 years

Levy M, Fujihara K, Palace J. New therapies for neuromyelitis optica spectrum disorder. Lancet Neurol 2021;20(1):60-7

	PREVENT (eculizumab)[35]		SAkuraSky (satralizumab)[17]		SAkuraStar (satralizumab)[16]		N-Momentum (inebilizumab)[37]	
	Placebo with or without IST (n=47)	Eculizumab with or without IST (n=96)	Placebo with or without IST (n=42)	Satralizumab with or without IST (n=41)	Placebo (n=32)	Satralizumab (n=63)	Placebo (n=56)	Inebilizumab (n=174)
Aquaporin-4-IgG seropositive, n (%)	47 (100%)	96 (100%)	28 (67%)	27 (66%)	23 (72%)	41 (65%)	52 (91%)	161 (91%)
Female, n (%)	42 (89%)	88 (92%)	40 (95%)	37 (90%)	31 (97%)	46 (73%)	50 (89%)	159 (91%)
Age, mean years (SD)	45 (13)	44 (13)	43 (12)	41 (16)	41 (11)	45 (12)	43 (14)	43 (12)
Age at initial clinical presentation, mean years (SD)	39 (15)	36 (14)	39 (12)	35 (17)	39 (13)	36 (11)	Not reported	Not reported
Baseline EDSS	4·0 (1·0–7·0)*	4·0 (1·0–6·5)*	3·6 (1·3)†	3·8 (1·6)†	3·6 (1·6)†	3·9 (1·2)†	4·0*	3·5*
Discontinuation rate, n (%)	3 (6%)	16 (17%)	10 (24%)	3 (7%)	4 (12%)	7 (11%)	2 (4%)	6 (4%)
Baseline ARR in previous 2 years, mean (SD)	2·1 (1·0)	1·9 (0·9)	1·4 (0·5)	1·5 (0·5)	1·4 (0·6)	1·5 (0·7)	1·6 (1·5)	1·7 (1·5)
Background immunotherapy, n (%)	None: 13 (28%); Corticosteroids: 11 (23%); Azathioprine with or without corticosteroids: 13 (28%); Mycophenolate mofetil with or without corticosteroids: 8 (17%); Other with or without corticosteroids: 2 (4%)	None: 21 (22%); Corticosteroids: 16 (17%); Azathioprine with or without corticosteroids: 37 (39%); Mycophenolate mofetil with or without corticosteroids: 17 (18%); Other with or without corticosteroids: 5 (5%)	Corticosteroids: 20 (48%); Azathioprine: 13 (31%); Mycophenolate mofetil: 8 (19%); Mycophenolate mofetil with corticosteroids: 1 (2%)	Corticosteroids: 17 (41%); Azathioprine: 16 (39%); Mycophenolate mofetil: 4 (10%); Azathioprine with corticosteroids: 3 (7%); Mycophenolate mofetil with corticosteroids: 1 (2%)	None: 32 (100%)	None: 63 (100%)	None: 56 (100%)	None: 174 (100%)

ARR=annualised relapse rate. EDSS=Expanded Disability Status Scale. IST=immunosuppressive therapy. *Median. †Mean.

Table 2: **Comparison of participants at baseline**

Levy M, Fujihara K, Palace J. New therapies for neuromyelitis optica spectrum disorder. Lancet Neurol. 2021;20(1):60-7.

