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What's new in neuromyelitis optica spectrum disorder treatment?

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Abstract

Optic neuritis, an optic nerve inflammatory disease presenting with acute unilateral or bilateral visual loss, is one of the core symptoms of neuromyelitis optica spectrum disorder (NMOSD). The diagnosis of NMOSD-related optic neuritis is challenging, and it is mainly based on clinical presentation, optical coherence tomography, magnetic resonance imaging scans, and the status of serum aquaporin-4 antibodies. In the pathogenesis, aquaporin-4 antibodies target astrocytes in the optic nerves, spinal cord and some specific regions of the brain eliciting a devastating autoimmune response. Current pharmacological interventions are directed against various steps within the immunological response, notably the terminal complement system, B-cells, and the pro-inflammatory cytokine Interleukin 6 (IL6). Conventional maintenance therapies were off-label uses of the unspecific immunosuppressants azathioprine and mycophenolate mofetil as well as the CD20 specific antibody rituximab and the IL6 receptor specific antibody tocilizumab. Recently, four phase III clinical trials demonstrated the safety and efficacy of the three novel biologics eculizumab, inebilizumab, and satralizumab. These monoclonal antibodies are directed against the complement system, CD19 B-cells and the IL6 receptor, respectively. All three have been approved for NMOSD in the US and several other countries worldwide and thus provide convincing treatment options.

Keywords:

Aquaporin-4-, eculizumab, inebilizumab, neuromyelitis optica spectrum disorder, optic neuritis, satralizumab

Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease of the central nervous system (CNS) which predominantly affects the optic nerves and spinal cord. The diagnosis is challenging because NMOSD-associated optic neuritis (NMOSD-ON) is mimicking other optic neuropathies^[1] and some patients may present subtle contrast sensitivity or color vision loss with nearly normal visual acuity and disc appearance initially. Current treatments for NMOSD include corticosteroids, plasmapheresis, and immunosuppressants. Recently, new biologics showed a better outcome in disease control with reduced relapse risk. In this paper, we provided a comprehensive review

of NMOSD and new biologic therapies from an ophthalmologist's perspective.

Disease Classification

Cases clinically diagnosed as NMOSD may include aquaporin 4 (AQP4)-antibody-seropositive (AQP4-IgG⁺) NMOSD, myelin oligodendrocyte glycoprotein-(MOG)-antibody-seropositive (MOG-IgG⁺) NMOSD, and double-seronegative NMOSD.

Epidemiology and Demographics

NMOSD is a rather rare disease with a worldwide prevalence between 0.5 and 10 per 100,000 persons.^[2,3] Several studies suggest geographic or ethnic differences in prevalence, with Asian and African descents having higher risk of NMOSD.^[3,4] The prevalence per 100,000 is around 1 in White populations, 3.5 in

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Asian populations (Japanese, Chinese, and Koreans) and 10 in African populations.^[2] The latest available epidemiological data for NMOSD in Taiwan from 2015 report an prevalence of only 1.47 and a respective age-standardized annual incidence rate of 0.61.^[5]

Geographic or ethnic differences are also evident regarding the age at disease onset. Blacks and Asians tend to be younger at disease onset than Whites (Blacks: 28–33 years, Asians: 35–40 years, Whites: 44 years).^[2] Cohort studies from the UK and Japan revealed that ON was the onset phenotype in 41% of the total NMOSD cases (UK: 37%, Japan 45%) and 86% of the patients showed relapsing disease courses.^[6] The age at disease onset appeared to be an important predictor of disability type. AQP4-IgG⁺ NMOSD patients with young-onset in the UK, but not in Japan, were more likely to have ON as onset attack with higher severity, while older-onset patients in both countries often developed myelitis with poor recovery as the initial presentations. There was prominent female predominance of 87% (UK: 81%, Japan 98%) in AQP4-IgG⁺ subpopulation.^[7,8] The majority of NMOSD patients are considered AQP4-IgG⁺.^[9] From the remaining cases, a significant proportion of 7% to 42% are seropositive for MOG-IgG.^[2] In the Catalonia NMOSD prevalence study, 12% of NMOSD cases were MOG-IgG⁺.^[10] The prevalence of MOG-IgG⁺ NMOSD was calculated to be 0.11 per 100,000. A recent meta-analysis revealed that 9.3% of all NMOSD patients present with MOG-IgG⁺.^[11] Unlike AQP4-IgG⁺ NMOSD, which is more common in Asian regions, Asian patients did not differ significantly from European patients in MOG-IgG⁺ frequency (31.0% vs. 34.3%). In addition, the female to male ratio is 1:1 in MOG-IgG⁺ NMOSD. MOG-IgG⁺ NMOSD is more common in children and coexisting autoimmunity is rare.

The relapses of NMOSD cause accumulating damage that leads to disability requiring a wheelchair or blindness in 50% or 62% of the cases, respectively, five years after onset,^[12] and consequently lead to an impaired quality of life.^[13]

Diagnosis

The evolution of NMOSD diagnosis shows the challenge in the diagnosis with variable clinical symptoms. In 1999, Wingerchuk *et al.* proposed the first diagnostic criteria for NMO based on clinical and radiographic features.^[14] After discovering AQP4-IgG, in 2007 these criteria were revised to consist of the presence of ON and transverse myelitis (TM), two out of three of a longitudinally extensive transverse myelitis (i.e., more than three vertebral segments), brain magnetic resonance imaging (MRI) lesions excluding multiple sclerosis (MS), and AQP4-IgG⁺ status.^[15] These criteria were 99%

sensitive and 90% specific for the diagnosis of NMO and have been independently validated. However, after then there were still some suspicious patients who were not able to fulfil the two out of three criteria and failed to confirm NMO diagnosis. In 2015, the diagnosis criteria from International Panel for Neuromyelitis Optica Diagnosis were revised to adapt the earlier diagnosis of acute ON named as NMOSD with or without positive AQP4-IgG.^[16] Thereafter, ophthalmologists take the essential role in the clinical diagnosis of NMOSD.

These new NMOSD diagnosis criteria are based on six core clinical characteristics, the presence of serum AQP4-IgG, and ancillary evaluation for AQP4-IgG seronegative (AQP4-IgG⁻) patients.^[16] These core clinical characteristics are ON, acute TM, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy, and symptomatic cerebral syndrome. For AQP4-IgG⁺ patients, only one core clinical characteristic is required for the diagnosis. Before confirming the status of AQP4-IgG, an ophthalmologist can narrow down to the diagnosis of NMOSD-ON by ruling out other retinal diseases, optic neuropathy or brain pathology by pupil response, contrast sensitivity testing (CST), visual field test (VF), optical coherence tomography (OCT) findings, and fluorescent angiography (FA).

Seronegative NMOSD requires some more characteristics to be diagnosed as detailed in Figure 1. For the assessment of AQP4-IgG, it is highly recommended to apply cell-based assays (CBA) that have been shown to be sensitive and highly specific with significantly better performance compared to tissue-based and ELISA assays.^[17] Recently, MOG-IgG⁺ of seronegative NMOSD is categorized into MOG antibody-associated disease, a representing a group of inflammatory demyelinating disorders. Therefore, the diagnosis of MOG-IgG⁺ NMOSD should be very cautious. CBA for MOG-IgG is recommended.^[18] The clinical differentiation between AQP4-IgG⁺ and MOG-IgG⁺ related ON can be assessed by contrast MRI evaluating disc morphology, laterality, thickness loss of the ganglion cell-inner plexiform layer (GC-IPL), and ON length and site involvement.

