NMOSD: nuove evidenze di patogenesi e terapia

Carla Tortorella
San Camillo Forlanini, Roma

NMOSD/MOGAD PAST HISTORY

Neuromyelits optica (NMO) is an inflammatory autoimmune demyelinating neurologic disease with a predilection for optic nerves and spinal cord

M. E. Devic, de Lyon. — **Myélite aiguë dorso-lombaire avec névrite optique. — Autopsie.**

Femme de 45 ans, migraineuse et nerveuse, ayant eu plusieurs crises d'hystérie pendant sa jeunesse. Ni maladies infectieuses récentes, ni intoxication professionnelle,
1890, son mari tombe gravem
avec un grand dévouement,
meurt en décembre de la m
mort, ayant dépensé ses der
travail peu rémunérateur, au
de symptômes neurasthéni
digestifs, asthénie neuro-mu
Ces symptômes augmentèren
la malade dut cesser tout tra
rale et la céphalée subirent
d'une vive frayeur.

Va an del SM

A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis

Lancet 2004; 364: 2106–12

Vanda A Lennon, Dean M Wingerchuk, Thomas J Kryzer, Sean J Pittock, Claudia F Lucchinetti, Kazuo Fujihara, Ichiro Nakashima, Brian G Weinshenker

Department of Neurology,

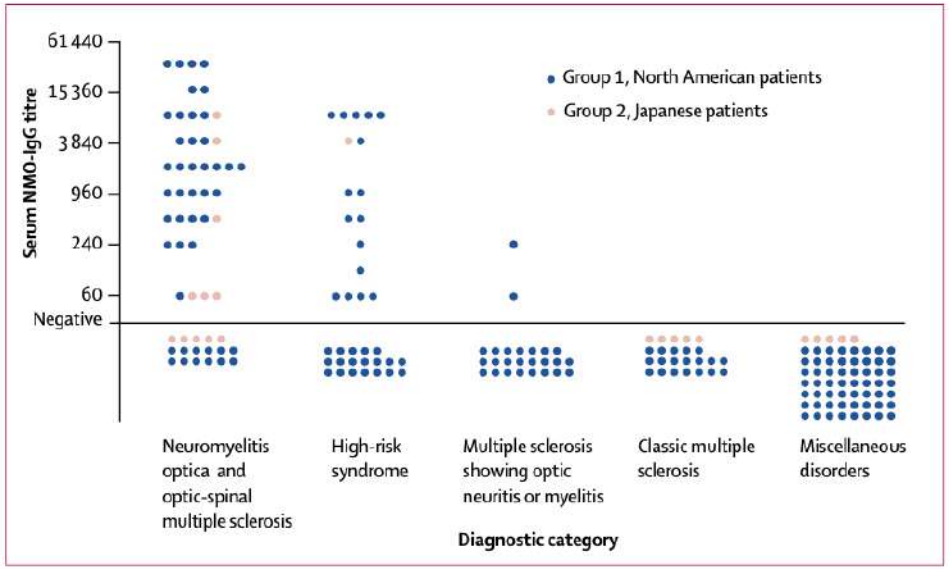
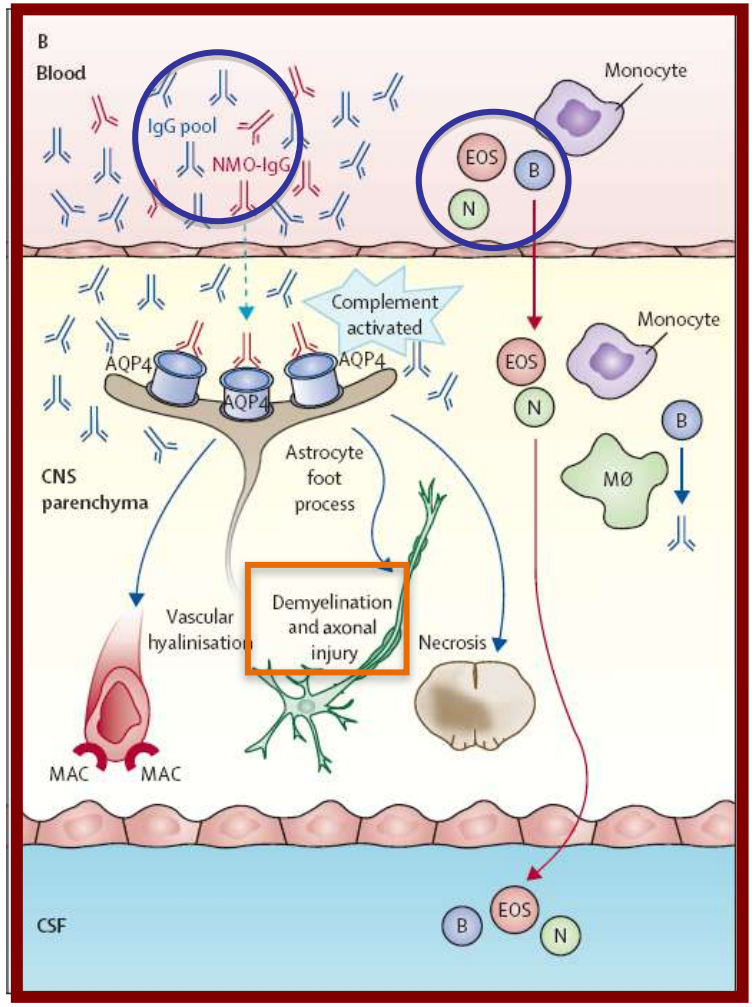
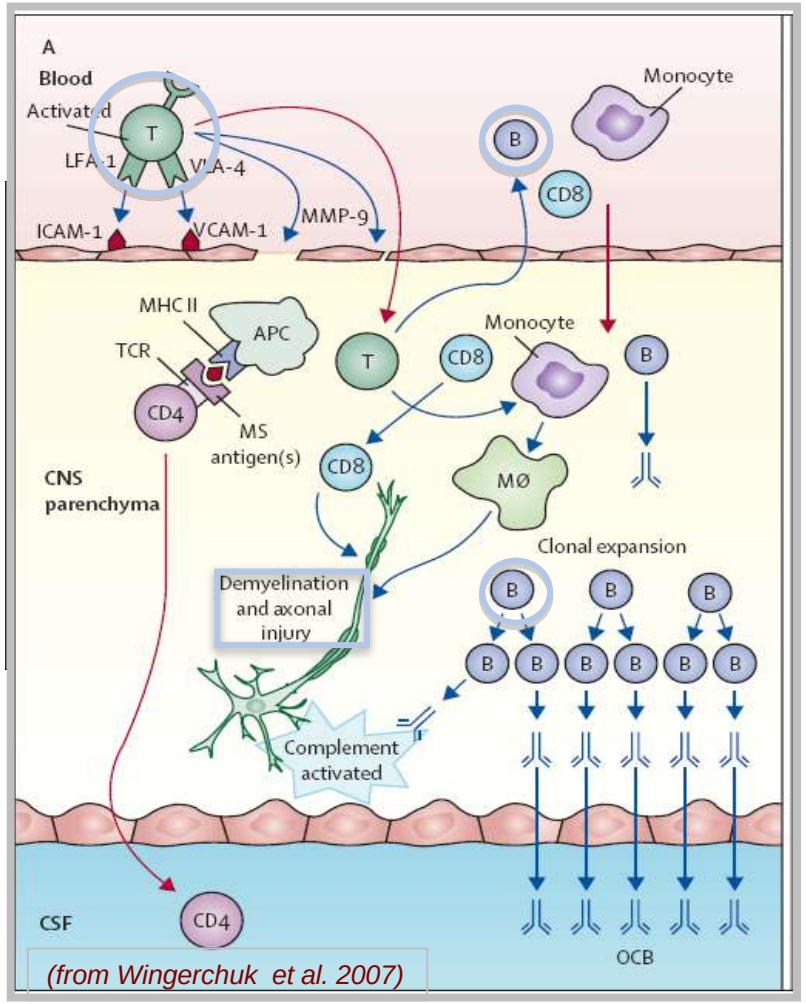


Figure 2: **Distribution of NMO-IgG titres in serum samples of patients**
Titres are expressed as the reciprocal of doubling serum dilutions. Serum samples below the horizontal line are negative. Lowest positive value is 1 in 60; highest is 1 in 30 720.

NMOSD pathogenesis

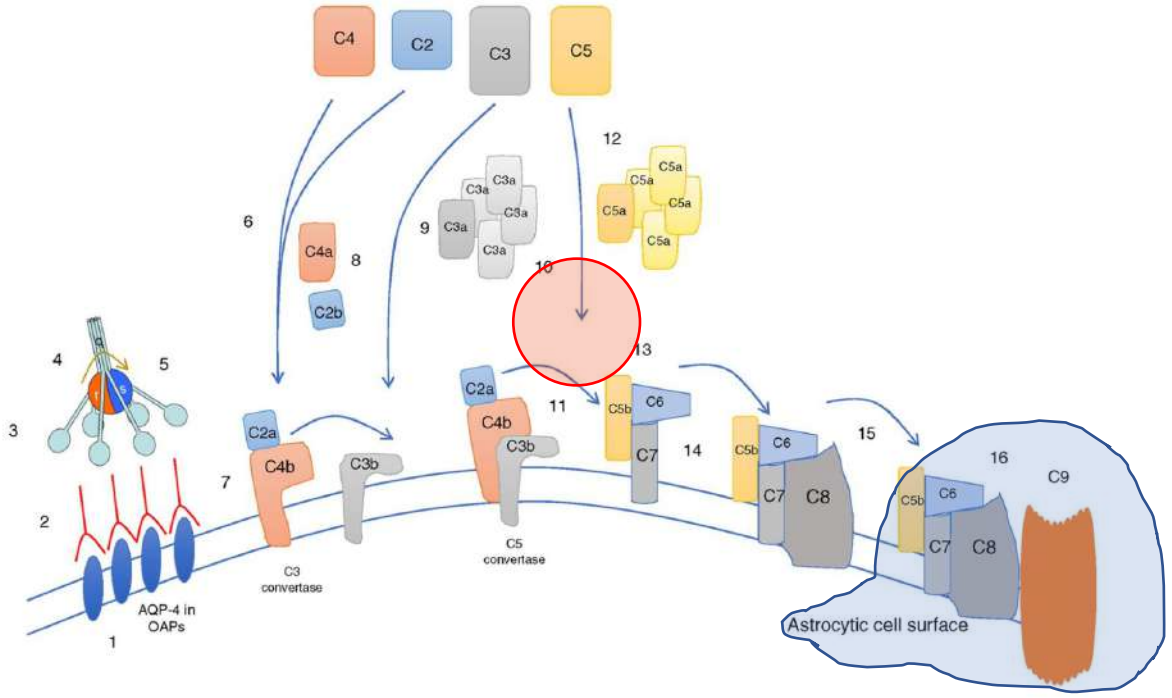




MS

[Wingerchuk et al. 2007, Whittam D 2017]

NMOSD pathogenesis

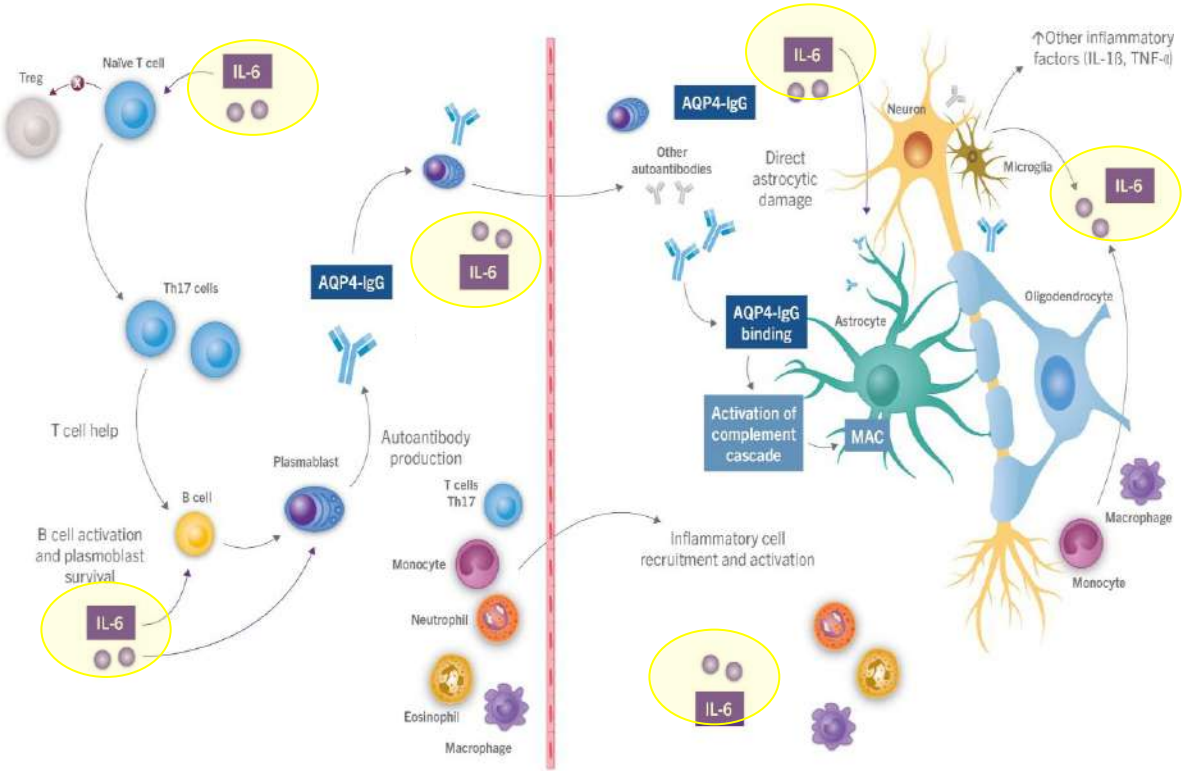


MEMBRANE ATTACK COMPLEX

Activation of autoimmune cascade[4-9]

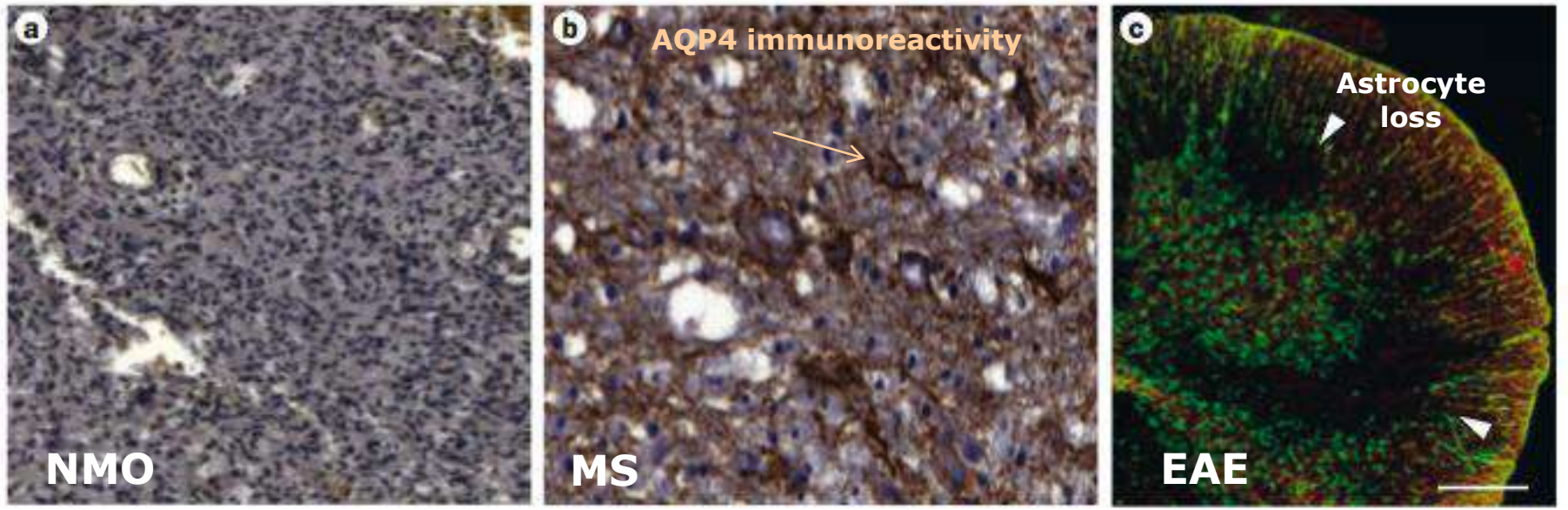
BBB disruption and increased permeability[4-9]