Study	Population	Study arm	Percentage relapse free		Risk reduction (%)	Hazard ratio (95%CI, *P*)	Summary of secondary outcomes in total population
			48 weeks	96 weeks			
PREVENT[23]	Total	Placebo	63.2	51.9	94	0.06 (0.02–0.2, <0.001)	ARR 0.02 with drug, 0.35 with placebo; change in EDSS score 0.18 with drug, –0.12 with placebo; change in mRS –0.24 with drug, –0.09 with placebo
		Treatment	97.9	96.4			
SAkuraSky[24]	Total	Placebo	66.0	58.7	62	0.38 (0.16–0.75, 0.018)	ARR 0.11 with drug, 0.32 with placebo; change in EDSS score –0.1 with drug, –0.21 with placebo
		Treatment	88.9	77.6			
	AQP4-IgG+	Placebo	59.9	53.3	79	0.21 (0.06–0.75, NA)	
		Treatment	91.5	91.5			
SAkuraStar[25]	Total	Placebo	61.9	51.2	55	0.45 (0.23–0.89, 0.018)	No significant changes from baseline to week 24 in pain scores or fatigue scores
		Treatment	76.1	72.1			
	AQP4-IgG+	Placebo	55.4	41.1	74	0.26 (0.11–0.63, 0.001)	
		Treatment	82.9	76.5			
N-MOmentum[22]	Total	Placebo	60.7[a]	NA	73	0.27 (0.15–0.49, <0.0001)	EDSS score worsening 16% with drug, 34% with placebo; 43% fewer new MRI lesions with drug than with placebo; 71% fewer disease-related hospitalizations with drug than with placebo
		Treatment	87.9[a]	NA			
	AQP4-IgG+	Placebo	56.6[a]	NA	77	0.23 (0.12–0.42, <0.0001)	
		Treatment	87.6[a]	NA			
RIN-1 (REF.[26])	Total	Placebo	Numbers too small for accurate quantification				ARR 0.0 with drug, 0.32 with placebo
		Treatment	Group difference 36.8% (95% CI 12.3–65.5, log-rank *P* = 0.0058)				

NMOSD RCT

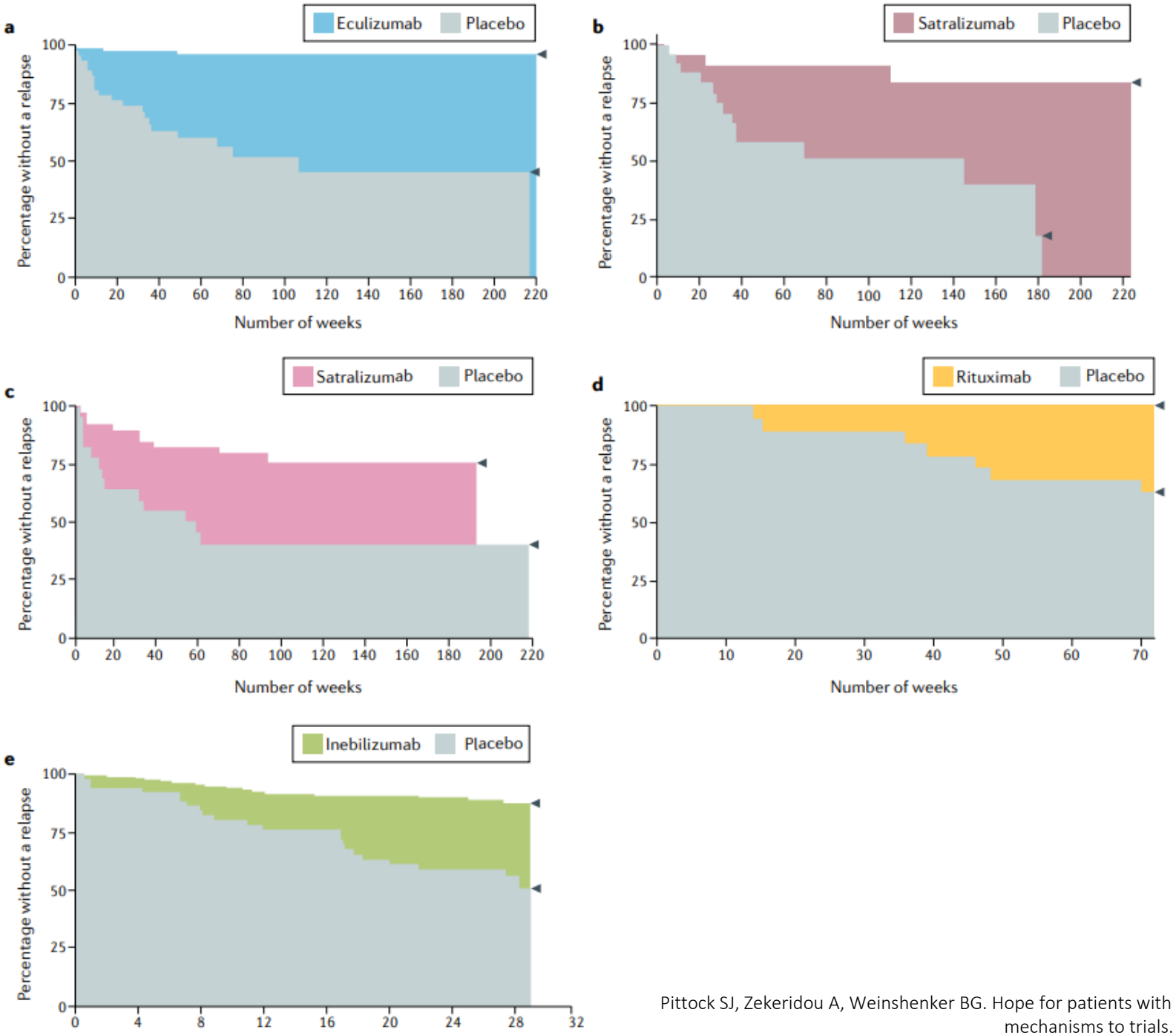
- The baseline characteristics of participants were similar across the five trials
- **AQP4-IgG positive is most benefit**
- No agent has been approved for AQP4-IgG– seronegative NMOSD
- For N-MOmentum, risk reductions were reported at 28 weeks, which is considerably earlier than in the other four trials
- N-MOmentum was the only trial in which a significant reduction was seen in the risk of disability worsening in indicated
- For RIN-1, the number of participants was too small to enable accurate quantification of risk reduction