The differential diagnosis of NMOSD-ON includes inflammatory, infectious, compressive, ischemic, infiltrative and hereditary optic neuropathy [Figure 2]. The diagnosis is based on various aspects including clinical history, physical examination, ancillary test, serum tests, and MRI. The physical examination including the relative afferent pupillary defect and the morphology of optic nerve head as well as reviewing medical history and the pattern of disease progression may guide to correct diagnosis of acute optic neuropathy. Ancillary testing in ophthalmology

Diagnosis according to AQP4-IgG-seropositive status	Diagnosis according to AQP4-IgG-seronegative status
<ul style="list-style-type: none"> • ≥ 1 core clinical characteristic • Positive test for AQP4-IgG • Exclusion of alternative diagnoses 	<ul style="list-style-type: none"> • ≥ 2 different core clinical characteristics as a result of ≥ 1 clinical attack and meeting all following requirements: <ul style="list-style-type: none"> • ≥ 1 core clinical characteristic must be ON, acute myelitis with LETM or area postrema syndrome • Dissemination in space (≥ 2 different core clinical characteristics) • Fulfilment of additional MRI requirements
Six core NMOSD clinical characteristics <ul style="list-style-type: none"> • Optic neuritis • Acute myelitis • Area postrema syndrome • Acute brainstem syndrome • Symptomatic narcolepsy or acute diencephalic clinical syndrome • Symptomatic cerebral syndrome with NMOSD-typical brain lesions 	<ul style="list-style-type: none"> • Negative test for AQP4-IgG • Exclusion of alternative diagnoses <p>Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status</p> <ol style="list-style-type: none"> 1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over $\geq 1/2$ optic nerve length or involving optic chiasm 2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥ 3 contiguous segments (LETM) OR ≥ 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis 3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions 4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

Figure 1: NMOSD diagnostic criteria for adult patients.^[16] NMOSD = Neuromyelitis optica spectrum disorder

such as VF, OCT, CST, and/or FA are performed for clinical differential diagnosis. Serum tests such as Treponema pallidum particle agglutination assay, rapid plasma reagin, and quantiferon TB gold test are crucial to rule out the infectious ON caused by syphilis or tuberculosis. Tests for antinuclear antibodies or rheumatoid factor are performed to exclude autoimmune optic neuropathies [Figure 3]. The NMOSD-ON is finally confirmed by the positivity of the serum AQP4-IgG or MOG-IgG and the inflammatory lesion of the optic nerve in orbital MRI. The NMOSD-ON patient will receive high-dose corticosteroid pulse therapy with methylprednisolone (IVMP) for 5 days with and without add-on plasmapheresis (plasma exchange [PLEX]) as soon as possible to reverse the visual function and lessen the acute inflammatory optic nerve damage via blood-optic nerve barrier disruption and decrease retinal ganglion cell die with axon loss in the end [Figure 4].

Clinical Presentation of Optic Neuritis in Neuromyelitis Optica Spectrum Disorder

The acute attack of ON and TM can occur sequentially or even simultaneously.^[19] In contrast to MS, disability in NMOSD arises from relapse episodes and progressive forms are rarely noted in NMOSD.^[20] In MS, the disease progression to disability including blindness is slow and takes 10 to 15 years.

Generally, ON presents as acute, unilateral, or bilateral vision loss [Table 1]. In NMOSD, the final best-corrected visual acuity of patients with MOG-ON is often better than that of AQP4-ON. In a 3-year-follow-up cohort in China, only 25% of the

patients with AQP4-ON had a VA $\geq 20/25$, and more than 45% had a VA $< 20/200$, whereas 85% of the patients with MOG-ON had a VA $\geq 20/25$.^[21] Optic disc may be swelling at presentation. The prevalence of disc swelling is higher in MOG-ON than AQP4-ON.^[22] There seems to be variable findings of VF defects in both AQP4-ON and MOG-ON compared to central scotoma in MS, and even hemianopia could be noted in AQP4-ON.^[27]

In the first acute attack, the NMOSD-related ON leads to variable peripapillary retinal nerve fibre layer (pRNFL) thickness and a remarkable thinning of the GC-IPL in OCT studies.^[28] In the subacute phase, the thinning of both pRNFL and GC-IPL is noticed. MOG-ON and AQP4-ON do not differ significantly in RNFL and GC-IPL thickness. Recently, the emerging OCT angiography gave more information about microvascularization. Reduced peripapillary and parafoveal vessel density was observed, and it seemed to be correlated with the visual potential of NMOSD-ON.^[29] The relevant functional and structural aspects of AQP4-IgG⁺ and MOG-IgG⁺ patients are presented in Figure 5 and Table 1.

MRI image characteristics add substantially to the differential diagnosis of NMOSD-ON [Figure 6a and b]. AQP4-ON preferentially presents with longer, unilateral, or bilateral, more posterior portion of optic nerve with T1 gadolinium enhancement [Figure 6c, e and g].^[30] However, MOG-ON usually presents with longer, bilateral, and more anterior portion of optic nerve accompanied by intraorbital optic nerve swelling, and perineural T1 gadolinium enhancement [outlined by arrow head along the optic nerve, Figure 6d, f and h].

Classification		Characteristics	Examination
Papilledema		Bilateral, related to intracranial hypertension	Brain image Check CSF pressure
Inflammatory optic neuritis - CNS	Isolated optic neuritis (associated with multiple sclerosis)	Unilateral VA loss, pain on eye movements normal or mild disc swelling Nadir in 7-10 days with spontaneous recovery	Brain MRI for rule out MS
	Neuromyelitis optica spectrum disorder (NMOSD)	Unilateral or bilateral severe VA loss Chiasma involvement May be associated with other neurological symptoms such as transverse myelitis	Check AQP4- Ab, check brain and spinal MRI
	Myelin oligodendrocyte glycoprotein antibody associated disease (MOG)	More bilateral Very common relapsing, may be associated with ADEM	Check MOG- Ab, check brain and spinal MRI
Inflammatory optic neuritis - systemic	Autoimmune disease	Granulomatous disease: associated with sarcoidosis and granulomatous polyangiitis SLE and Sjogren syndrome related optic neuritis	Check ANA, RF→check other antibodies (such as ACE for sarcoidosis, anti-dsDNA for SLE)
	Paraneoplastic optic neuropathy	Painless progressive vision loss, bilateral but may asymptomatic Optic disc edema and/or optic atrophy History of cancer	Check immunohistochemical assays for autoantibodies Check CSF
Ischemic optic neuropathy	Arteritic Anterior Ischemic Optic Neuropathy (AAION)	Systemic symptoms such as temporal headache, jaw claudication, myalgia, fever chalky white optic disc edema ± CWL increased age	Check PLT, CRP, ESR Temporal artery biopsy
	Non-arteritic Anterior Ischemic Optic Neuropathy (NAAION)	Painless visual loss Altitudinal VFD, optic disc sectoral edema, crowded disc Vascular risk factors	Check vascular risk factor, such as blood sugar, blood pressure, lipid profile
	Posterior ischemic optic neuropathy (AION)	Abrupt, often severe vision loss Initially normal-appearing optic nerve head	Diagnosis of exclusion
Compressive optic neuropathy	Intraorbital or intracranial compressive lesions	Slowly progressive vision loss Normal or mildly atrophic disc at presentation Optociliary shunt vessels or choroidal folds may also be present	Check brain and orbital image
Infiltrative optic neuropathy	Inflammatory, infection or neoplastic	Cellular infiltration Atypical disc edema and progressive severe vision loss	Brain and orbits image to rule out compressive lesions and to confirm pachymeningeal or meningeal infiltration Check blood test includes screening tests for the myeloproliferative, inflammatory, and infectious disorders. Check CSF for r/o Malignant cells, infectious, or inflammatory causes
Infectious optic neuritis	Viral: VZV, HIV, WNV	May be associated with neurological symptoms May be associated with viral retinopathy	Check blood test for antibodies or PCR test
	Bacterial: TB, syphilis, bartonella, Toxoplasma, Lyme disease	May be associated with neuroretinitis May be associated with neurological symptoms	Check blood test for antibodies or PCR test
Hereditary optic neuropathy	Leber Hereditary Optic neuropathy	Young male, family history, one eye preceding another for weeks to months Peripapillary telangiectasia, optic disc pseudoedema	Check gene test for LHON