Astrocyte injury and lesion propagation[4-9]



NMOSD pathology

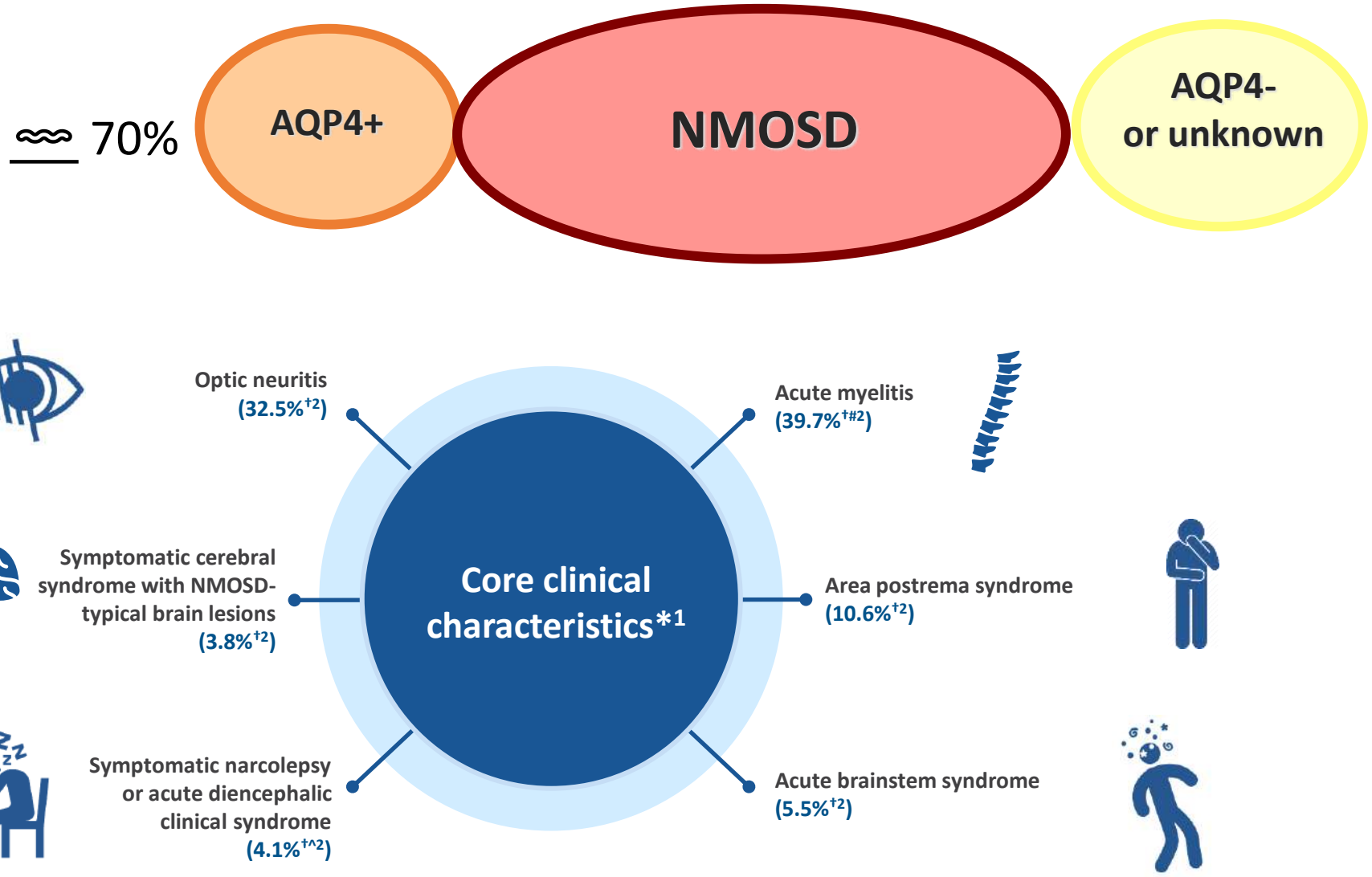
Lesions are characterized by marked AQP4 loss



Human IgG derived from patients with NMO injected in animal models caused a characteristic inflammatory infiltrate consisting in macrophages, neutrophilis and eosinophilis.
Astrocyte marker (GFAP) is lost in parallel with AQP4 while myelinated fibers seemed to be preserved.

[Misu et al. 2007]

NMOSD/MOGAD: PRESENT HISTORY



[Wingerchuk et al. Neurology 2015]

NMOSD diagnostic criteria IPND 2015

Table 1 NMOSD diagnostic criteria for adult patients

Diagnostic criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses[a]

AQP4- or unknown

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses[a]

[Wingerchuk et al. Neurology 2015]

NMOSD IPND 2015 diagnostic criteria

Characterization of the heterogeneity of AQP4 seronegative NMOSDs:

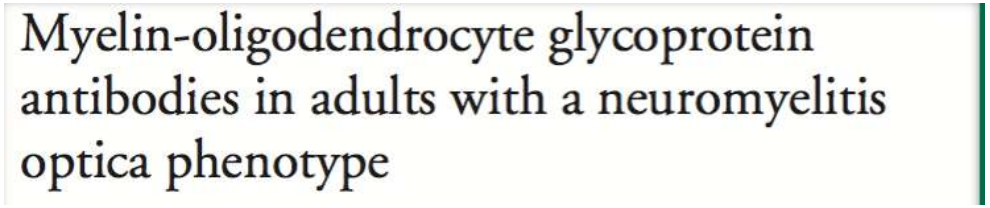
- **False negative assay**
- **Other "NMOSD variants"**

RESEARCH Open Access

Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders

Simone Mader[1], Viktoria Gredler[1], Kathrin Schanda[1], Kevin Rostasy[2], Irena Dujmovic[3], Kristian Pfaller[4], Andreas Lutterotti[1], Sven Jarius[5], Franziska Di Pauli[1], Bettina Kuenz[1], Rainer Ehling[1], Harald Hegen[1], Florian Deisenhammer[1], Fahmy Aboul-Enein[6], Maria K Storch[7], Peter Koson[8,9], Jelena Drulovic[3,10], Wolfgang Kristoferitsch[11], Thomas Berger[1] and Markus Reindl[1*]

[Journal of Neuroinflammation, 2011]

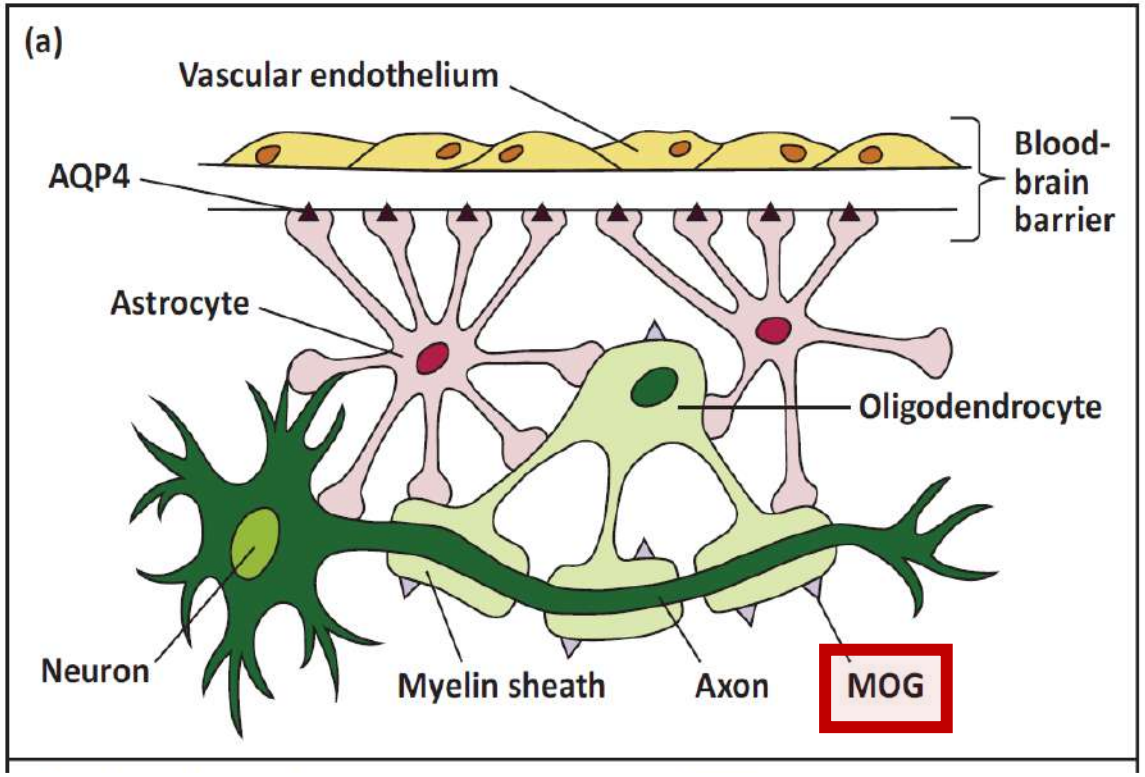


Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype

[Kitley J et al. Neurology, 2012]

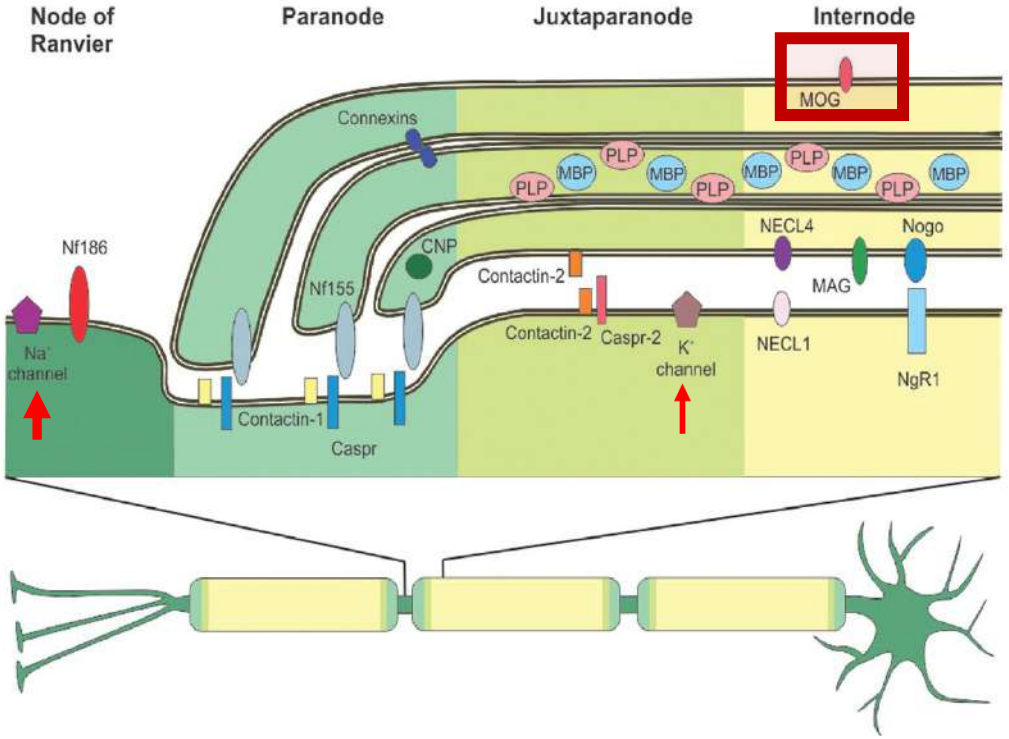
About 20-30% of AQP4 seronegative

MOGAD pathogenesis



MOG is a minor component of myelin sheats

Myelin proteins

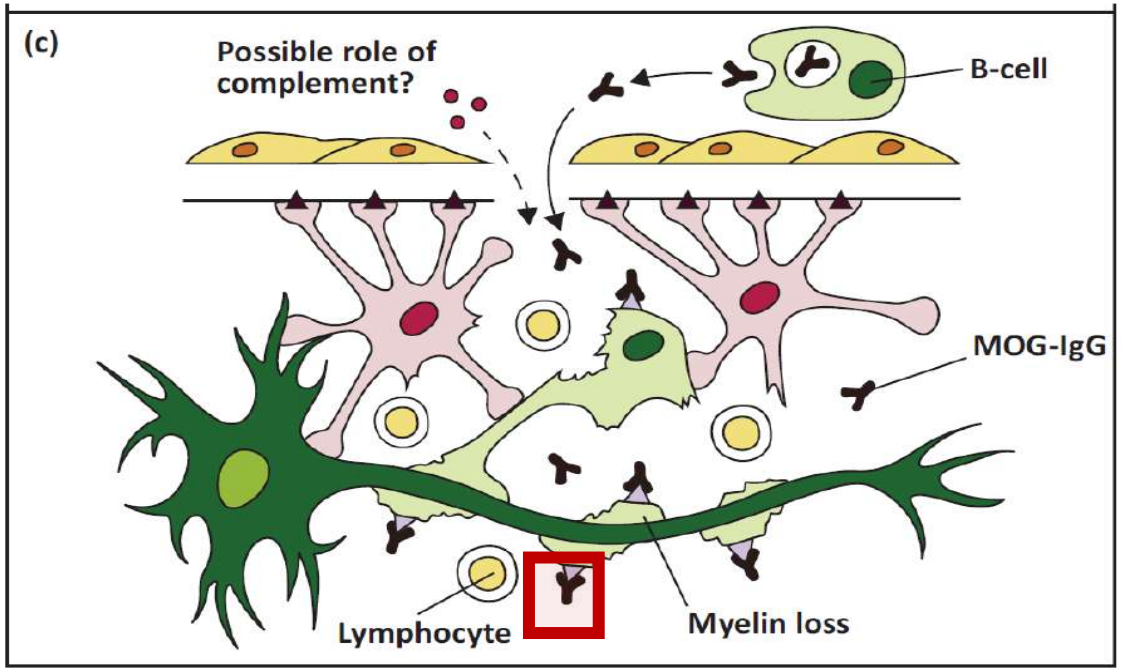


MOG lack of specific central immune tolerance
Located at the **outermost surface** of the myelin sheath