Pittock SJ, Zekeridou A, Weinshenker BG. Hope for patients with neuromyelitis optica spectrum disorders — from mechanisms to trials. Nature Reviews Neurology. 2021;17(12):759-73.

Summary of Adverse Events

Study	Study arm	n	Total adverse events (%)	Serious adverse events (%)	No. of deaths in RCP	No. of deaths in OLP	Infections (%)	Injection/ infusion-related reactions (%)
PREVENT[23]	Placebo	47	91	28[a]	0	NR	NR	NR
	Treatment	96	92	26	1[b]		NR	NR
SAkuraSky[24]	Placebo	42	95	21	0	0	62	5
	Treatment	41	90	17	0		68	12
SAkuraStar[25]	Placebo	32	75	16	0	0	44	16
	Treatment	63	92	19	0		54	13
N-MOmentum[22]	Placebo	56	73	9	0	2[c]	41	11
	Treatment	174	72	5	0		38	9
RIN-1 (REF.[26])	Placebo	19	90	21	0	NR	NR	0
	Treatment	19	90	21	0		NR	37

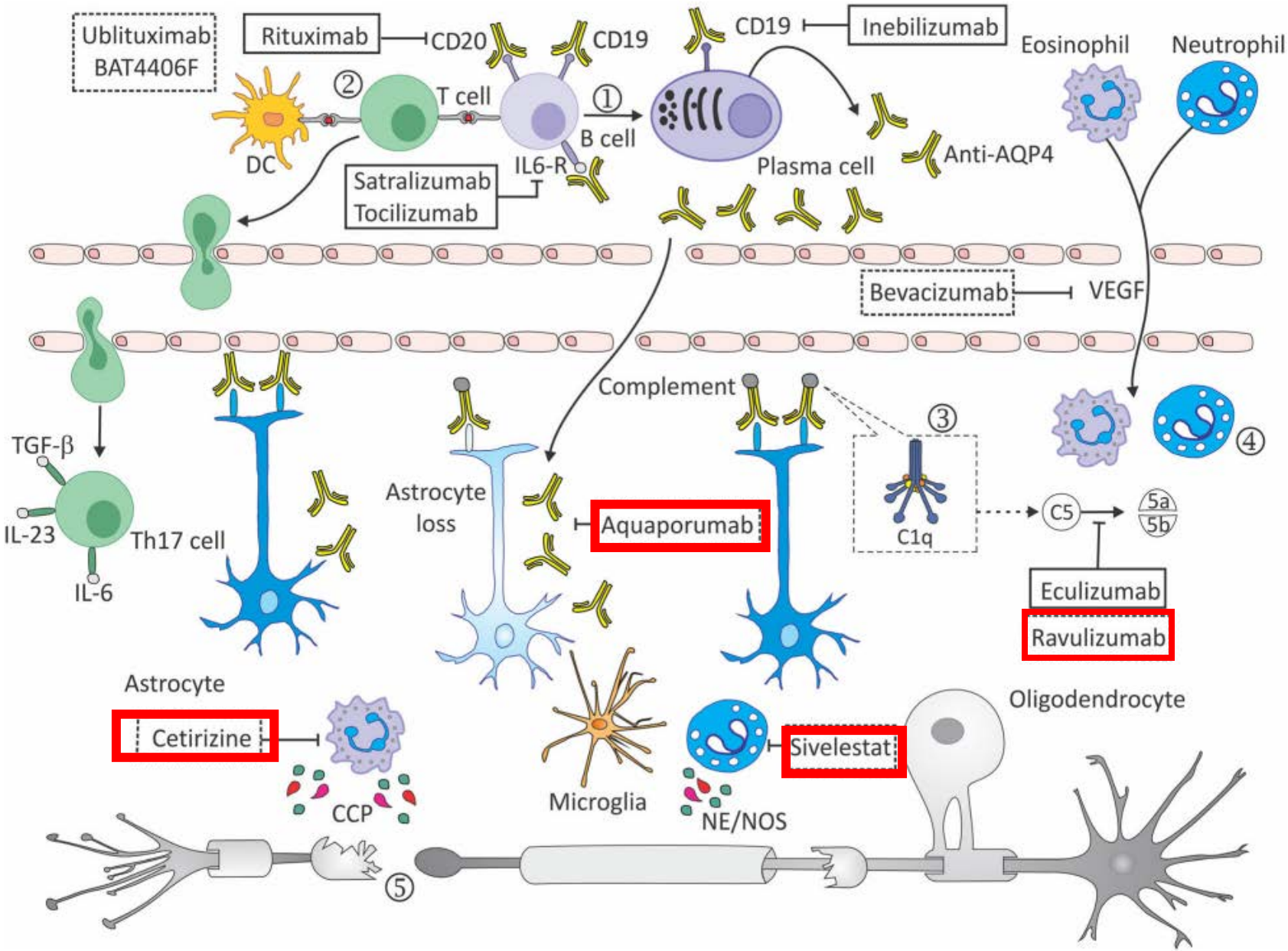
Pittock SJ, Zekeridou A, Weinshenker BG. Hope for patients with neuromyelitis optica spectrum disorders — from mechanisms to trials. Nature Reviews Neurology. 2021;17(12):759-73.