Figure 2: Classification of optic neuropathy. CNS = Central nervous system, NMOSD = Neuromyelitis optica spectrum disorder, MOG = Myelin oligodendrocyte glycoprotein, NAAION = Non arteritic anterior ischemic optic neuropathy, AION = Anterior ischemic optic neuropathy, VA = Visual acuity, ADEM = Acute disseminated encephalomyelitis, ANA = Antinuclear antibody, MRI = Magnetic resonance imaging, MS = Multiple sclerosis, SLE = Systemic lupus erythematosus, VFD = Visual field defects, LHON = Leber's hereditary optic neuropathy, PCR = Polymerase chain reaction, PLT = Platelets, CRP = C-reactive protein, ESR = Erythrocyte sedimentation rate, CSF = Cerebrospinal fluid, CWL = Cotton wool spots

Pathological Mechanism

The pathological mechanism of NMOSD may be caused by peripheral autoimmune dysregulation which in turn leads to CNS damage [Figure 7]. AQP4-IgG has been found to have an important role in the pathological mechanism for NMOSD. An impaired innate immune system is thought to promote autoreactive AQP4-IgG specific CD20 B-cells^[31-33] that are then differentiated to CD19 positive autoantibody producing plasmablasts. A leaky blood brain barrier (BBB) contributes to

the migration of AQP4-IgG from the periphery into the CNS. AQP4-IgG bind to AQP4, expressed on the perivascular astrocyte foot, and activates the complement cascade (complement-dependent cytotoxicity; complement-dependent cell-mediated cytotoxicity) eliciting antibody-dependent cellular cytotoxicity (ADCC) by its Fc domain.^[34] Cytokine and chemokine production recruits eosinophils and neutrophils to the inflammation site. After degranulation of neutrophils, astrocytes and nearby oligodendrocyte are damaged. This leads to secondary axonal degeneration and neuronal death.^[20]

Interleukin 6 (IL6) signalling is the key player in NMOSD pathophysiology.^[35] This is reflected by a strong association of IL6 CSF and serum levels with important disease markers, e. g. EDSS score and CSF cell counts.^[35,36] Notably, the elevated IL6 levels are observed in both AQP4 IgG and MOG IgG NMOSD, but not MS patients. In the pathological mechanisms, IL6 signaling is thought to contribute in multiple ways.^[35] IL6 induces naïve T-cell differentiation to Th17 that are supportive for AQP4 specific activated B-cells. IL6 activates B-cell differentiation to plasmablasts and the production of AQP4-IgG. IL6 contributes to an increased BBB permeability and thus antibody and cell infiltration into the CNS. In response to stimulation by proinflammatory cytokines produced by infiltrated granulocytes and microglia, astrocytes produce IL6 as well. Thus, this contributes to the vicious circle of inflammation. Inflammation causes secondary demyelination, contributes to oligodendrocyte and axon damage and leads to neuron loss. In a novel *in vitro* BBB model, the proposed role of IL6 on the BBB could be recently confirmed.^[37] AQP4-IgG induced the IL6 release from astrocytes, the BBB was impaired by the IL6 signalling to the endothelial cells, and the BBB impairment was reversed by an anti IL6 receptor (IL6R) antibody.^[37]

There are several pharmacological targets within these pathways for the maintenance therapies of NMOSD [Figure 7]: Azathioprine and mycophenolate mofetil lead to an unselective suppression of fast-dividing immune cells and thus depleting of T-cell and B-cell. Monoclonal antibodies, rituximab (specifically binds to CD20) and inebilizumab (specifically binds to CD19), induce B-cell depletion as well. Eculizumab specifically binds to complement C5 and blocks all terminal pathways of complement activation. Tocilizumab and satralizumab specifically bind to IL6 receptors and therapy interfering with pathological pathways at multiple sites.

AQP4⁺ NMOSD is damaged from astrocytopathy. On the contrary, the pathological mechanism of MOG-IgG⁺ NMOSD is caused by oligodendrocyte injury, while its astrocytes remain intact.^[18,38] The pathology for MOG-IgG⁺ NMOSD remains unclear but apparently involves peripheral MOG-autoantibody generation from specific B cell.^[38,39] The MOG-IgG crosses the BBB binds to MOG expressed in myelin of oligodendrocyte and activates complement and ADCC. Meanwhile, the MOG specific plasma cells and MOG-IgG may enhance T-cells-induced proinflammation cytokine, and chemokines, and then lead to oligodendrocyte damage and sequential demyelination.

Blood tests for differential diagnosis (based on epidemiology/clinical history)	
<ul style="list-style-type: none"> NMO Ab(AQP4-IgG and MOG-IgG by CBA) ANA, Anti-dsDNA Ab RF ENA panel SSA, SSB p/cANCA Antiphospholipid Ab ACE Homocysteine 	<ul style="list-style-type: none"> Syphilis (RPR/VDRL TPPA), HIV Virology (CMV, HSV, VZV) Tuberculosis (Quantiferon TB gold)
	<ul style="list-style-type: none"> Paraneoplastic antibody panel (Anti-CV2/CRMP5/Anti-Yo/Anti-Hu/Recoverin) Coagulopathy profile Genetic testing (LHON) Methylmalonic acid

Figure 3: Blood tests for differential diagnosis of acute optic neuropathy. Tests in the left column and the right upper column are used to exclude autoimmune and infectious optic neuropathy. Tests in the right lower column are less applied, to rule out paraneoplastic, hereditary or other rare optic neuropathy. NMOAb = Neuromyelitis Optica antibody, AQP4 = Aquaporin 4, MOG-IgG = Myelin oligodendrocyte glycoprotein immunoglobulin G, ANA = Antinuclear antibody, RF = Rheumatoid factor, LHON = Leber's hereditary optic neuropathy, RPR = Rapid plasma regain, VDRL = Venereal disease research laboratory, TPPA = Treponema pallidum particle agglutination, TB = Tuberculosis, SSA = Anti-Sjogren's Syndrome A antibody, SSB = Anti-Sjogren's Syndrome B antibody