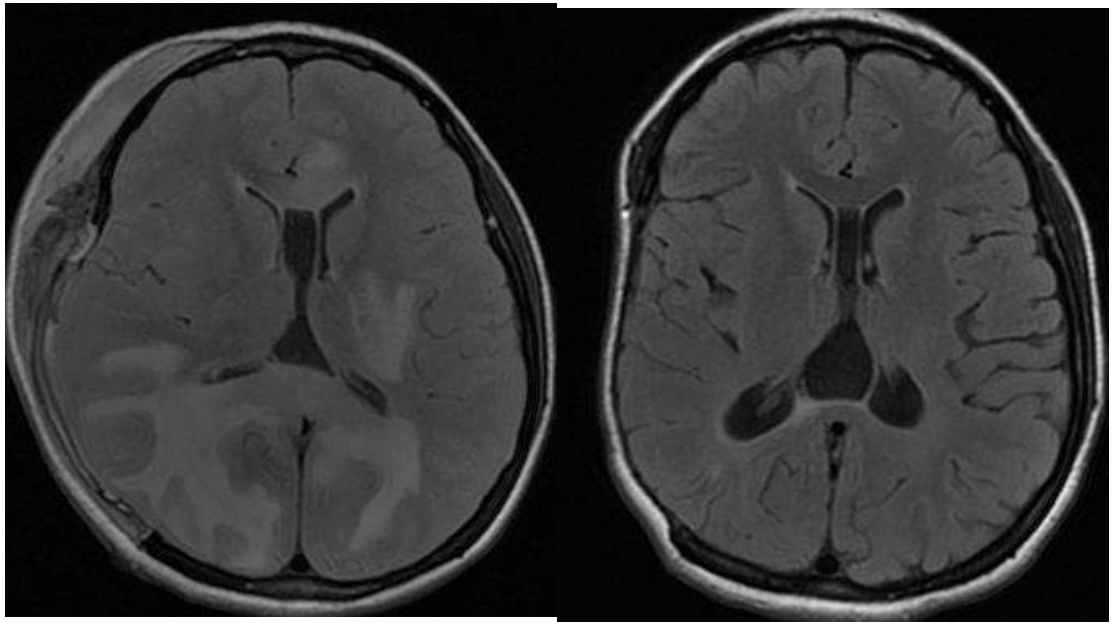
Ideal candidate target of the immune attack in inflammatory demyelinating CNS diseases

[Huda S, et al. Clin Med 2019;19:169]

ADEM mechanisms of repair



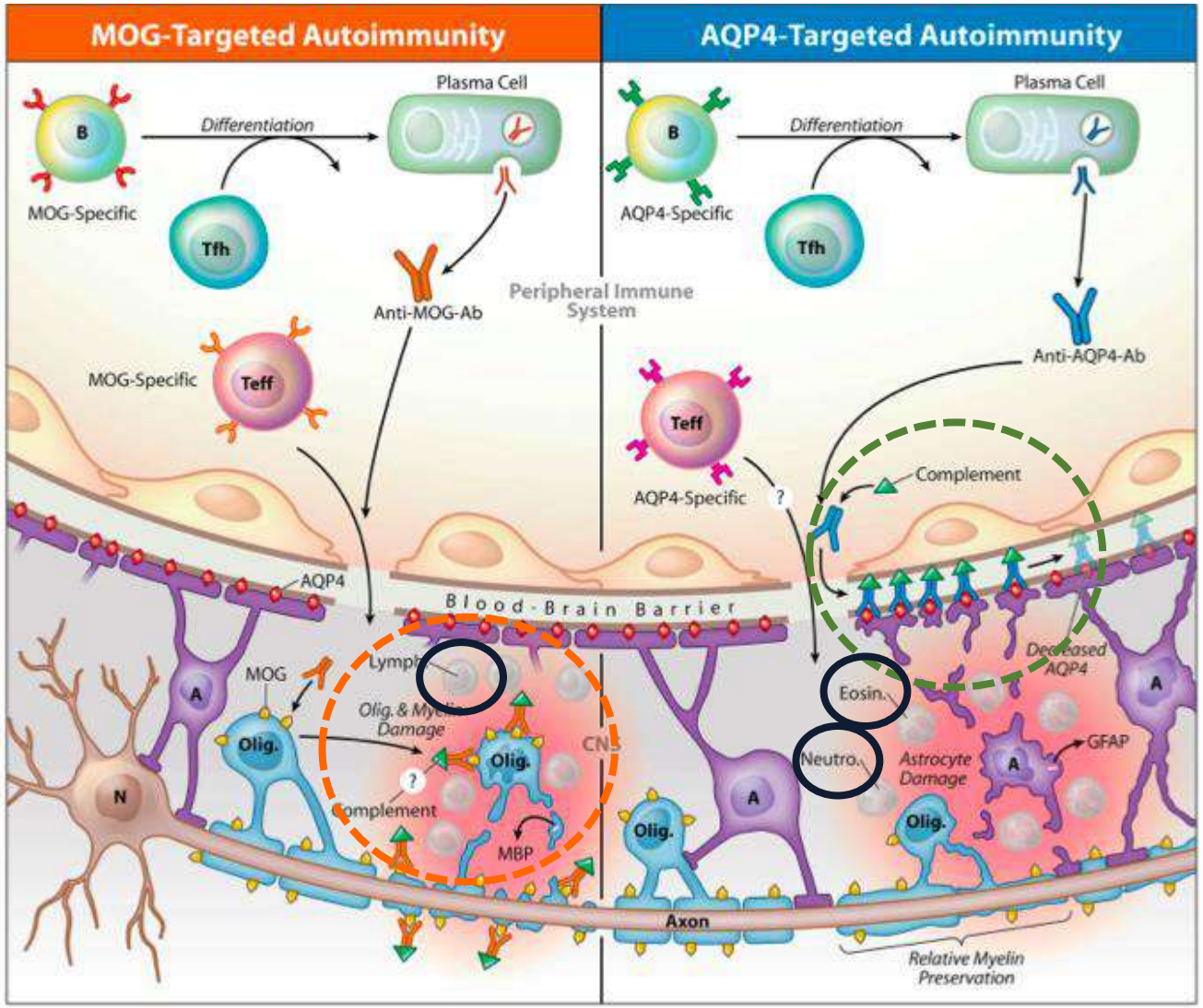
[Huda S, et al. Clin Med 2019;19:169]



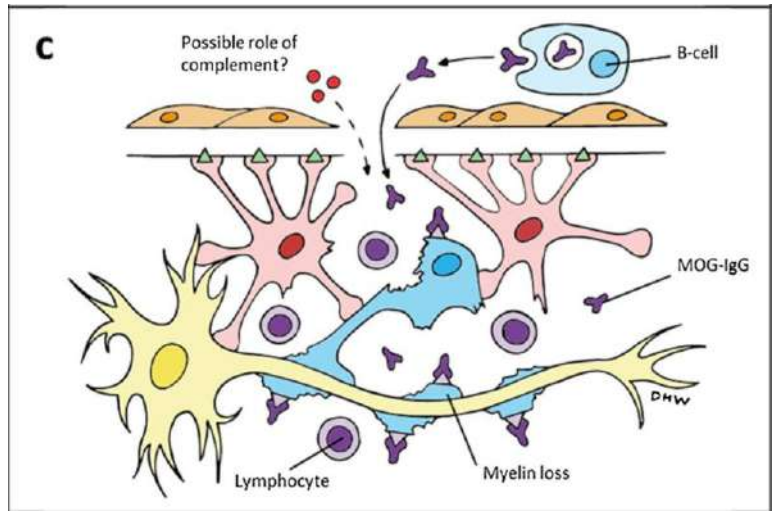
Since MOG is expressed on **mature oligodendrocytes**, but not on ***oligodendrocyte progenitor cells***, rapid recruitment of new oligodendrocytes occurs in the lesions, which is associated with rapid and complete remyelination

Anti-MOG vs anti-AQP4 related autoimmunity

Oligodendrocytes

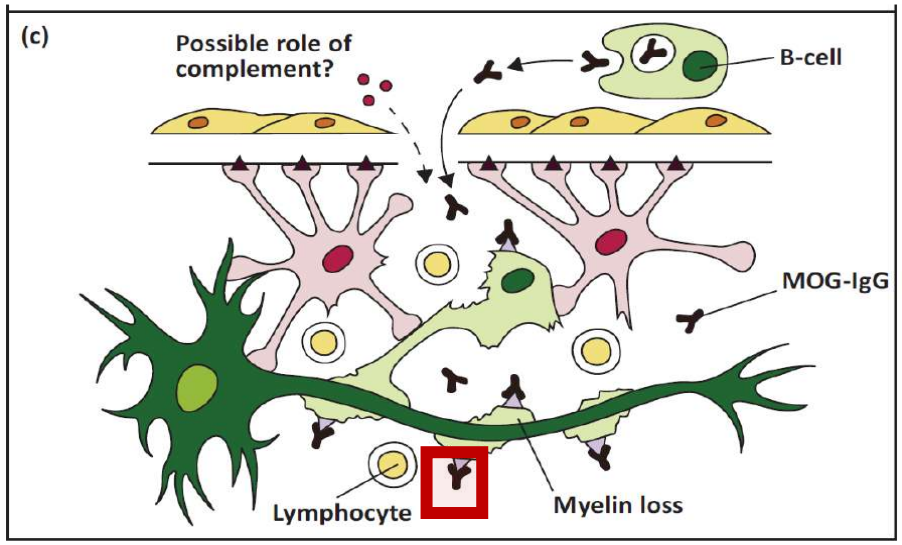


Astrocytes



[Zamvil S and Slavin AJ Neurol Neuroimmunol Neuroinflamm 2015]

MOGAD pathology



[Huda S, et al. Clin Med 2019;19:169]

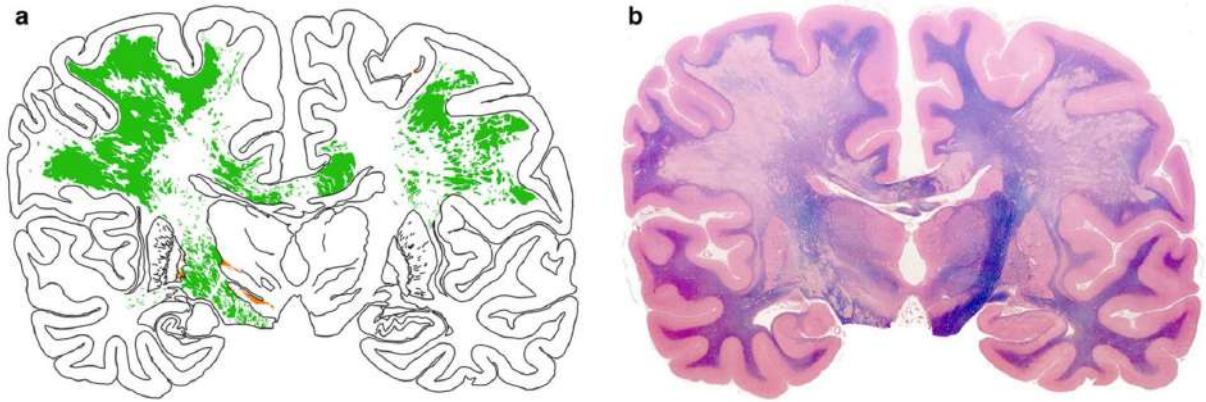
Acta Neuropathologica (2020) 139:875–892
https://doi.org/10.1007/s00401-020-02132-y

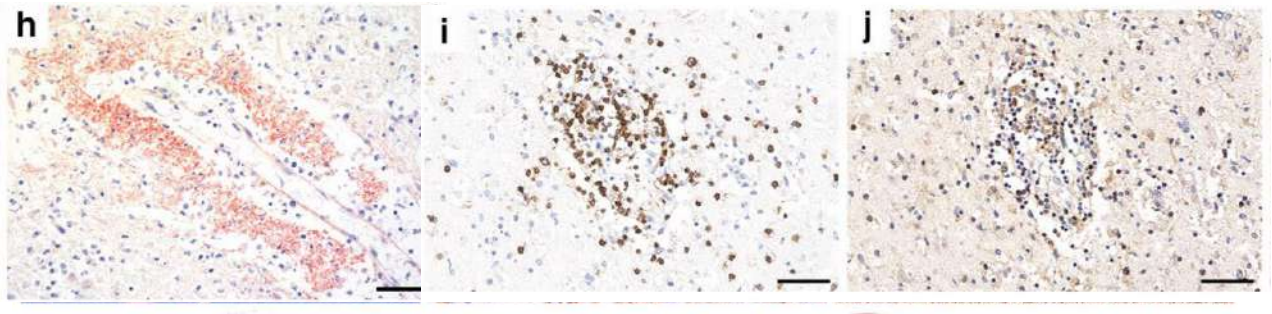
ORIGINAL PAPER

The pathology of central nervous system inflammatory demyelinating disease accompanying myelin oligodendrocyte glycoprotein autoantibody

Romana Höftberger[1] · Yong Guo[2] · Eoin P. Flanagan[2,3] · A. Sebastian Lopez-Chiriboga[2] · Verena Endmayr[1] · Sonja Hochmeister[4] · Damir Joldic[5] · Sean J. Pittock[2,3] · Jan Mendelt Tillema[2] · Mark Gorman[6] · Hans Lassmann[7] Claudia F. Lucchinetti[2]

- 2 autopsies and 22 brain biopsies



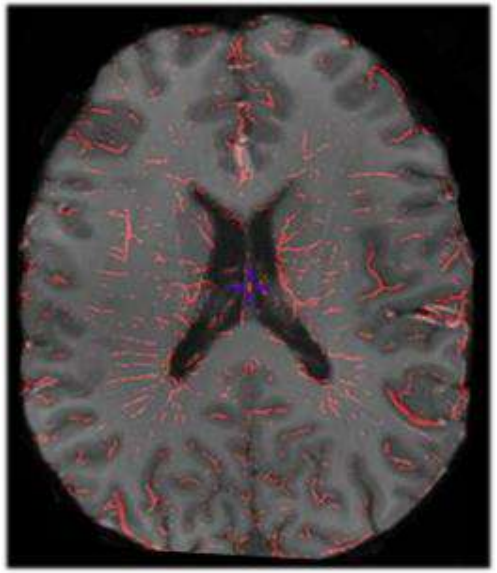


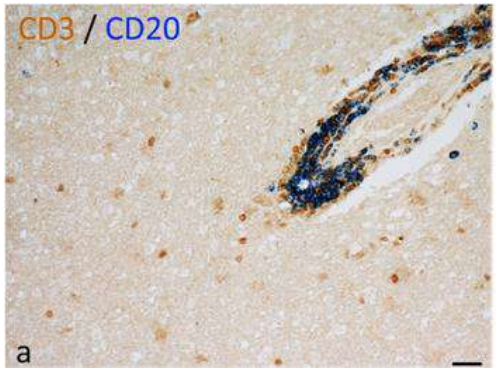
Perivenous deposition of activated complement complex

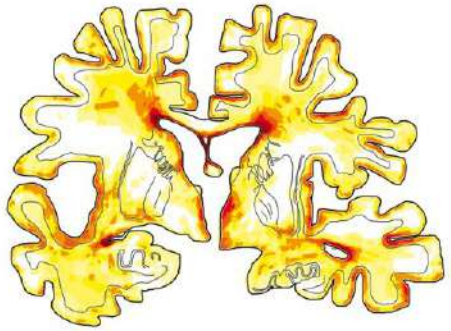
The inflammatory infiltrates mainly contain CD3 and CD4 positive T cells, less CD8-positive T cells

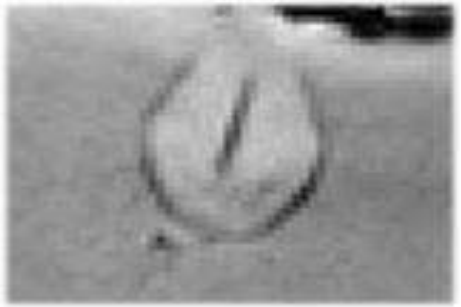
Pathological Differences between MS and MOGAD

Höftberger et al 2020, Grabner et al 2014, Haider et al 2016, Machado Santos et al 2018