Pittock SJ, Zekeridou A, Weinshenker BG. Hope for patients with neuromyelitis optica spectrum disorders — from mechanisms to trials. Nature Reviews Neurology. 2021;17(12):759-73.

	Eculizumab	Satralizumab	Inebilizumab	Rituximab
Trial	**PREVENT**	**SAkuraSky/ SAkuraStar (no background IST)**	**N-Momentum**	**RIN-I**
Mechanism	C5 inhibitor	IL-6 receptor blocker	CD19 B-cell blocker	CD-20 B-cell blocker
Size	96 treated/47 placebo (100% AQP4+)	41 treated/42 placebo 63 treated/32 placebo	174 treated/56 placebo	19 treated /19 placebo
Dose	900 mg IV wekly x 4 wks, then 1200 mg IV q 2 weeks	120 mg SC at week 0,2,4 then q 4 weeks	300 mg IV on day 1, 15 Then q 6 months	1000 mg q 2 weeks then 1000 mg q 6 months
Risk reduction (%)	94%	74 – 79%	77%	0/19 vs 7/19 relapses
Side effects	Severe meningococcal infection ** (vaccination recommended), encapsulated organism	Skin reactions, high cholesterol, abnormal LFT, infection	Infusion reaction, hypogammaglobulinemia, PML	Infusion reactions, PML, hypogammaglobulinemia
Cost /year/person **USD**	$710,000	$219,000 → $190,000	$393,000 → $262,000	$18,000