Management of Acute Attacks

The timely management of acute attacks is crucial as the physical impairment in NMOSD accumulates with each relapse.^[40] Irreversible damages may be prevented by a reduction of the acute inflammation. The mainstay of acute treatment is high-dose IVMP with 1000 mg for 3–5 days.^[41] An early initiation of treatment within a few days seems to be associated with a better clinical outcome.^[42,43] In an observational study of ON with AQP4-IgG and MOG-IgG, even a 7 days delay in treatment initiation was detrimental to vision.^[44] Another study emphasized the importance of an early intervention to reduce retinal nerve fiber layer loss.^[45] In any way, a complete response to high-dose corticosteroids is observed in only 36% of NMOSD cases.^[40] For severe and steroid refractory cases, an escalation therapy with PLEX alone or in

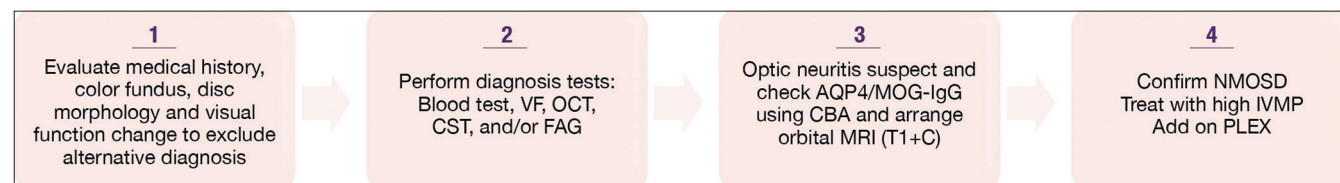


Figure 4: Flowchart for NMOSD diagnosis. (1) Initial diagnosis of optic neuropathy (2) Rule out other optic neuropathy. (3) If the NMOSD is most likely, AQP4-IgG and MOG-IgG was tested and a brain-orbital MRI is arranged. (4) Treatment as soon as possible. NMOSD = Neuromyelitis Optica Spectrum Disorder, AQP4-IgG = Aquaporin 4 immunoglobulin G, MOG-IgG = Myelin oligodendrocyte glycoprotein immunoglobulin G, MRI = Magnetic resonance imaging, VF = Visual field, OCT = Optical coherence tomography, CST = Contrast sensitivity testing, FAG = Fluorescent angiography, CBA = Cell-based assays, PLEX = Plasma exchange

Table 1: Clinical characteristics of inflammatory optic neuritis^[20]

Examine item ^[20]	Characteristics	MS-ON	AQP4-ON (80%)	MOG-ON (4%-11%)
Visual acuity ^[21]	Visual impairment	Mild to moderate	Severe	Moderate to severe
	Visual recovery	Good	Poor (~32.4%)	Good (~70.3%)
	BCVA nadir <0.1 (20/200)		60.1%	22.0%
	BCVA 3 years <0.1 (20/200)		18.2%	0.0%
	BCVA 3 years >0.8 (20/25)		25.0%	84.6%
Fundoscopy ^[22]	Disc morphology finding	Retrobulbar neuritis/disc edema (35%) ^[22]	Retrobulbar neuritis >papillitis/disc edema (variable) ^[22]	Bilateral papillitis/disc edema (85%) ^[22]
		Segmental disc atrophy without venous sheathing	Disc atrophy and vascular changes with "frosting"	
			Disc hemorrhage (rare)	
			Normal disc	
OCT ^[21-25]	Optic nerve OCT finding ^[22,23]	Mild RNFL increase acutely, GC-IPL thinning in early weeks	Variable RNFL thickening acutely, with profound GC-IPL loss	Significant RNFL thickening acutely, early GC-IPL loss
		MS may have RNFL in non-ON eyes	Ganglion cell complex loss in a short time	
		MME	MME	
	Average RNFL thickness	72 (68.2~81.75 μm) ^[24]	60 (54.3~65.8 μm) ^[24] 59.40±11.46 (48~71 μm) ^[21]	63.41±13.39 (50~77 μm) ^[21]
	Average GC-IPL thickness	63.5 (59,-) ^[24] 71~79.5 μm ^[25]	AQP4+: 53 (50~60 μm) ^[24] 59.5~79 μm ^[25]	
OCTA ^[26]	OCTA finding	Non-ON eyes, the RPC vessel density was reduced ^[26]	Decreased microvascular densities in macular area and smaller FAZ	
VF ^[27]	VF finding	Diffuse and arcuate, most were (90%) central scotoma	Diffuse, variable, central scotoma (76%), Variable noncentral scotoma (23%)	
MRI	MRI finding	T1 gadolinium enhancement	T1 gadolinium enhancement	T1 gadolinium enhancement
		Most affected segments are canalicular and retrobulbar, focal lesion <50% of length involved	Most affected posterior segments are canalicular and intracranial, chiasmatal and optical tract, longitudinal lesion >50% length involved	Most affected anterior segments are retrobulbar, canalicular and intraorbital, longitudinal lesion >50% length involved
			Presence of nerve enhancement and thickening	Perineural sheath and perineural orbital tissue enhancement

OCT=Optical coherence tomography, OCTA=Optical coherence tomography angiography, VF=Visual field, MRI=Magnetic resonance imaging, BCVA=Best-corrected visual acuity, RNFL=Retinal nerve fibre layer, GC-IPL=Ganglion cell-inner plexiform layer, MS=Multiple sclerosis, ON=Optic neuritis, MME=Microcystic macular edema, RPC=Radial peripapillary capillary, FAZ=Foveal avascular zone, AQP4=Aquaporin-4, MOG=Myelin oligodendrocyte glycoprotein

combination with steroids can be considered.^[46,47] PLEX in combination with corticosteroids increases the chances for the returning of EDSS to baseline as well as improves VA compared steroid monotherapy.^[48] PLEX, even as monotherapy, showed superiority over steroid monotherapy for VA and VF.^[49,50] However, an early intervention of PLEX <20 days after onset, with or without concomitant use of high-dose IVMP, is strongly encouraged to improve clinical outcome.^[43] After confirmation of diagnosis and complete pulse therapy, tapering oral methylprednisolone (1 mg/kg) for several months can be considered until preventive immunosuppressive treatment is initiated and effective.^[51] A small study in ten patients suggested that intravenous immunoglobulin (IVIg) followed by oral steroids was effective in four patients with bilateral NMO-ON who did not respond to previous IVMP and

PLEX therapy.^[52] A recent retrospective study showed that IVIg monotherapy for acute NMO-ON is in debate, however, the sequential treatment for IVIg and high-dose intravenous corticosteroids can be justified for patients with high EDSS at onset.^[53]

Maintenance Therapy – Prevention of Relapses

The prevention of recurrent attacks is crucial for NMO-ON treatment as the disability in patients mainly arise from the accumulation of relapses.^[40,54] Conventional maintenance therapies are based mainly on the off-label use of rituximab, azathioprine, and mycophenolate mofetil.^[41] More recently, tocilizumab was proposed as an alternative treatment option. All of them reduce the relapse risk and will be discussed below in more detail.