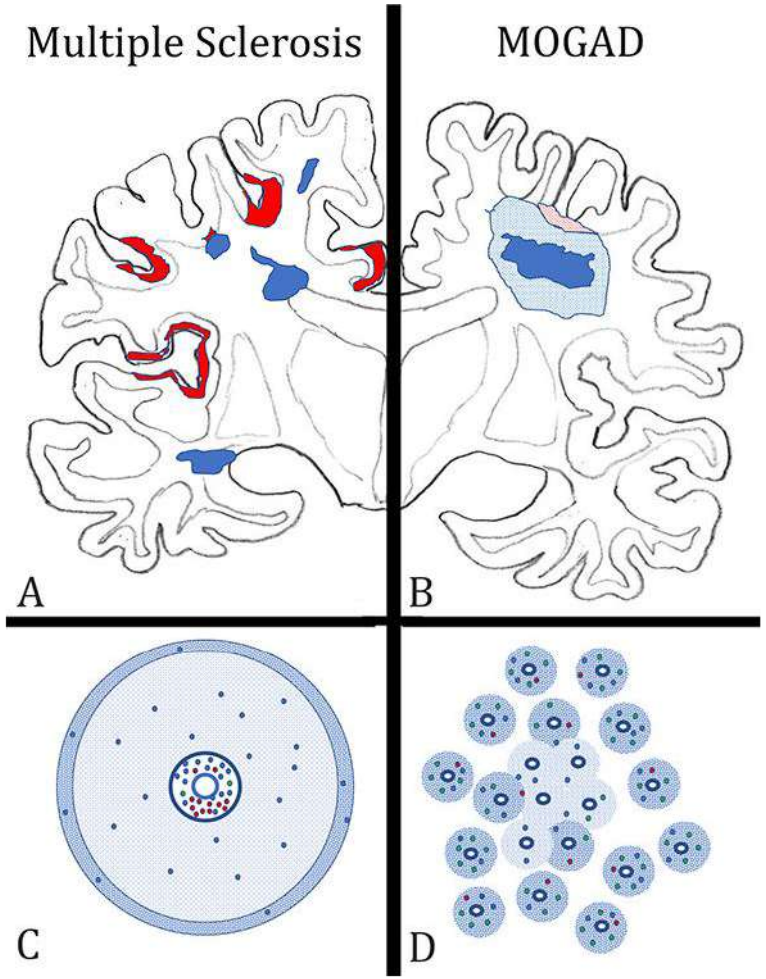


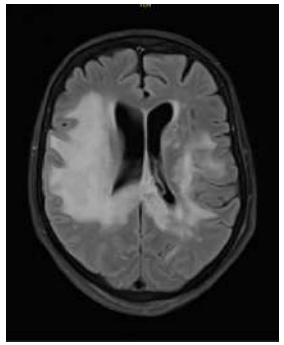


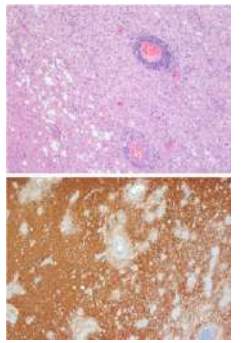




Large Veins
Central Vein Sign
Focal Chronic Active
Expanding Lesions
Periventricular
Iron Rim Lesions





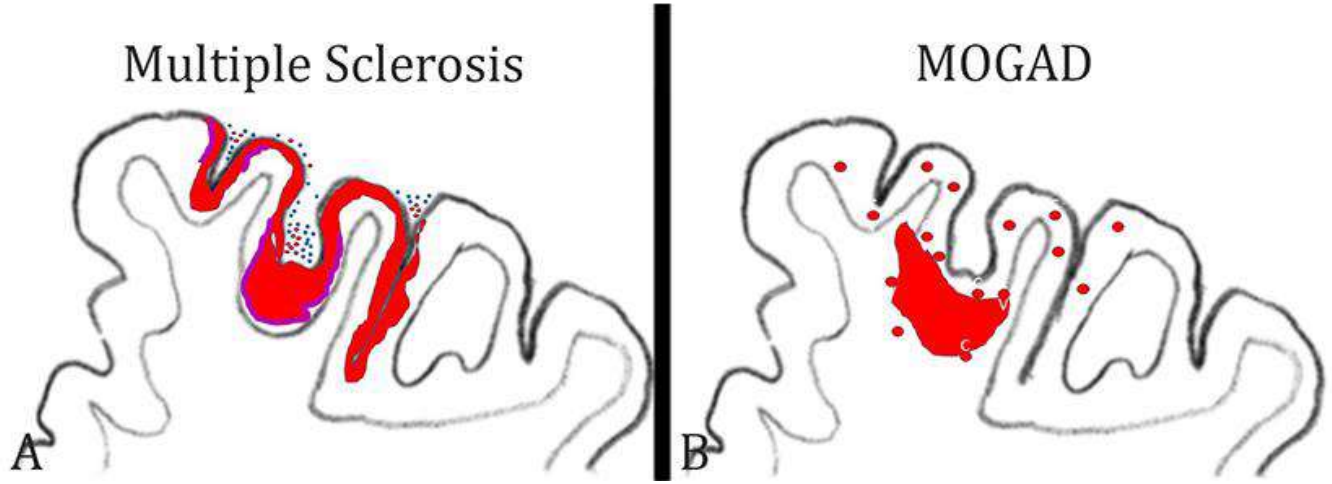


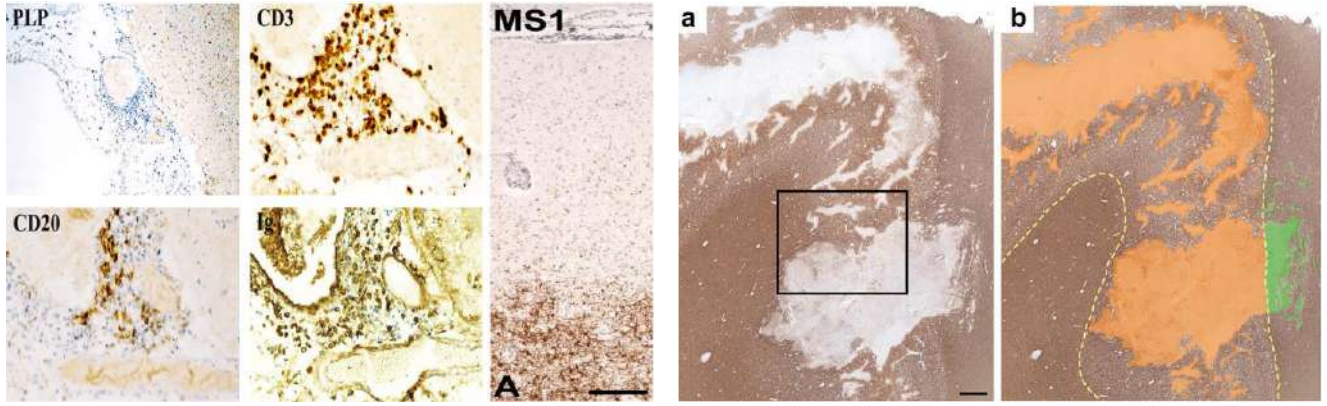
Small Veins and Venules
Perivenous Confluent ADEM-Like Lesions
No Central Vein Sign
Deep White Matter
Active and Inactive Lesions
No Chronic Active or Slowly Expanding Lesions
No Iron Rim Lesions

[Courtesy of H. Lassman]

Pathology of Cortical Lesions in MS and MOGAD

Fischer et al 2013, Höftberger et al 2020





MS:

- **Meningeal inflammatory aggregates** with features of tertiary lymphofolicles
- **Band-like subpial demyelination** underneath the meningeal inflammation

MOGAD:

- **Perivenous cortical inflammation**
- Perivenous confluent **intracortical demyelination**, focal lesions
- Meningeal inflammation with subpial cortical demyelination is rare

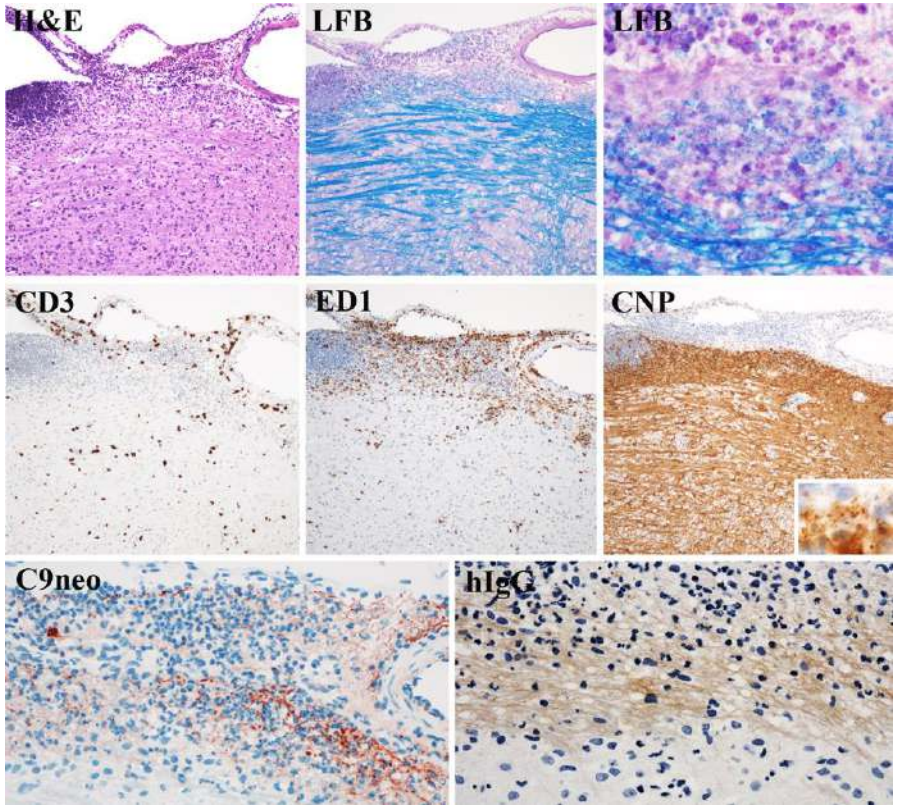
[Courtesy of H. Lassman]

Pathogenic role of MOG-antibodies in MOGAD

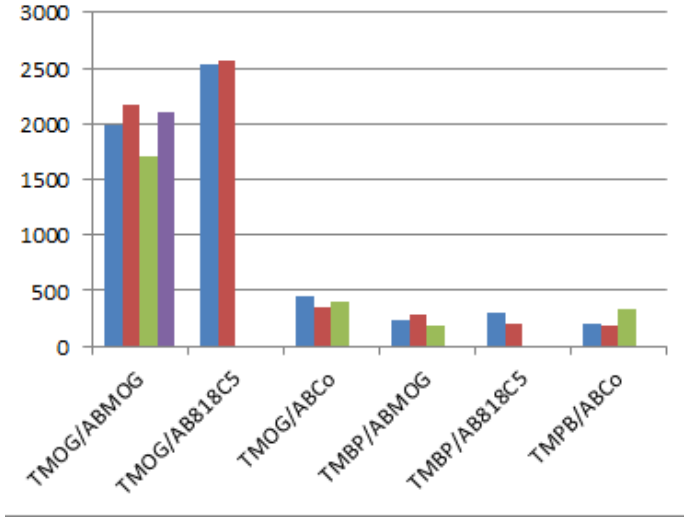
Transfer of Patient derived MOG-Abs into rodents:

- **Increased inflammation** through supported MOG antigen presentation to CD4+ T-cells
- **Induction of demyelination through complement activation and antibody dependent cellular cytotoxicity**

Induction of Demyelination



Amplification of CD4⁺ T-Cell mediated Inflammation



[Spadaro et al 2018]

MOGAD diagnostic criteria

Box. Proposed Diagnostic Criteria for Myelin Oligodendrocyte Glycoprotein (MOG-IgG)–Associated Disorders[a]

1. Laboratory finding[b]: serum positive for MOG-IgG by cell-based assay[c]
2. Clinical findings: any of the following presentations:
   1. ADEM
   2. Optic neuritis, including CRION
   3. Transverse myelitis (ie, LETM or STM)
   4. Brain or brainstem syndrome compatible with demyelination
   5. Any combination of the above
3. Exclusion of alternative diagnosis

Abbreviations: ADEM, acute demyelinating encephalomyelitis; CRION, chronic relapsing inflammatory optic neuropathy; LETM, longitudinally extensive transverse myelitis; STM, short-segment transverse myelitis.

[a] Must meet all 3 criteria.

[b] Transient seropositivity favors lower likelihood of relapse.

[c] In abscense of serum, positivity in cerebrospinal fluid would allow fulfillment of criteria 1.

International MOGAD Criteria
Including MRI criteria

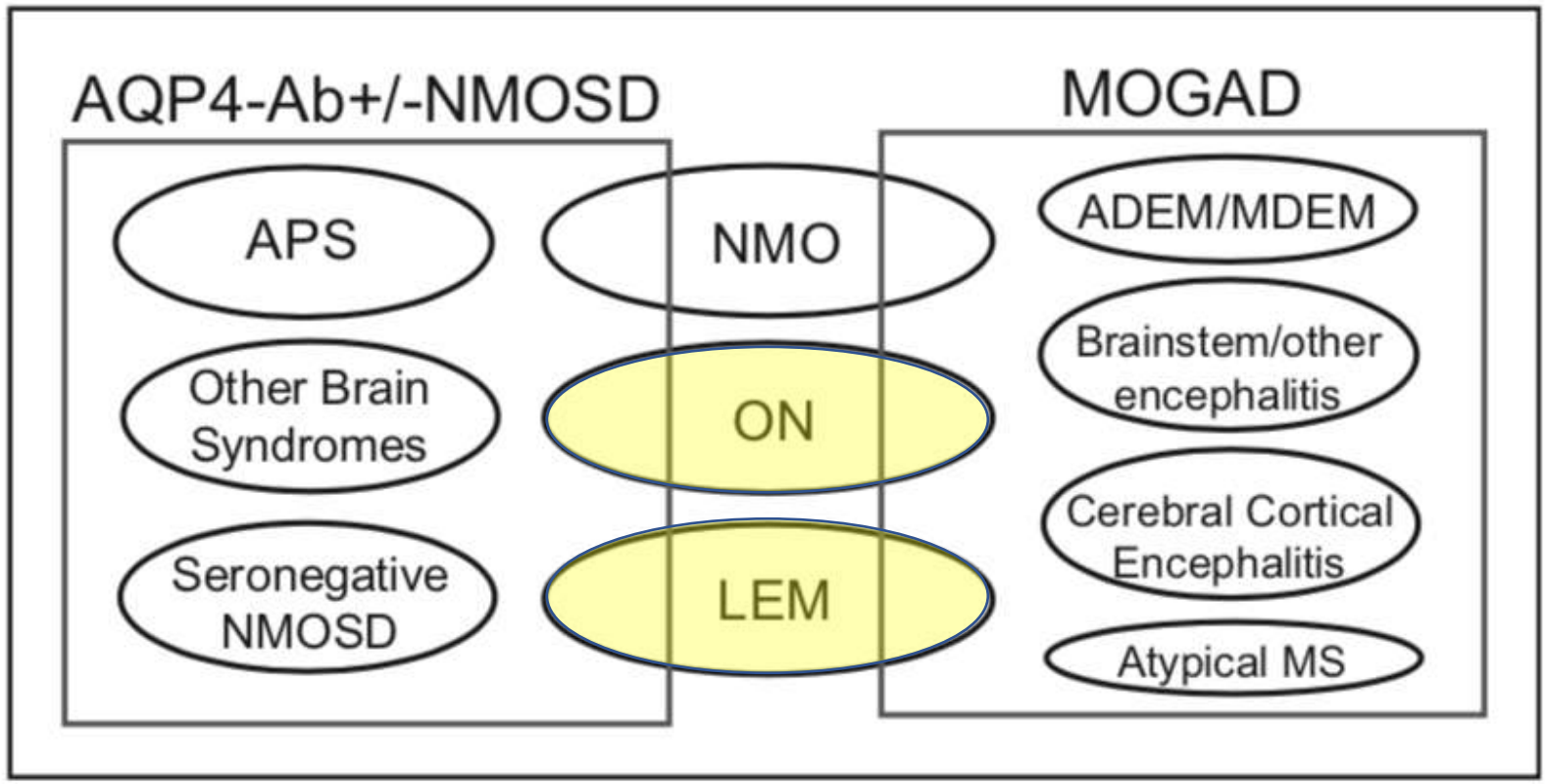
work in progress

[López-Chiriboga SA et al JAMA 2018]

NMOSD/MOGAD and MS CLINICAL OVERLAP

Autoimmune astrocitopathic disease

Inflammatory demyelinating disease



Clinical spectrum of AQP4-Ab/NMOSD and MOGAD.
ADEM/MDEM, acute disseminated encephalomyelitis/multiphasic disseminated encephalomyelitis; APS, are postrema syndrome; LEM, longitudinally extensive myelitis; ON, optic neuritis.