Long-term Treatment Future Era



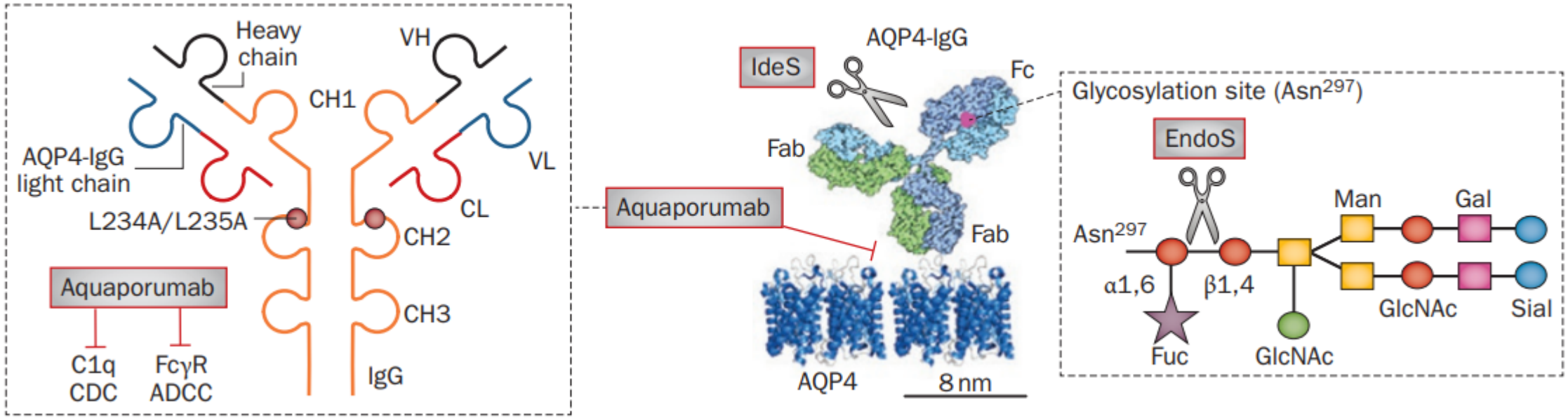
Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021;18(1):208.

Long-term treatment: future era

Drug/Dose/Route of administration	
Ravulizumab Intravenous Infusion on day 1, followed by weight-based maintenance doses on day 15, then once every 8 weeks	Second-generation anti-C5 monoclonal antibody (binds to complement protein 5 (C5) and blocks its activation by complement pathway convertase, thus inhibiting C5 cleavage into fragments C5a and C5b, engineered from eculizumab. It is a long-lasting recycling IgG monoclonal antibody with increased affinity for FcRn and rapid endosomal dissociation of the ravulizumab-C5 complex, allowing lysosomal degradation of C5 while recycling ravulizumab to the vascular space through the FcRn [113].
Bortezomib [114] Subcutaneous 1 mg/m^2 of body surface area on days 1, 4, 8, and 11 per cycle followed by a 10-day treatment-free interval.	Binds the catalytic site of the 26S proteasome with high affinity and specificity leading to elimination of both plasmablasts and plasma cells by activation of the unfolded terminal protein response. Bortezomib may protect astrocytes from NFκB-dependent inflammatory damage in early events in NMOSD pathogenesis.
Cetirizine (add-on) [115] **Oral** 10 mg each day	Cetirizine (antihistaminic) could prevent damage by blocking eosinophils which have been implicated in the pathophysiology of NMOSD.
BAT4406F Intravenous Open-label dose escalation starting from 20 mg.	Fully humanized anti-CD20 monoclonal antibody
SHR1459 Oral Tablets taken once daily	Bruton's tyrosine kinase (BTK) inhibitor. BTK plays a crucial role in B cell development by transmitting intracellular signals from the pre-B cell receptor
Precinical study	
Aquaporumab (mAb-53) (animal model) [119] mAb-53 has not been clinically applied to patients	Aquaporumab is an engineered monoclonal antibody with high affinity for AQP4 channels that contain Fc mutations blocking cell- and complement-mediated cytotoxicity effector functions (possible mechanism of competitive inhibition as a steric inhibitor). Aquaporumab has shown beneficial effects in an NMOSD mouse model, but has not been clinically tested in NMOSD patients.
Long-term relapse prevention treatment: future era	
Telitacicept Subcutaneous 160 mg weekly	Recombinant transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI-Fc; located on CD27+ memory B cells and plasma cells) fusion antibody that works by binding to two cell-signaling molecules, B lymphocyte stimulator (BLyS), and a proliferation-inducing ligand (APRIL), both are a member of the tumor necrosis factor (TNF) family [115].

Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021;18(1):208.

AQUAPORUMAB



- High-affinity, nonpathogenic anti-AQP4 antibody (aquaporumab) competes with pathogenic AQP4-IgG for AQP4 binding
- Fc portion mutated → not activate complement

Drug	Study design	Study phase/ ClinicalTrials.gov Identifier (status 01/2021)	Number of patients (randomization)	NMOSD serostatus	Free of relapses/ relapse reduction (RR)	Follow-up	Disability (EDSS stabilization or improvement)	Safety concerns
Ravulizumab	Multicenter, open-label, external placebo-controlled	Phase 3 study (active, recruiting) NCT04201262	55 (estimated enrollment)	AQP4-ab +*	NA	Time frame: 2 years	NA	NA
Bortezomib	Single-center, Open Label Trial (USA)	Phase 2 add-on study (completed) NCT02893111	5	AQP4-ab+*	NA	Time frame: 1 year	NA	NA
Cetirizine	Single-center, Open Label Trial (USA)	Phase 2 add-on study (completed) NCT02865018	16	AQP4-ab+ (with ON or TM)**	NA	Time frame: 1 year	NA	NA
BAT4406F	Single-center, Open Label Trial (China)	Phase 1 dose-escalation study (not yet recruiting) NCT04146285	48 (estimated enrollment)	AQP4-ab + and -*	NA	NA	NA	NA
SHR1459	Single-center, Open Label Trial (China)	Phase 2 study (not yet recruiting) NCT04670770	10 (estimated enrollment)	AQP4-ab +*	NA	Time frame: 52 weeks	NA	NA
Hematopoietic Stem Cell Transplantation	Single Group Assignment; Open Label study (USA)	Phase 1, 2 study (completed) NCT00787722	13 (12 completed the study)	AQP4-ab+ (n=12) and unknown (n=1)	80%	5 years	at baseline: 4.4 at FU: 3.3	1/13 died due to unrelated complications from SLE Neutropenic fever (5/13), Hypophosphatemia (9/13) Infections (1/13)

Carnero Contentti E, Correale J. Neuromyelitis optica spectrum disorders: from pathophysiology to therapeutic strategies. Journal of Neuroinflammation. 2021;18(1):208.

Take Home Message

- AQP4 antibody binding leads to AQP4 internalization, complement-dependent and antibody-dependent cellular cytotoxicity, and water channel dysfunction
- Cumulative attack-related injury causes disability in NMOSD, so the prevention of attacks is expected to prevent disability accrual
- Traditional immunosuppressant therapies, including mycophenolate mofetil, azathioprine and rituximab, were widely used but their benefits have not been assessed in controlled studies
- No direct comparison with conventional therapy and approved therapy
- Decisions on choosing treatment depend on cost, convenience, health care provider and availability
- Pregnancy and long-term safety limited data
- No license on age <12 years