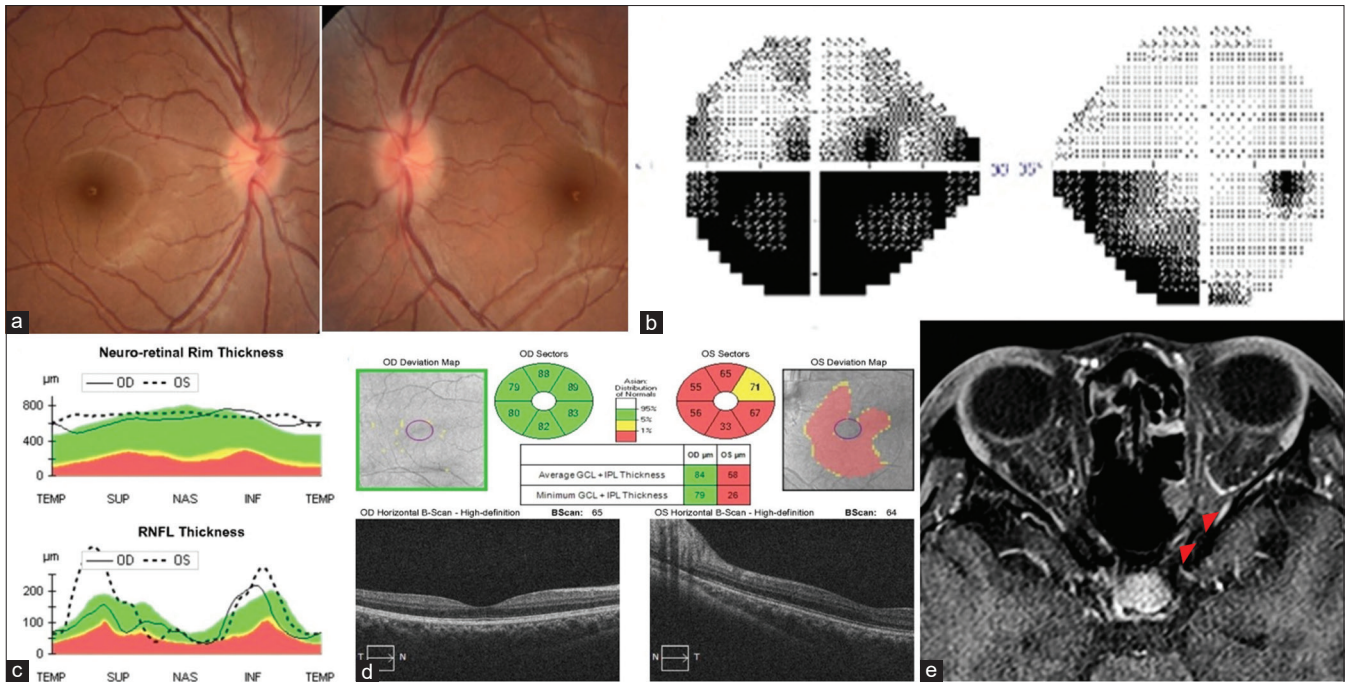


Figure 5: Ophthalmological features in NMOsD. A patient with AQP4-ON had left optic disc oedema (a). VF showed bilateral obscuration (b). OCT demonstrated more oedematous of pRNFL and thinner GC-IPL in the left eye (c and d). Orbital MRI revealed mild contrast enhancement within the left optic nerve (arrow head) (e). NMOsD = Neuromyelitis Optica Spectrum Disorder, AQP4-ON = Aquaporin 4 optic neuritis, VF = Visual field, OCT = Optical coherence tomography, pRNFL = Peripapillary retinal nerve fibre layer, GC-IPL = Ganglion cell-inner plexiform layer, MRI = Magnetic resonance imaging

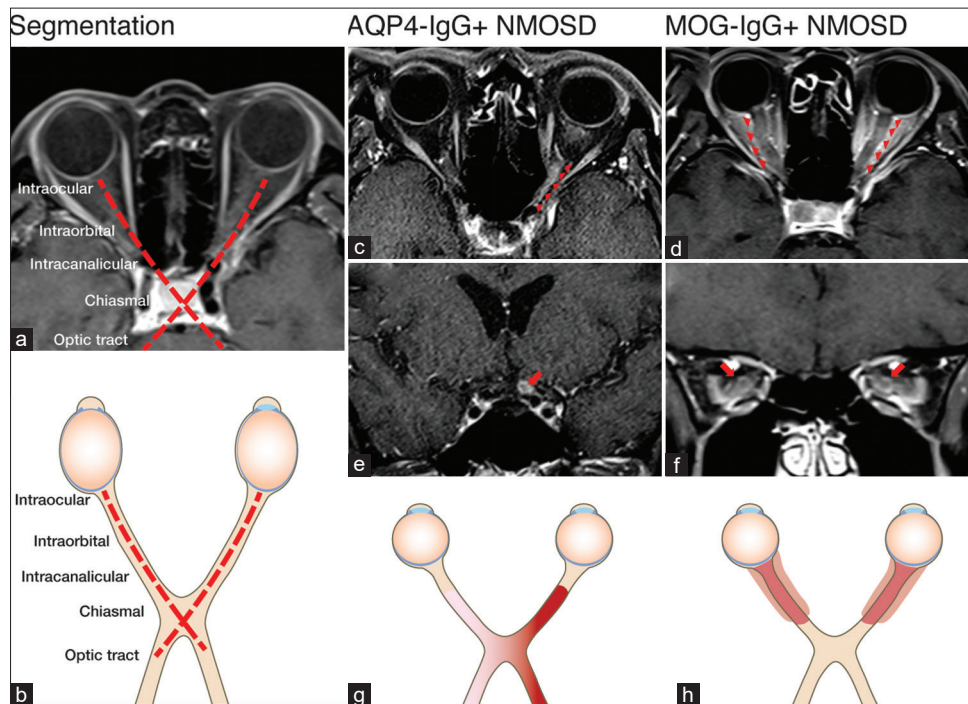


Figure 6: Distinctive orbital MRI features of AQP4-ON and MOG-ON. Orbital MRI for orbital segmentations (a) and cartoon demonstration (b). Distinctive imaging features AQP4-ON and MOG-ON in apical section (c and d), coronal section (e and f) and cartoon feature (g and h) respectively. MRI = Magnetic resonance imaging, AQP4-ON = Aquaporin-4 optic neuritis, MOG-ON = Myelin oligodendrocyte glycoprotein optic neuritis

Although with less evidence, low-dose corticosteroids commonly are used as well to reduce relapses in NMOsD, either as monotherapy or as add-on to conventional immunosuppressants.^[55] They may as well be very slowly

tapered following the acute therapy of relapses.^[56] A recent study on long-term disease course and efficacy of maintenance therapies in Taiwan showed that rituximab and immunosuppressants (i.e. azathioprine or