Published Ahead of Print on May 1, 2019 as 10.1212/WNL.0000000000007573

ARTICLE OPEN ACCESS

"Better explanations" in multiple sclerosis diagnostic workup

A 3-year longitudinal study

Massimiliano Calabrese, MD, Claudio Gasperini, MD, Carla Tortorella, MD, Gianmarco Schiavi, MD, Giovanni Frisullo, MD, Paolo Ragonese, MD, Roberta Fantozzi, MD, Luca Prosperini, MD, Pietro Annovazzi, MD, Cinzia Cordioli, MD, Massimiliano Di Filippo, MD, Diana Ferraro, MD, Alberto Gajofatto, MD, Simona Malucchi, MD, Salvatore Lo Fermo, MD, Giovanna De Luca, MD, Maria L. Stromillo, MD, Eleonora Cocco, MD, Antonio Gallo, MD, Damiano Paolicelli, MD, Roberta Lanzillo, MD, Valentina Tomassini, MD, Ilaria Pesci, MD, Maria E. Rodegher, MD, and Claudio Solaro, MD, the RIREMS group (Rising Italian Researchers in Multiple Sclerosis)

Neurology® 2019;92:e1-e11. doi:10.1212/WNL.0000000000007573

695 patients;
23 MS centre
3 yrs follow-up

Published Ahead of Print on May 1, 2019 as 10.1212/WNL.0000000000007566

EDITORIAL

Differential diagnosis of multiple sclerosis

The better explanations in clinical practice

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Neurology® 2019;92:1-2. doi:10.1212/WNL.0000000000007566

Alternative diagnoses were formulated in 163 (**24.4%**) cases

- Nonspecific neurologic symptoms in association with atypical MRI lesions of suspected vascular origin
- Migraine with atypical lesions
- Neuromyelitis optica spectrum disorders

NMOSD/MOGAD and MS RADIOLOGICAL OVERLAP

	Total	MOG -	MOG +	p
N. Pts (%)	57	38 (67%)	19 (33%)	
Follow-up (years)	3.3±3.2	3.5±3	3±3.8	ns
II clinical episode [n.pts]	25	17 (68%)	8 (32%)	ns
Time between I-II clinical episode, (months)	18± 21	15±12.3	24.4±32.9	ns
DIT[a] and DIS[b] MRI at FU [n.pts (%)]	**33**	**25(65%)**	**8(42%)**	**0.07**

[Tortorella C et al ECTRIMS 2017]

Wingerchuk's 2015 criteria for NMOSD were met in **32 %**
McDonald criteria for MS were met by **33 %** (mean follow-up 75 ± 46.5 months)

[Jarius S et al J Neurol Neuroinflamm, 2016]

Patients with MOGAD are less likely to develop clinically silent MRI lesions than are patients with MS

[Ramanathan et al JNNP, 2017]

Table 1 Cohort summary of relapsing paediatric and adult MOG antibody-positive patients: clinical and laboratory characteristics

Clinical and laboratory characteristics	Total cohort (n=59)	Paediatric patients (n=33)	Adult patients (n=26)	P value*
Age at onset (years) Mean; median (range)	21; 12 (1-74)	7; 6 (1–16)	40; 37 (18-74)	NA
Fulfills 2015 NMOSD criteria	15/59 (25%)	7/33 (21%)	8/26 (31%)	0.403
Fulfills revised McDonald criteria for MS	9/59 (15%)	6/33 (18%)	3/26 (12%)	0.481
Follow-up duration (months) Mean; median (range)	61; 45 (12–288)	66; 63 (12–206)	54; 39 (12–288)	0.225

[Ramanathan et al JNNP, 2017]

NMOSD vs MS: RADIOLOGICAL differences

Annals of NEUROLOGY
An Official Journal of the American Neurological Association and the Child Neurology Society
AMERICAN NEUROLOGICAL ASSOCIATION

Research Article

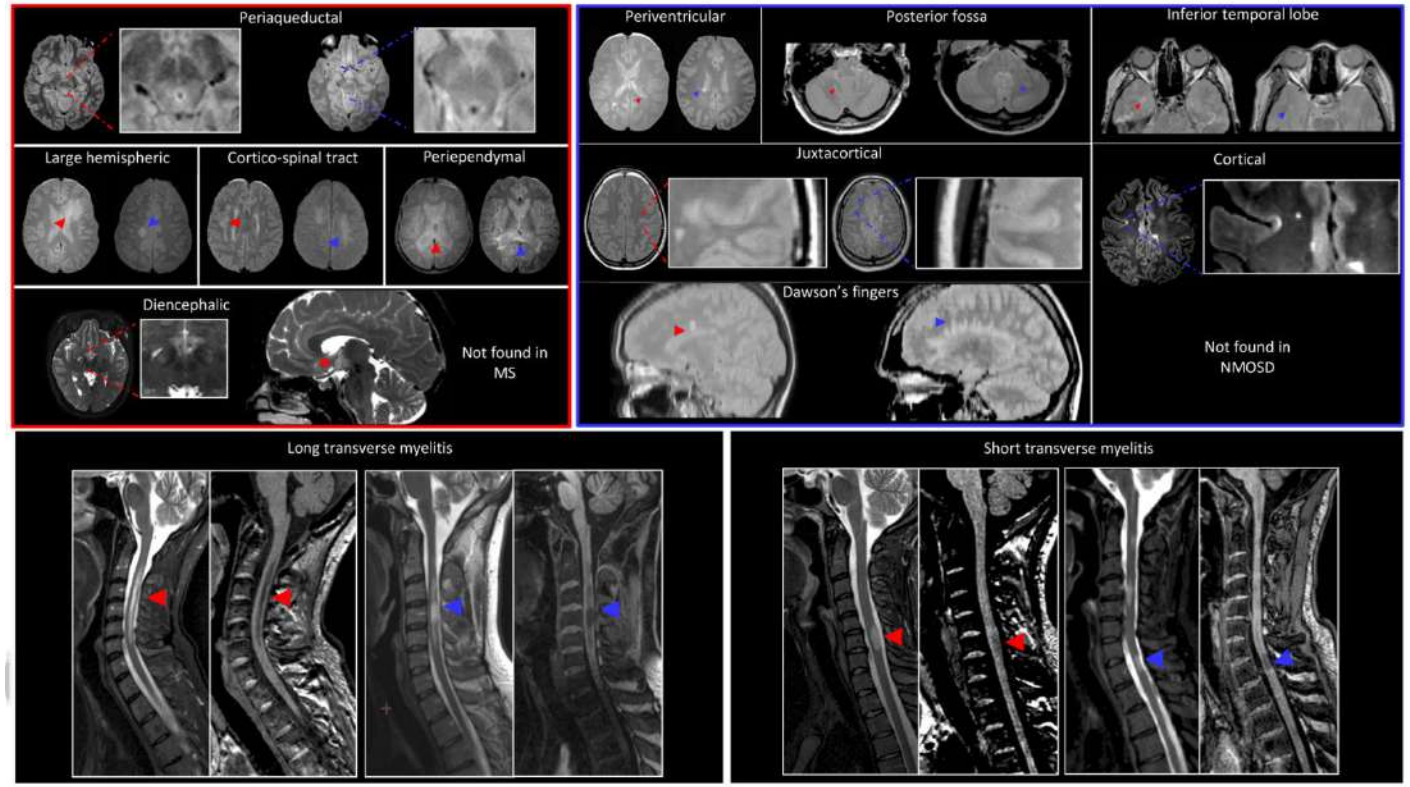
Brain and cord imaging features in neuromyelitis optica spectrum disorders

Cacciaguerra et al. 2019

At least 2/5:

- Absence of juxtacortical/cortical lesions
- Absence of periventricular lesions
- Absence of Dawson's fingers
- **Presence of long transverse myelitis**
- **Presence of periependymal lesions along lateral ventricles**

82% Sensitivity, 91% Specificity for NMOSD



MOGAD non ACUTE phase: RADIOLOGICAL discriminators

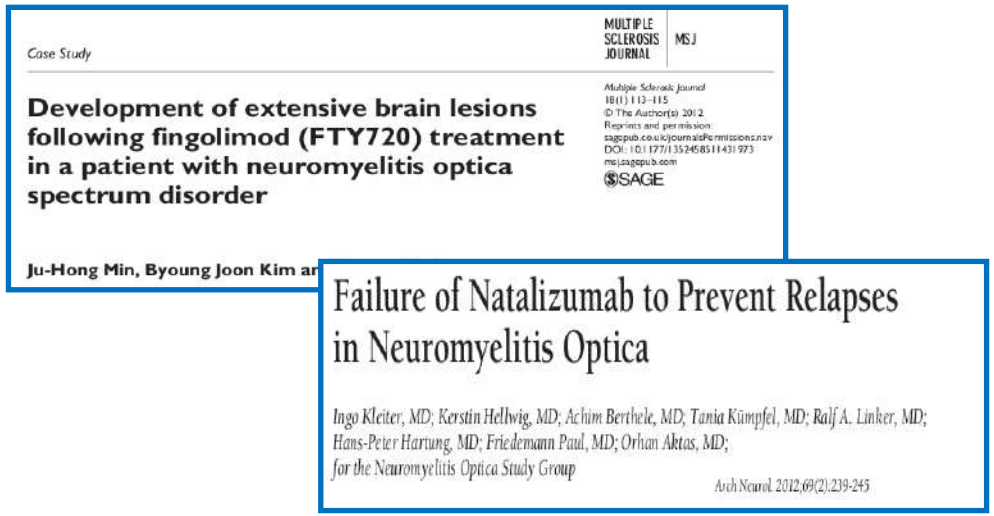
Forest model using the best sets of discriminators and the imputed set of data.

	Variable importance			Mean Decrease Impurity	Mean Decrease Accuracy	Accuracy (LOOCV)	Kappa (LOOCV)	AUC (95%CI)
	MOGAD	AQP4-NMOSD	RRMS					
	MRI							
Dawson's fingers lesion	77.4	5.3	58.6	72.9	88.4	0.68	0.52	0.75 (0.72-0.78)
Temporal lobe lesion	71.7	12.4	31	16.3	72			
LETM	42.6	76.1	26	23.4	73			
	Clinical & MRI							
Dawson's fingers lesion	48.1	34.9	38.5	55.6	65.2	0.76	0.64	0.85 (0.82-0.88)
Temporal lobe lesion	39.9	20.2	15.3	30.9	42.7			
LETM	36.4	30.0	12.9	19.5	41.4			
Age at MRI	-0.4	15.2	10.9	43.0	14.8			
EDSS	23.1	33.8	9.4	40.4	36.8			

[Cortese R et a al submitted]

NMOSD/MOGAD and MS DIFFERENT TREATMENT RESPONSE

- Different Pathogenesis
- Overlapping Phenotypes
- Different Treatments



Case Study

MULTIPLE SCLEROSIS JOURNAL | MSJ

Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder

Ju-Hong Min, Byoung Joon Kim ar

Failure of Natalizumab to Prevent Relapses in Neuromyelitis Optica

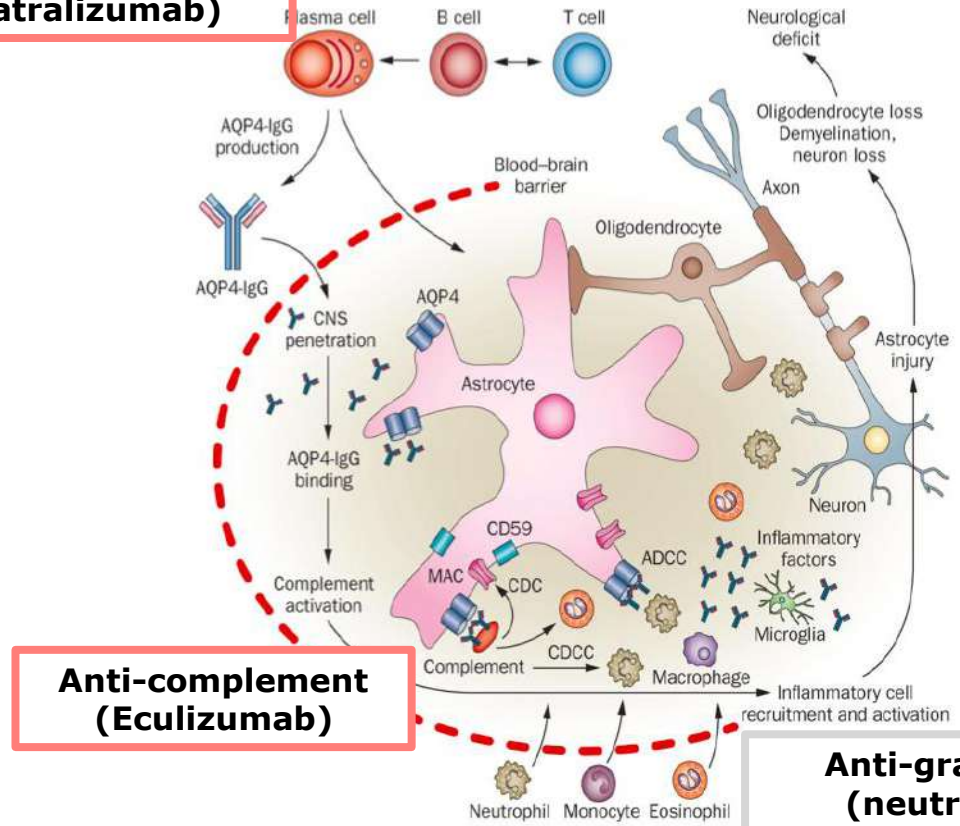
Ingo Kleiter, MD; Kerstin Hellwig, MD; Achim Berthele, MD; Tania Kümpfel, MD; Ralf A. Linker, MD; Hans-Peter Hartung, MD; Friedemann Paul, MD; Orhan Aktas, MD; for the Neuromyelitis Optica Study Group

Arch Neurol. 2012;69(2):239-245

Anti IL6R (Toclizumab; Satralizumab)

Anti CD19 (Rituximab)

Immunosoppressant



Anti-complement (Eculizumab)

Anti-granulocytes (neutrophil and eosinophil)

JAMA Neurology | Original Investigation

Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders

A Systematic Review and Meta-analysis

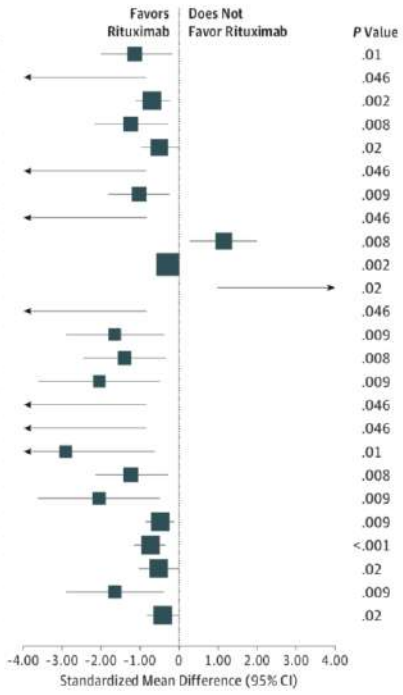
Valentina Damato, MD; Amelia Evoli, MD; Raffaele Iorio, MD, PhD

JAMA Neurol. 2016;73(11):1342-1348. doi:10.1001/jamaneurol.2016.1637
Published online September 26, 2016.