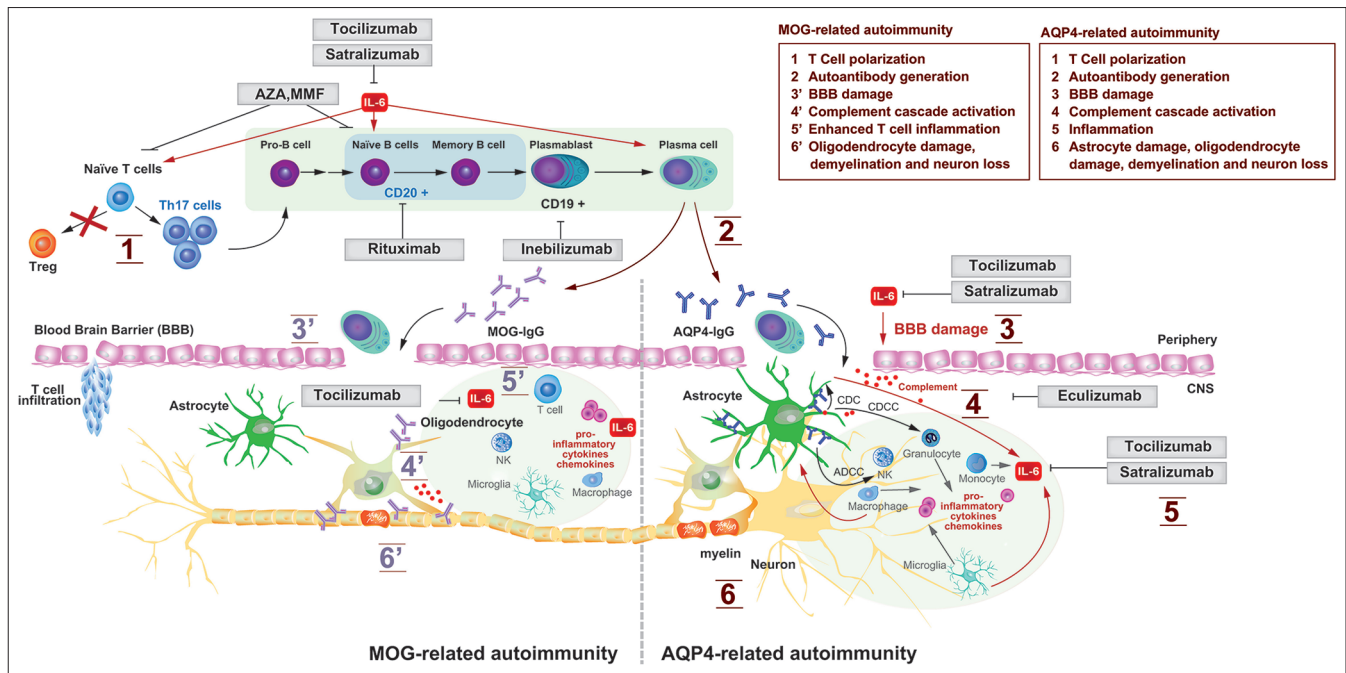


Figure 7: Pathogenesis and drug targets in NMOSD. NMOSD = Neuromyelitis Optica Spectrum Disorder, AQP4-IgG = Aquaporin 4 immunoglobulin G, MOG-IgG = Myelin oligodendrocyte glycoprotein immunoglobulin G, BBB = Blood – brain barrier, CNS = Central nervous system, IL6 = Interleukin 6, ADCC = Antibody-dependent cellular cytotoxicity, CDC = Complement-dependent cellular cytotoxicity, CDC = Complement-dependent cellular

mycophenolate mofetil) significantly reduce the relapse risks.^[57]

Methotrexate, mitoxantrone, tacrolimus, and cyclosporine A are less used for NMOSD due to significant side effects.^[58] Importantly, fingolimod, natalizumab, or interferon beta commonly used in MS, may be harmful in NMOSD because it may exacerbate disease activity.^[59-61]

The US-Food and Drug Administration (US-FDA) approved the three monoclonal antibodies eculizumab, inebilizumab, and satralizumab. The clinical trials that led to the approvals will be discussed in detail below. Relevant off-label and FDA approved therapies that are currently in use are summarized in Figure 8.^[62]

Azathioprine interferes with lymphocyte proliferation and thereby decreases total lymphocyte and B cell counts for several weeks to months. A recent meta-analysis with 1016 NMOSD patients reported an annual relapse rate (ARR) reduction of 1.16.^[63] However, several further studies suggest that azathioprine might be less effective than rituximab and Mycophenolate mofetil.^[64-66] Additionally, a poor tolerability and relapses from breakthrough or delayed onset of action cause discontinuation rates of up to 50% during 18 months of treatment.^[67]

Mycophenolate mofetil is another inhibitor of lymphocyte proliferation. Two recent meta-analysis with 1047 and 930 patients reported ARR reductions of 1.13 and

1.17 respectively.^[68,69] A comparative study revealed that mycophenolate mofetil is similar to rituximab in terms of ARR and EDSS, but with a failure rate of 36%.^[70] According to two studies, efficacy and safety of mycophenolate mofetil was comparable in AQP4-IgG⁺ and AQP4-IgG⁻ patients.^[64,71]

Rituximab, initially approved for the treatment of non-Hodgkin B-cell lymphomas, is a chimeric monoclonal anti-CD20 antibody inducing B-cell depletion. The pathogenic role of B-cells, differentiating to auto-antibody producing plasmablasts, justifies the use of rituximab in NMOSD. Based on several open-label, uncontrolled and nonrandomized observational studies demonstrating safety and efficacy in NMOSD, rituximab became a well-established option for relapse prevention. Main safety concerns are infections, Hepatitis B reactivation, infusion-related reactions, and, at long-term use, hypogammaglobinemia and prolonged neutropenia. Recently, rituximab was tested in phase III rituximab was tested in the RIN1 trial,^[72] a multicenter, randomized, double-blind, placebo-controlled Phase III clinical trial in Japan for treating NMOSD. At 72 weeks, 7 of 19 patients (37%) who received placebo experienced relapse, while rituximab (0 of 19 patients) completely prevented relapse. A limitation of this trial is the small sample size, which does not allow for quantification risk reduction by rituximab. Under B cell monitoring, the interval of infusions was extended to 9 months, while NMO relapse was suppressed with an ARR of

	Therapy	Type	Mechanism	Route	Safety
Off-label	Azathioprine	Small molecule	Inhibits lymphocyte proliferation	PO	Increased incidence of malignancy (3%) or rare bone marrow suppression
	Mycophenolate mofetil	Small molecule	Inhibits lymphocyte proliferation	PO	Teratogenicity, hair loss, rare skin cancer
	Rituximab	Chimeric monoclonal antibody	CD20 B-cell depletion	IV	Infusion related reactions; lower immunoglobulins over time
FDA approved	Eculizumab	Humanized monoclonal antibody	Inhibits complement 5 component	IV	Risk of infection with encapsulated organisms; requires pre-treatment vaccination for <i>Neisseria meningococcus</i>
	Inebilizumab	Humanized monoclonal antibody	CD19 B-cell depletion	IV	No short term concerns; long term potential concern for hypogammaglobulinemia and impaired immunity.
	Satralizumab	Humanized recycling monoclonal antibody	IL6 receptor blocker	SC	Injection site reactions; long term risk of hyperlipidemia

Figure 8: Maintenance therapies for NMOSD. NMOSD = Neuromyelitis Optica Spectrum Disorder, FDA = Food and Drug Administration, IL6 = Interleukin 6, SC = Subcutaneous, PO = Per os, IV = Intravenous

0.035, 10-fold lower than placebo, suggesting a more cost-effective regimen using rituximab.^[73]

Tocilizumab is a humanized monoclonal antibody that targets the IL6 receptor and is used for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis. In NMOSD, Tocilizumab is supposed to block the IL6 mediated inflammatory cascade, notably the stimulation of plasmablasts and thereby reducing the production of auto-antibodies AQP4-IgG as well as MOG-IgG that are the keys of NMOSD pathogenesis [Figure 7]. Several retrospective studies showed the efficacy and safety of Tocilizumab in NMOSD.^[74] Tocilizumab was compared with azathioprine in a head-to-head prospective, randomized open label phase II study (TANGO trial) in NMOSD.^[75] Both groups had 59 patients with 85% and 90% AQP4-IgG⁺, respectively. Whereas only eight patients (14%) relapsed in the tocilizumab group, 28 (47%) patients relapsed in the azathioprine group (76% reduction). In the AQP4-IgG⁺ subgroup, risk reduction was 79% in the tocilizumab group compared to azathioprine. Although the effect of tocilizumab was not significant for the AQP4-IgG⁻ patients of the TANGO trial, a reduced relapse probability was recently shown in MOG IgG patients.^[76]

Eculizumab

Eculizumab is a humanized monoclonal antibody that targets C5 of the complement, preventing its cleavage into C5a and C5b and thus inhibiting downstream effector mechanisms of the complement system.^[77] The involvement of the complement system in the pathogenesis of NMOSD is well established^[78] and an early open-label study showed very encouraging results with eculizumab in NMOSD patients.^[79] Eculizumab was then the first one entering a pivotal phase III trial in NMOSD.^[80]

PREVENT was a multicenter, international, phase III, double blind, randomized, placebo-controlled, time-to-event clinical trial in NMOSD.^[80] Importantly, the trial included only AQP4-IgG⁺ patients and patients were allowed continuing their prior immunosuppressive therapies (e.g., azathioprine and mycophenolate mofetil) in addition to the trial medication. Based on previous safety observations, patients were vaccinated against *Neisseria meningitides* before inclusion.

In the eculizumab group, the risk of adjudicated relapses was significantly reduced by 94% compared with placebo. The subgroup analysis for patients without concomitant immunosuppressive therapies revealed that none of the patients receiving eculizumab had any relapses at 96 weeks compared to 40% relapse free participants in the placebo group. As regards secondary endpoints, significant effects for adjudicated ARR but no inferences for disability and QoL were observed in eculizumab compared to placebo. Adverse events were comparable among treatments. There was one death in the eculizumab group due to pulmonary empyema. In June 2019, it became the first US-FDA approved treatment for AQP4-IgG⁺ NMOSD in addition to approval for paroxysmal nocturnal haemoglobinuria and atypical haemolytic uremic syndrome.

Inebilizumab

Targeting B-cells turned out to be a successful strategy in NMOSD treatment. Rituximab, an anti-CD20 antibody, led to the development of inebilizumab, a humanized monoclonal antibody targeting CD19. Inebilizumab eliminated a broader lineage of CD-19-expressing B cells, ranging from pre-B cells to plasmablasts and some plasma cells.

Inebilizumab was tested in the Phase II/III trial, N-MOMentum,^[81] that led to the approval of inebilizumab in the US and several other countries worldwide.

N-MOmentum was a multicentre, international, phase III, double blind, randomized, placebo-controlled, time-to-event clinical trial in NMOSD. The trial enrolled AQP4-IgG⁺ (n = 212) or negative (n = 18) patients. All participants started with a short course of oral prednisolone as co-medication to prevent early relapses after B-cell therapy initiation but thereafter no background immunosuppressive therapy was allowed. Compared with placebo, inebilizumab reduced the risk of a relapse by 73%. In the AQP4-IgG⁺ subgroup, risk reduction was 77% in the inebilizumab group compared to placebo. In addition, inebilizumab was associated with the improvements in disability, MRI lesions and NMOSD-related hospitalizations. Type and frequency of adverse events were similar in inebilizumab and placebo groups. Two patients died during the open-label phase, one due to respiratory insufficiency and the second death was indeterminate.

Satralizumab

Satralizumab originates from tocilizumab but is a next-generation antibody specifically designed for NMOSD. The introduction of a novel antibody-recycling technology led to increased duration of antibody circulation.^[82] Similarly to tocilizumab, satralizumab is a humanized monoclonal antibody targeting the IL6 receptor in both membrane-bound and soluble forms. Due to the modifications by the antibody-recycling technology, satralizumab rapidly dissociate from IL-6R within the acidic environment of the endosome while maintaining its binding affinity to IL-6R in plasma.^[83] This improved the half-life of antigen (~30 days) and thereby allows extending the interval of re-dosing. In addition, satralizumab's isoform is IgG2 which reduces the undesired responses such as ADCC and CDC caused by general IgG1 therapeutic antibodies. Moreover, satralizumab exhibits 4-fold higher binding affinity for IL-6R compared with tocilizumab under neutral pH condition and a low isoelectric point to reduce nonspecific clearance in the bloodstream. The engineering of satralizumab for NMOSD enables maximal suppression of IL-6 signalling and practical dosing, while minimizing safety risks in a chronic disease setting.

Satralizumab was tested in two Phase III trials, SAKuraStar^[84] and SAKuraSky,^[85] that both were multicenter, international, phase III, double blind, randomized, placebo-controlled, time-to-event, clinical trials in NMOSD. The trials were not restricted to AQP4-IgG⁺ patients.

SAKuraSky (on immunosuppressive background) revealed a 62% relapse risk reduction in satralizumab compared with placebo. In the AQP4-IgG⁺ subgroup,

satralizumab significantly reduced the risk of relapse by 79% compared with placebo.

In SAKuraStar (monotherapy), a 55% relapsed risk reduction was observed. In the AQP4-IgG⁺ subgroup, satralizumab significantly reduced the risk of relapse by 74% compared with placebo. However, the secondary endpoints for fatigue, pain and EDSS change did not significantly improve under satralizumab. Adverse events were similar among treatments in both satralizumab trials. No deaths and anaphylactic reactions were reported.

SAKuraStar and SAKuraSky finally led to the approval of satralizumab in Taiwan and several other countries worldwide. In Taiwan, where satralizumab is currently the only approved drug for NMOSD, it is marketed as Enspryng® for the treatment of NMOSD in adult and adolescent over 12 years old AQP4-IgG⁺ patients.

Summary of Eculizumab, Inebilizumab, and Satralizumab

The four pivotal Phase III clinical trials for eculizumab, inebilizumab, and satralizumab are summarized in Table 2. Many major differences in the design of these trials are discussed below.