No RCT
Approved for 648 use in Italy
G.U. 05/03/2018 n. 53

Figure 2. Forest Plot Showing the Annualized Relapse Rate Ratio of Patients With Neuromyelitis Optica Spectrum Disorders After Rituximab Therapy

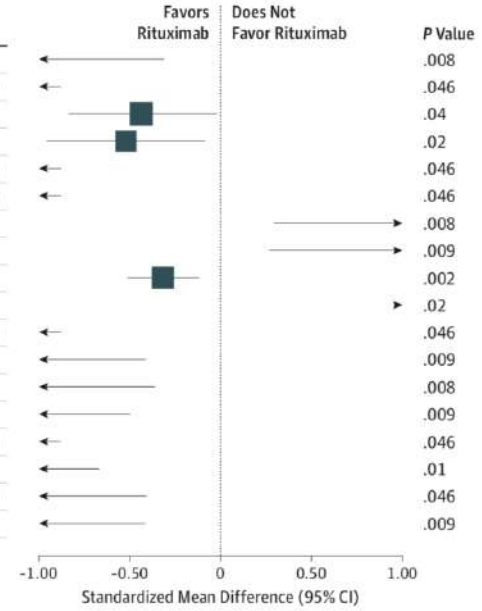
Source	Standardized Mean Difference (95% CI)	*P* Value
Cree et al,[17] 2005	-1.123 (-2.007 to -0.238)	.01
Capobianco et al,[19] 2007	-45.012 (-89.145 to -0.879)	.046
Jacob et al,[13] 2008	-0.693 (-1.130 to -0.257)	.002
Jarius et al,[22] 2008	-1.237 (-2.158 to -0.317)	.008
Bedi et al,[29] 2011	-0.523 (-0.959 to -0.087)	.02
Mahmood et al,[31] 2011	-45.012 (-89.145 to -0.879)	.046
Pellkofer et al,[33] 2011	-1.028 (-1.794 to -0.262)	.009
Tosello et al,[36] 2012	-45.012 (-89.145 to -0.879)	.046
Lindsey et al,[34] 2012	1.118 (0.286 to 1.951)	.008
Kim et al,[58] 2015	-0.317 (-0.518 to -0.117)	.002
Ayzenberg et al,[37] 2013	5.730 (1.008 to 10.453)	.02
Bourre et al,[38] 2013	-45.012 (-89.145 to -0.879)	.046
Gredler et al,[42] 2013	-1.646 (-2.874 to -0.418)	.009
Ip et al,[43] 2013	-1.401 (-2.444 to -0.358)	.008
Yang et al,[46] 2013	-2.059 (-3.607 to -0.511)	.009
Alsharoqui et al,[47] 2014	-45.012 (-89.145 to -0.879)	.046
Musafir et al,[55] 2014	-45.012 (-89.145 to -0.879)	.046
Weinfurtner et al,[57] 2015	-2.920 (-5.169 to -0.672)	.01
Beres et al,[48] 2014	-1.237 (-2.158 to -0.317)	.008
Longoni et al,[53] 2014	-2.059 (-3.607 to -0.511)	.009
Mealy et al,[54] 2014	-0.503 (-0.883 to -0.123)	.009
Zéphir et al,[61] 2015	-0.745 (-1.137 to -0.354)	<.001
Radaelli et al,[59] 2016	-0.552 (-1.011 to -0.093)	.02
Perumal et al,[16] 2015	-1.646 (-2.874 to -0.418)	.009
Torres et al,[60] 2015	-0.434 (-0.796 to -0.071)	.02



Standardized mean differences of the annualized relapse rate ratio before and after rituximab therapy are shown with 95% CIs.

Figure 3. Forest Plot Showing the Expanded Disability Status Scale Score of Patients With Neuromyelitis Optica Spectrum Disorders After Rituximab Therapy

Source	Standardized Mean Difference (95% CI)	*P* Value
Cree et al,[17] 2005	-1.237 (-2.158 to -0.317)	.008
Capobianco et al,[19] 2007	-45.012 (-89.145 to -0.879)	.046
Jacob et al,[13] 2008	-0.434 (-0.844 to -0.024)	.04
Bedi et al,[29] 2011	-0.523 (-0.959 to -0.087)	.02
Mahmood et al,[31] 2011	-45.012 (-89.145 to -0.879)	.046
Tosello et al,[36] 2012	-45.012 (-89.145 to -0.879)	.046
Lindsey et al,[34] 2012	1.118 (0.286 to 1.951)	.008
Pellkofer et al,[33] 2011	1.028 (0.262 to 1.794)	.009
Kim et al,[58] 2015	-0.317 (-0.518 to -0.117)	.002
Ayzenberg et al,[37] 2013	5.730 (1.008 to 10.453)	.02
Bourre et al,[38] 2013	-45.012 (-89.145 to -0.879)	.046
Gredler et al,[42] 2013	-1.646 (-2.874 to -0.418)	.009
Ip et al,[43] 2013	-1.401 (-2.444 to -0.358)	.008
Yang et al,[46] 2013	-2.059 (-3.607 to -0.511)	.009
Alsharoqui et al,[47] 2014	-45.012 (-89.145 to -0.879)	.046
Weinfurtner et al,[57] 2015	-2.920 (-5.169 to -0.672)	.01
Torres et al,[60] 2015	-22.501 (-44.594 to -0.407)	.046
Perumal et al,[16] 2015	-1.646 (-2.874 to -0.418)	.009



Standardized mean differences of the Expanded Disability Status Scale score before and after rituximab therapy are shown with 95% CIs.

Rituximab e NMOSD: RIN-1 study

Lancet Neurol 2020; 19: 298–306

Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial

Masayuki Tahara, Tomoko Oeda, Kazumasa Okada, Takao Kiriyama, Kazuhide Ochi, Hirofumi Maruyama, Hikoaki Fukaura, Kyoichi Nomura, Yuko Shimizu, Masahiro Mori, Ichiro Nakashima, Tatsuro Misu, Atsushi Umemura, Kenji Yamamoto, Hideyuki Sawada

- 8 Centri in Japan
- *38 NMOSD AQP4+*
- 16–80 years old
- Add on to steorids (5–30 mg/day)
- 19: placebo and 19: RTX
- 9 included at first clinical event

RTX (375 mg/m^2) every week for 4 weeks, then 6-month interval (1000 mg every 2 weeks, at 24 weeks and 48 weeks after randomisation)

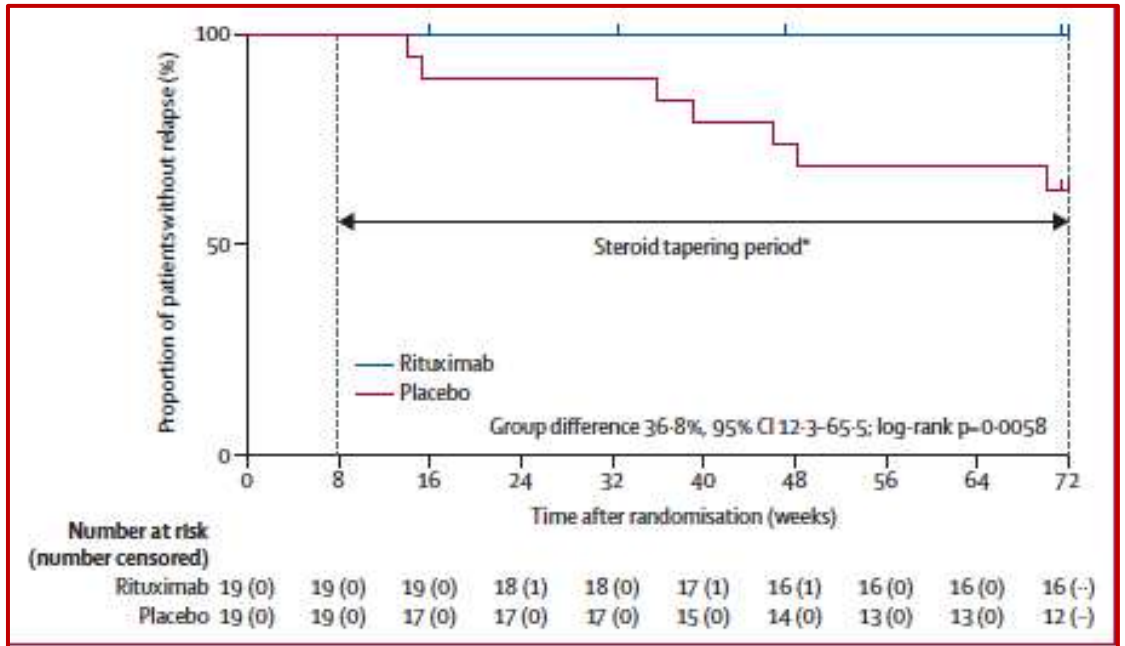


Figure 2: **Proportion of patients without relapse**
*The dose of oral steroids was tapered according to the protocol from 8 weeks after randomisation.

NMOSD: Randomized Clinical Trials

Table 2. Comparison of randomized controlled trials of three monoclonal antibodies in NMOSD (published in 2019)

Compound (RCT)	Eculizumab (PREVENT)	Satralizumab (SAkuraSky)	Inebilizumab (N-MOmentum)
Target	C5	IL-6R	CD19
Trial design (participating countries)	Phase III, placebo-cotrolled, DB, add-on to IST or monotherapy (18 countries)	Phase III, placebo-controlled, DB, add-on to IST (CS/ AZA/ MMF) (EU, Japan, Taiwan)	Phase II/III placebo-controlled, DB, monotherapy (24 countries)
Regimen (dose)	IV, induction (900 mg) weekly for 4 weeks; maintenance (1200 mg) every 2 weeks; all received *Neisseria meningitidis* vaccination before trial	SC (120 mg) every 2 weeks (three times), then every 4 weeks	IV (300 mg) on days 1 and 15, and then 6 months later
Patients	AQP4-Ab+ NMO/NMOSD, age ≥18, DSS ≤7.0	NMO or AQP4–Ab+NMOSD, age 12–74 y	NMO or AQP4-Ab+NMOSD, age ≥ 18 y, EDSS ≤ 8.0
Relapse	≥2 relapses in past year or ≥3 in past 2 years (with ≥1 in past year); patients receiving IST eligible if stable-dose regimens	≥2 relapses in the last 2 years (+ ≥1 relapse in the last 1 years); receiving baseline medication (AZA, MMF, and/or CS)	≥ 1 NMOSD relapse in the past year or ≥2 in past 2 years
Publication	Pittock *et al.*, N Engl J Med 2019	Yamamura *et al.*, N Engl J Med 2019	Cree *et al.*, Lancet 2019

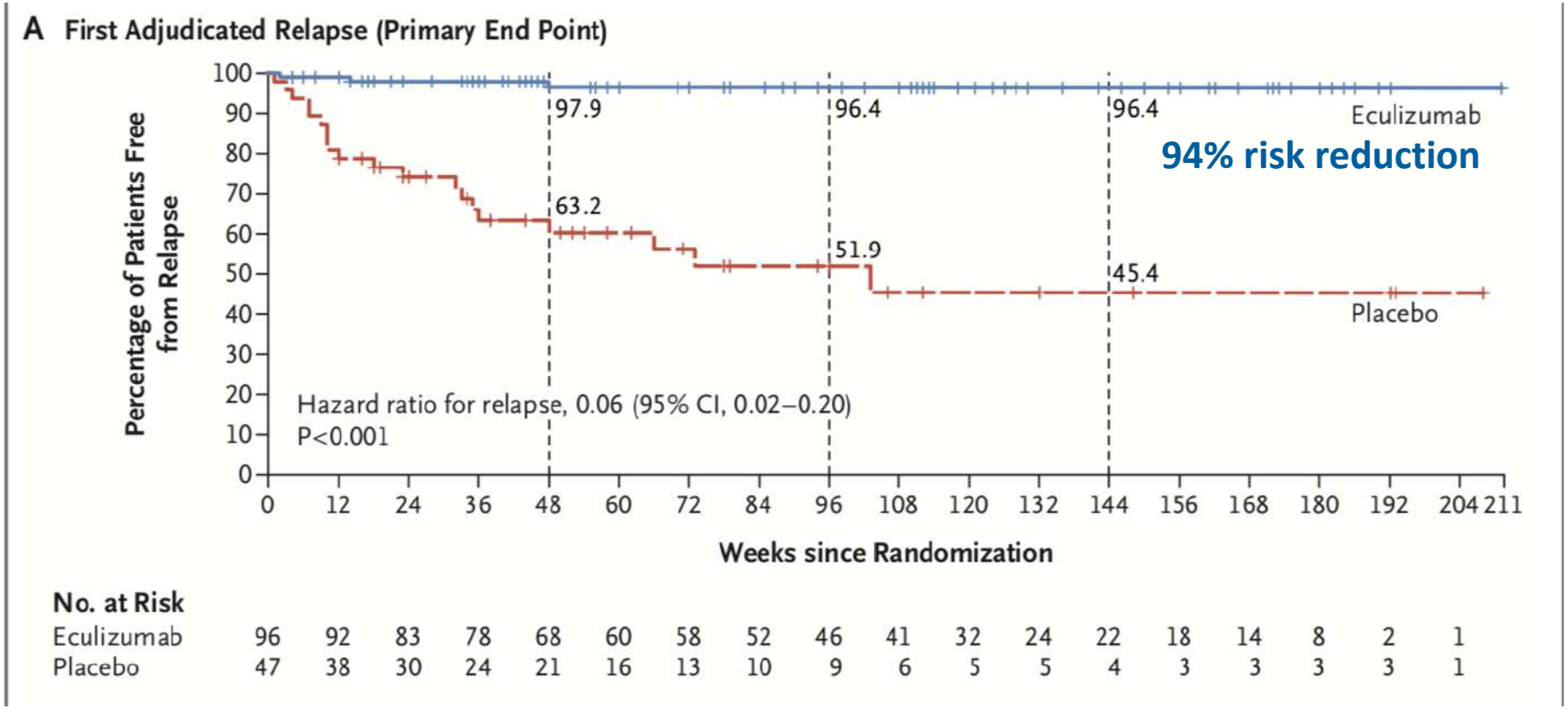
(AQP4-IgG+/-)

(AQP4-IgG+/-)

Another satralizumab's RCT (SAkuraStar in North America, **monotherapy** otherwise similar to SAkuraSky) was also completed and the results were very similar to those in SAkuraSky

Eculizumab: PREVENT study

Primary endpoint: Time to first protocol-defined relapse (PDR) in double-blind study period



(AQP4-IgG+)

[Pittock S et al. et al NEJM 2019]

Eculizumab PREVENT study: safety

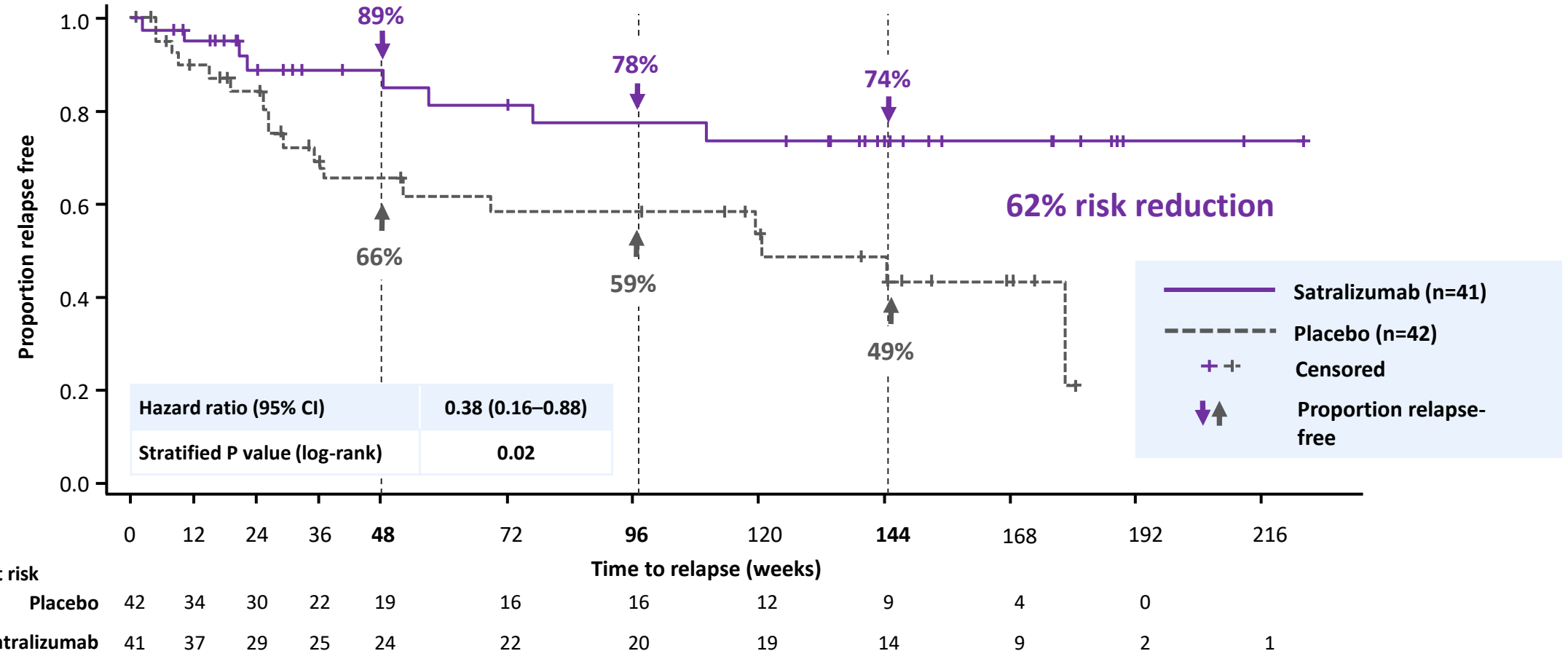
Upper respiratory tract infections and headaches were more common in the eculizumab group. There was one death from pulmonary empyema in the eculizumab group.

	Eculizumab (N = 96)			Placebo (N = 47)		
	no. of events	*events/ 100 patient-yr*	*no. of patients (%)*	*no. of events*	*events/ 100 patient-yr*	*no. of patients (%)*
Adverse event reported in ≥15% of patients in either group**						
Upper respiratory tract infection	54	31	28 (29)	10	19	6 (13)
Headache	95	55	22 (23)	20	38	11 (23)
Nasopharyngitis	50	29	20 (21)	15	28	9 (19)
Nausea	30	17	16 (17)	19	36	12 (26)
Diarrhea	23	13	15 (16)	19	36	7 (15)
Urinary tract infection	45	26	13 (14)	13	24	10 (21)
Limb pain	13	8	11 (11)	11	21	10 (21)
Vomiting	10	6	10 (10)	10	19	8 (17)

[Pittock S et al. et al NEJM 2019]

Sakura SKY: satralizumab in “add on” reduced the risk of relapse

Primary endpoint: Time to first protocol-defined relapse (PDR) in double-blind study period



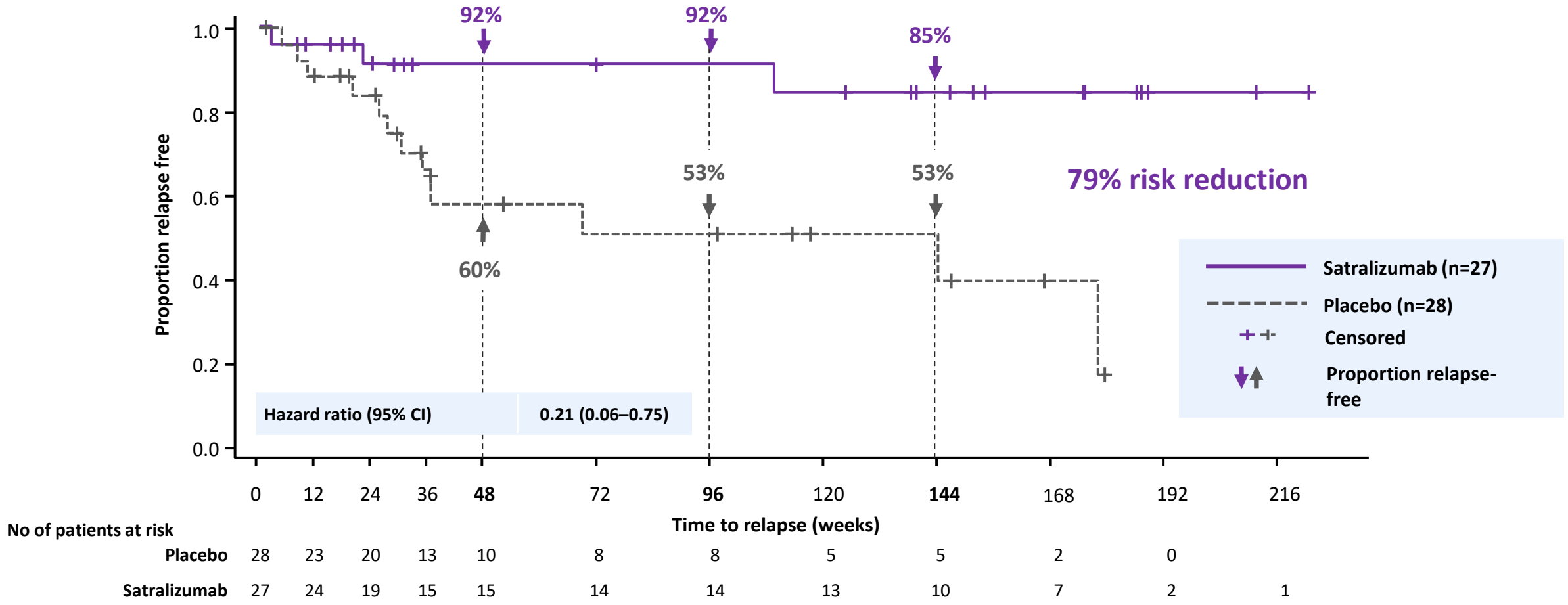
No of patients at risk

Placebo	42	34	30	22	19	16	16	12	9	4	0
Satralizumab	41	37	29	25	24	22	20	19	14	9	2	1

Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and baseline relapse rate. Percentage figures are proportion of relapse-free patients. Protocol-defined relapse as adjudicated by the independent clinical endpoint committee. EDSS/FSS was assessed within 7 days of relapse reporting. CI, confidence interval; EDSS, Expanded Disability Status Scale; FSS, functional system scores; ITT, intent-to-treat; NMOSD, neuromyelitis optica spectrum disorder.

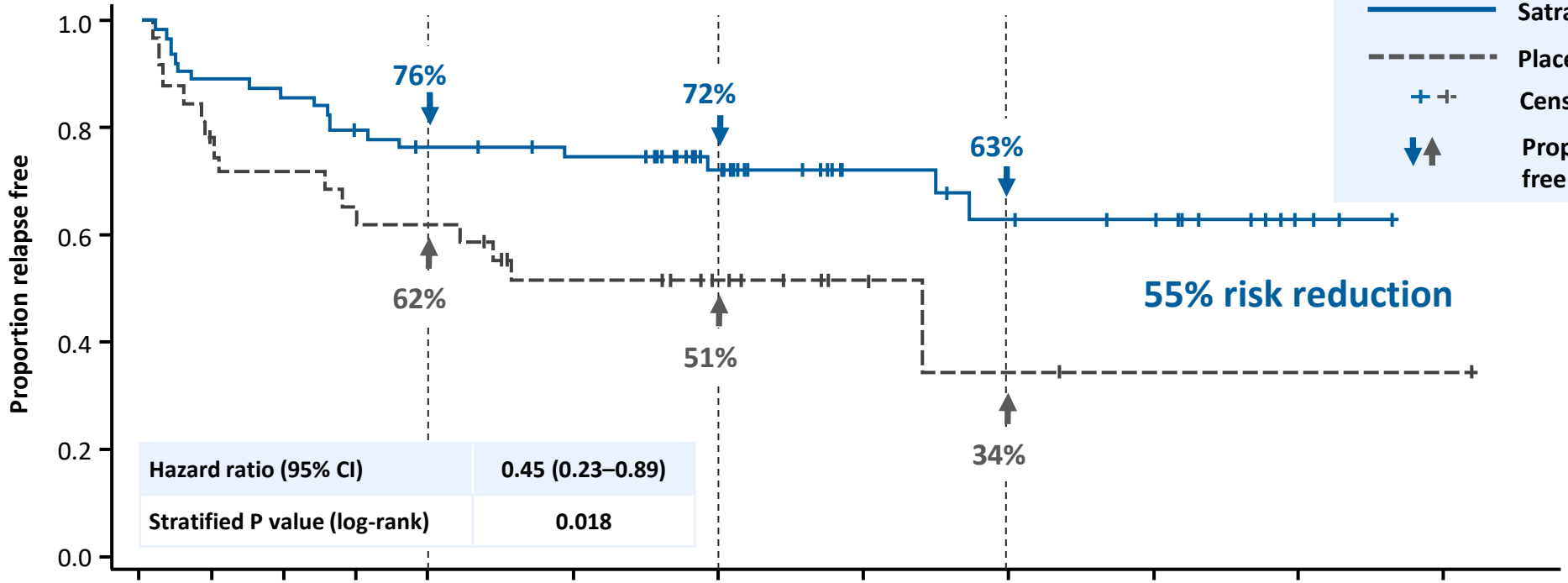
Yamamura T, et al. *N Engl J Med* 2019;381:2114–2124.

Sakura SKY: satralizumab reduced the risk of relapse in AQP4-IgG +



Protocol-defined relapse as adjudicated by the independent clinical endpoint committee. EDSS/FSS was assessed within 7 days of relapse reporting.
AQP4-IgG, antibodies against aquaporin-4; CI, confidence interval; EDSS, Expanded Disability Status Scale; FSS, functional system scores; ITT, intent-to-treat.
Yamamura T, et al. *N Engl J Med* 2019;381:2114–2124.

Sakura STAR: satralizumab monotherapy reduced the risk of relapse



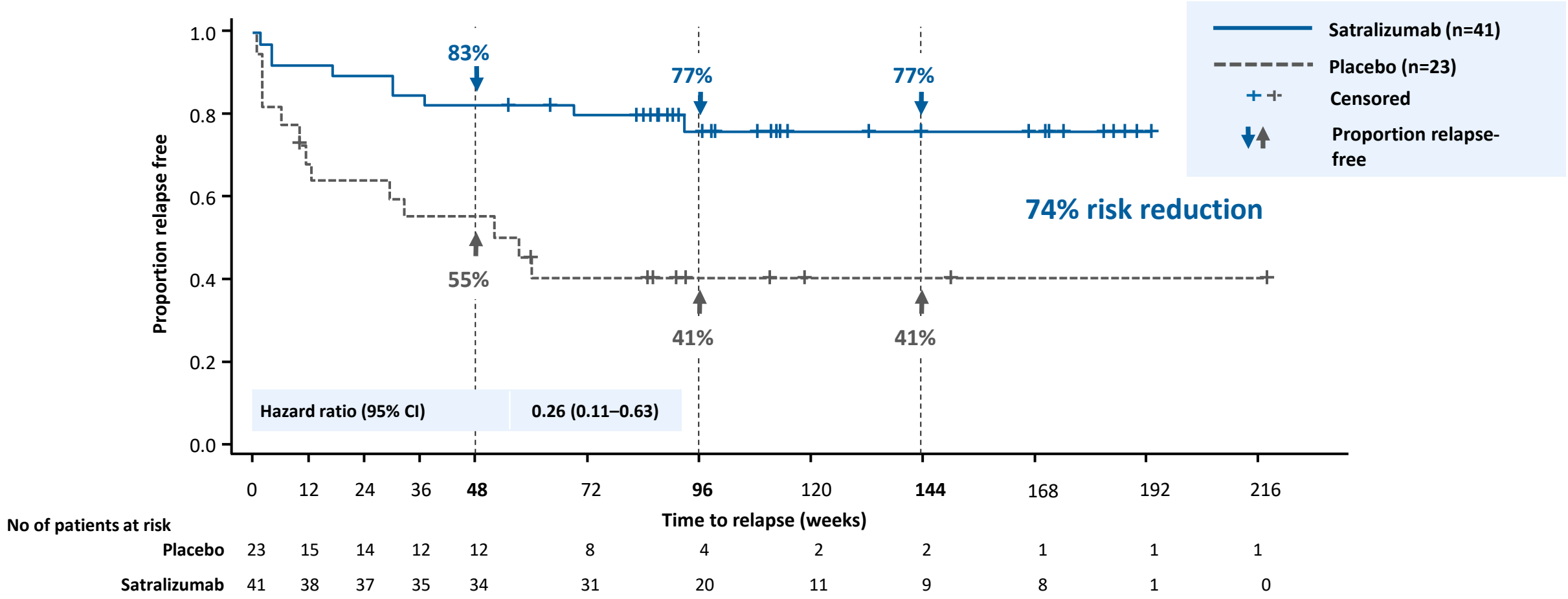
No of patients at risk

Placebo	32	23	22	19	19	13	9	3	2	1	1	1
Satralizumab	63	56	54	49	46	43	30	16	12	10	3	0

Analysis based on ITT population; p-value (based on log-rank test) and hazard ratio (using Cox proportional-hazards model) stratified by prior therapy for prevention of NMOSD attack (B-cell-depleting therapy or immunosuppressants/other) and by nature of the most recent attack in the year prior to screening (patient's first clinical attack vs relapse). CI, confidence interval; HR, ITT, intention to treat.

Traboulsee A, et al. *Lancet Neurol* 2020;19(5):402–12.