First, the age for enrolment in both PREVENT (eculizumab) and N-MOmentum (inebilizumab) trials was ≥ 18 years; SAKuraSky (satralizumab) enrolled adolescent (<18 years), adult and elderly patients (>65 years), and SAKuraStar (satralizumab) enrolled patients aged 18–74 years. Second, the status of antibodies in enrolled patients was different. PREVENT trial restricted the population to AQP4-IgG⁺ patients. Less than 10% of patients in the N-MOmentum trial were AQP4-IgG seronegative. SAKura studies contain approximately one third of AQP4-IgG seronegative patients. Third, continuing other medication is different between trials. PREVENT and SAKuraSky allowed continuing prior immunosuppressive therapies, N-MOmentum and SAKuraStar were conducted as monotherapies. Finally, inclusion criteria are not equal to each other trial. PREVENT recruited patients with at least 2 relapses in the past 12 months or a history of 3 relapses in the past 24 months. N-MOmentum enrolled patients with at least 1 attack in the past 12 months or at least two relapses in the 24 months. SAKuraStar enrolled patients who had experienced at least one attack or relapse in the past 12 months. SAKuraSky enrolled patients with at least 2 relapses within 24 months and one of those relapses within the previous 12 months.

All four trials used an adjudication committee for relapse assessment, but different relapse criteria were

Table 2: Overview of Phase III double blind, placebo controlled, time-to-event clinical trials of three monoclonal antibodies in neuromyelitis optica spectrum disorder patients (Wingerchuk *et al.*, 2007 criteria^[15])

Trial	Prevent	N-MOMentum	SAkuraSky	SAkuraStar
Drug	Eculizumab	Inebilizumab	Satralizumab	Satralizumab
Target	C5	CD19	IL6 receptor	IL6 receptor
Route and dose	IV, 900 mg q1 weekx4 doses then 1200 mg q2 weeks	IV, 300 mg 2 weeks apart then q6 months	SC, 120 mg on weeks 0, 2, 4 then q4 weeks	SC, 120 mg on weeks 0, 2, 4 then q4 weeks
Randomization	2:1	3:1	1:1	2:1
Concomitant immunosuppression	Yes	No	Yes	No
Preceding disease activity inclusion criteria	≥2 relapses in 12 months or ≥3 relapses in 24 months with 1 in 12 months	≥1 relapse in 12 months or ≥2 relapse in 24 months	≥2 relapses in 24 months with 1 in 12 months	≥1 relapse in 12 months
Age inclusion criteria (years)	≥18	≥18	12-74	18-74
EDSS inclusion criteria	≤7	≤8	≤6.5	≤6.5
Number of patients (verum: placebo)	143 (96:47)	230 (174:56)	83 (41:42)	95 (63:32)
Age (verum vs. placebo)	43.9 versus 45.0	43.0 versus 42.6	40.8 versus 43.0	45.3 versus 40.5
Female sex (%)	92 versus 89	91 versus 89	90 versus 95	73 versus 97
AQP4-IgG ⁺ :IgG ⁻ (%)	143:0 (100)	213:17 (93)	55:28 (66)	64:31 (67)
EDSS at basal	4.0 versus 4.0 (median)	3.5 versus 4.0 (median)	3.8 versus 3.6 (mean)	3.9 versus 3.7 (mean)
Primary endpoint	Time to first relapse individual judgement changed to adjudicated later on	Time to first adjudicated relapse	Time to first protocol defined relapse	Time to first protocol defined relapse
Relapse rate (%) (HR, 95 CI)	3 versus 43 (0.06, 0.02-0.20)	12 versus 39 (0.272, 0.15-0.496)	20 versus 43 (0.38, 0.16-0.88)	30 versus 50 (0.45, 0.23-0.89)
Relapse rate reduction (%)	94	73	62	55
Relapse rate reduction in AQP4-IgG ⁺ (%)	94	77	79	74
Relapse free at 48 weeks (%)	89 versus 51	-	89 versus 66	76 versus 62
Relapse free at 96 weeks (%)	85 versus 36	-	78 versus 59	72 versus 51
Relevant secondary outcomes	Improved adjudicated ARR; but no impact on EDSS and QoL	Reduced participants with EDSS worsening	No change in fatigue or pain	No change in fatigue or pain
Common adverse events (death)	Upper respiratory infection, headache (1 death pulmonary empyema)	Urinary tract infection, arthralgia (2 deaths in open label extension; 1 respiratory insufficiency related to NMOSD, 1 indeterminate)	Nasopharyngitis, upper respiratory infection, headache (no deaths or anaphylactic reactions)	Upper respiratory infection, urinary tract infection (no deaths or anaphylactic reactions)
Infections	3xversus placebo	Not reported	Similar to placebo	Similar to placebo
Reference	Pittock <i>et al.</i> , 2019 ^[80]	Cree <i>et al.</i> , 2019 ^[81]	Yamamura <i>et al.</i> , 2019 ^[85]	Trabousee <i>et al.</i> , 2020 ^[84]
Trial registration	NCT01892345	NCT02200770	NCT02028884	NCT02073279

EDSS=Expanded disability status scale, AQP4=Aquaporin-4, IgG=immunoglobulin G, AQP4-IgG⁺=AQP4-IgG seropositive, AQP4-IgG⁻=AQP4-IgG seronegative, HR=Hazard ratio, CI=Confidence interval, IL6=Interleukin 6, IV=Intravenous, SC=Subcutaneous, ARR=Annualized relapse rate, QoL=Quality of life, NMOSD=Neuromyelitis optica spectrum disorder

adopted. For PREVENT, the adjudication systems with criteria with EDSS/Optico-Spinal Impairment Scale score were installed only after 88 participants were already enrolled. N-MOMentum study used a complex 18 clinical criteria including imaging to minimize the risk of missing an event. The SAkura study criteria for relapse adjudication were solely clinically based (EDSS/FSS change) and may be more applicable in clinical practice.

In clinical practice, IV infusions of eculizumab are required every 2 weeks and must be rigorously followed as complement component 5 activity begins to rise within a few days of a missed dose.^[86] Inebilizumab requires two infusions at start and then only two infusions per year. The SC formulation of satralizumab allows self-administration at home.

Due to these differences between the four trials, comparisons across trials cannot be made, and should be interpreted based

on the study designs. All the approved drugs are effective and safe for treating NMOSD. The choice of treatment depends on the decision of the health care professional and the patient, taking into account medical and patient assessments such as efficacy and safety of the treatment, previous medication and current disease state, comorbidities, preferred route of administration, and lifestyle.

Emerging Therapies

Despite the three new biologicals eculizumab, inebilizumab, and satralizumab as well as the off-label maintenance therapies like azathioprine, mycophenolate mofetil, or rituximab were established, therapy-refractory patients still pose a challenge. Restoring immune tolerance might provide an interesting treatment strategy in the future. Some success was achieved by using autologous hematopoietic stem cell transplantation,^[87] peptide-loaded tolerogenic dendritic cells,^[88] DNA vaccine encoding myelin basic protein,^[89] autoreactive T cell vaccination and regulatory T cells.^[90,91] Further alternative targets for NMOSD treatments are blood-brain barrier,^[92] complement cascade,^[93] granulocytes,^[94] and B cells.^[95,96] Another approach are engineered, monoclonal anti-AQP4 antibodies that block the binding of AQP4-IgG autoantibodies and lack cytotoxicity effector functions.^[97,98]

Conclusion

Quick diagnosis and prompt treatment are crucial for saving visual or neurology function in acute stage. Effective maintenance treatment is the other key to prevent patient from disability. We have to keep in mind that patients with NMOSD-ON may develop concurrent transverse myelitis or other CNS disease. Therefore, the patient may be referred to a diversified care team, including neurologists, physiatrists and psychiatrists, to implement further management.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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