Sakura STAR: satralizumab monotherapy reduced the risk of relapse in AQP4-IgG+

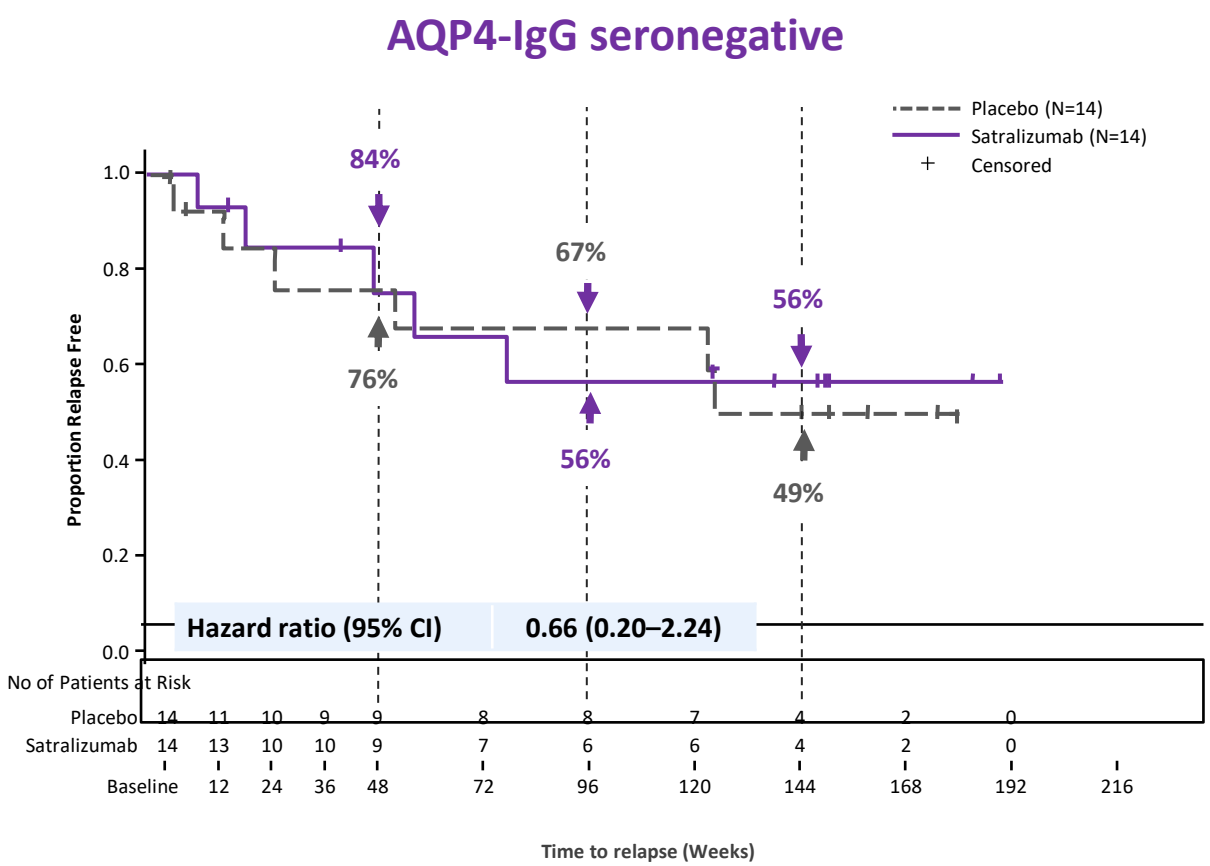


Protocol-defined relapse as adjudicated by the independent clinical endpoint committee. EDSS/FSS was assessed within 7 days of relapse reporting.
AQP4-IgG, antibodies against aquaporin-4; CI, confidence interval; EDSS, Expanded Disability Status Scale; FSS, functional system scores; ITT, intent-to-treat.

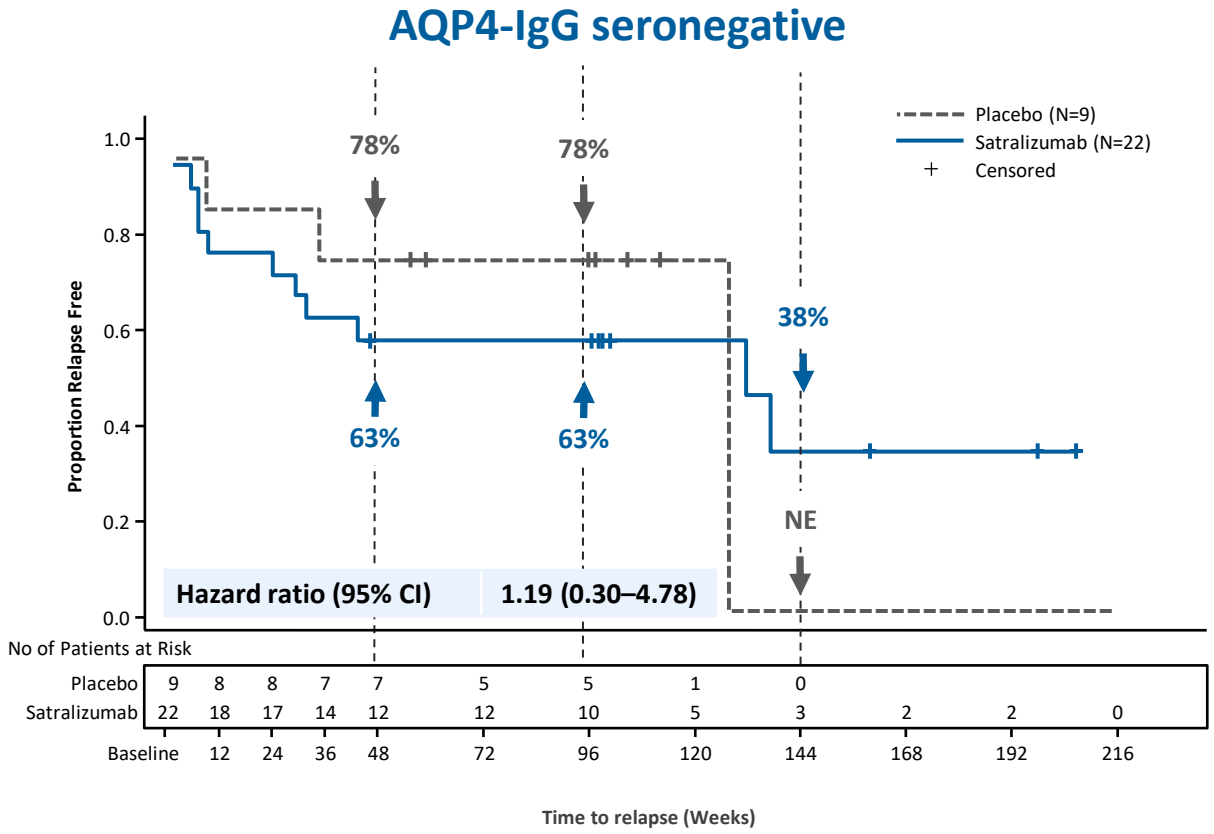
Traboulsee A, et al. *Lancet Neurol* 2020;19(5):402–12.

Satralizumab: findings in the AQP4-IgG seronegative population

SAKURA SKY



SAKURA STAR



Protocol-defined relapse as adjudicated by the independent clinical endpoint committee. EDSS/FSS was assessed within 7 days of relapse reporting.
AQP4-IgG, antibodies against aquaporin-4; CI, confidence interval; EDSS, Expanded Disability Status Scale; FSS, functional system scores; ITT, intent-to-treat.

Traboulsee A, et al. *Lancet Neurol* 2020;19(5):402–12.

SAkuraStar and SAkuraSky: Satralizumab safety profile

	Patients receiving satralizumab (n=63; 115·2 patient-years)		Patients receiving placebo (n=32; 40·6 patient-years)	
	Number of patients	Events per 100 patient-years (95% CI)	Number of patients	Events per 100 patient-years (95% CI)
Adverse events	58 (92%)	473·9 (435·0–515·4)	24 (75%)	495·2 (429·1–568·6)
Serious adverse events	12 (19%)	17·4 (10·6–26·8)	5 (16%)	14·8 (5·4–32·2)
Severe adverse events	17 (27%)	32·1 (22·6–44·3)	2 (6%)	9·9 (2·7–25·2)
Deaths	0	0 (NE–3·2)	0	0 (NE–9·1)
Infections*	34 (54%)	99·8 (82·4–119·8)	14 (44%)	162·6 (125·8–206·9)
Serious infections*	6 (10%)	5·2 (1·9–11·3)	3 (9%)	9·9 (2·7–25·2)
Injection-related reactions	8 (13%)	13·9 (7·9–22·6)	5 (16%)	17·3 (6·9–35·5)
Anaphylactic reactions†	0	0 (NE–3·2)	0	0 (NE–9·1)

Data are n (%) unless otherwise specified. NE=not evaluable. *MedDRA system organ class; infections and infestations. †Standardised MedDRA Queries anaphylaxis narrow term.

Table 3: **Adverse events in the double-blind period in the safety analysis population**

Traboulsee A, et al. Lancet Neurol 2020

Table 3. Summary of Adverse Events in the Double-Blind Period (Safety Population).*

Event	Satralizumab (N=41)		Placebo (N=42)	
	Patients	Events (95% CI)	Patients	Events (95% CI)
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*
Adverse event	37 (90)	485.2 (437.7–536.5)	40 (95)	514.3 (458.2–575.2)
Serious adverse event	7 (17)	11.5 (5.2–21.8)	9 (21)	20.2 (10.4–35.2)
Death	0	0	0	0
Infection	28 (68)	132.5 (108.2–160.5)	26 (62)	149.6 (120.1–184.1)
Serious infection	2 (5)	2.6 (0.3–9.2)	3 (7)	5.0 (1.0–14.7)
Injection-related reaction	5 (12)	21.7 (12.6–34.7)	2 (5)	3.4 (0.4–12.1)
Anaphylactic reaction†	0	0	0	0
Neoplasm‡	3 (7)	3.8 (0.8–11.2)	3 (7)	5.0 (1.0–14.7)

* The safety population included patients who received at least one dose of satralizumab or placebo.
† Anaphylactic reaction was defined as anaphylaxis (with narrow searches) in the standardized queries of the *Medical Dictionary for Regulatory Activities*, version 16.1.
‡ Benign neoplasm of thyroid gland, colon adenoma, and uterine leiomyoma occurred in one patient each in the satralizumab group. Breast cancer, hepatic cancer, and lipoma occurred in one patient each in the placebo group.

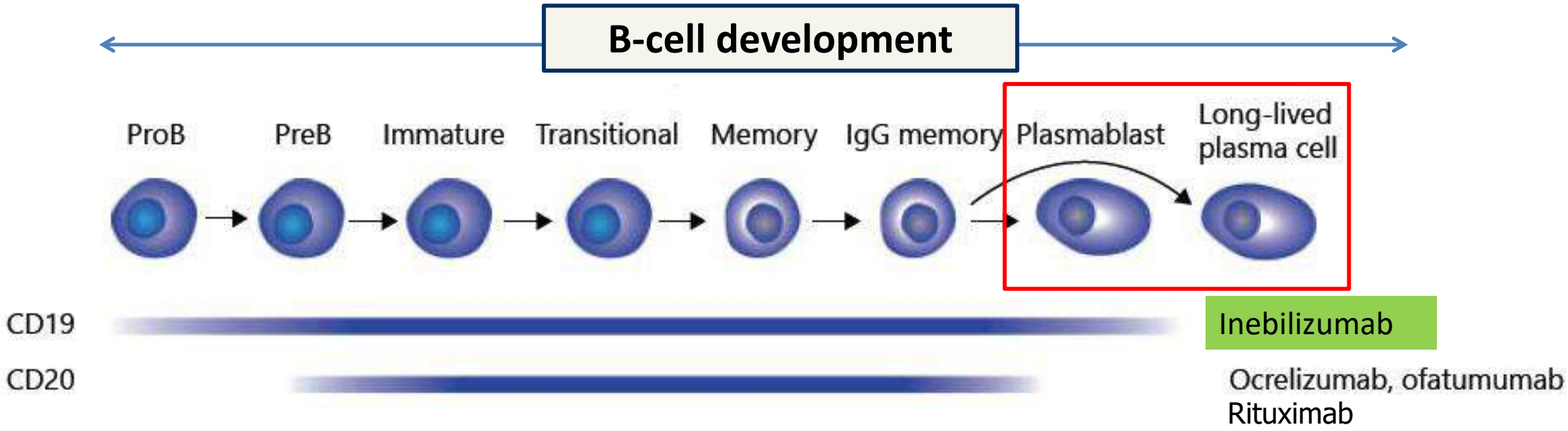
Yamamura T, et al. NEJ 2019

Inebilizumab

Inebilizumab is a humanized monoclonal antibody

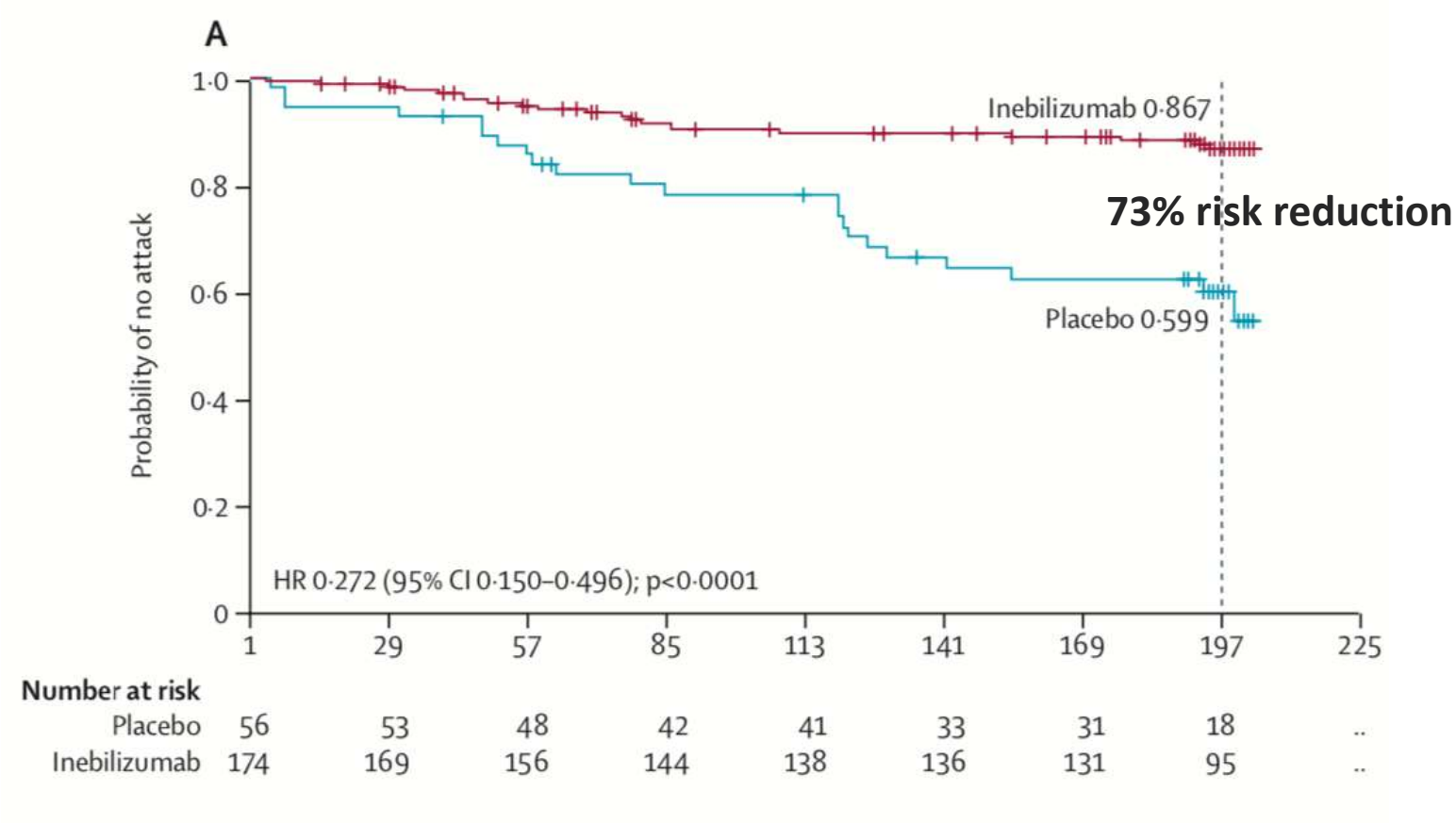
Inebilizumab targets a broader spectrum of B cells

-momab: murine
-ximab: chimeric
-zumab: humanized
-mumab: human



It does not interfere with the small quote of CD20 positive T lymphocytes

Inebilizumab efficacy



21 (**12%**) of 174 participants receiving inebilizumab had an attack versus 22 (**39%**) of 56 participants receiving placebo

[Cree BA et al. NEJM 2019]

The RC period was stopped before complete enrolment because of a clear demonstration of efficacy.

NMOSD & MoA: positioning consideration

B-cells

- Broad mechanism of action
- Hypogammaglobulinemia, late onset neutropenia
- Potential risk of infections (> on long term)
- Low load for patients and Centres
- ***CD19>CD20***

IL6

- Broad mechanism of action
- Potential risk of infections
- Moderate load for patients and Centres
- ***Satr>Toci***

Complement

- Rapid onset of action
- Vaccination for capsulated bacteria
- High load for patients and Centres
- ***Ravalizumab > eculizumab***

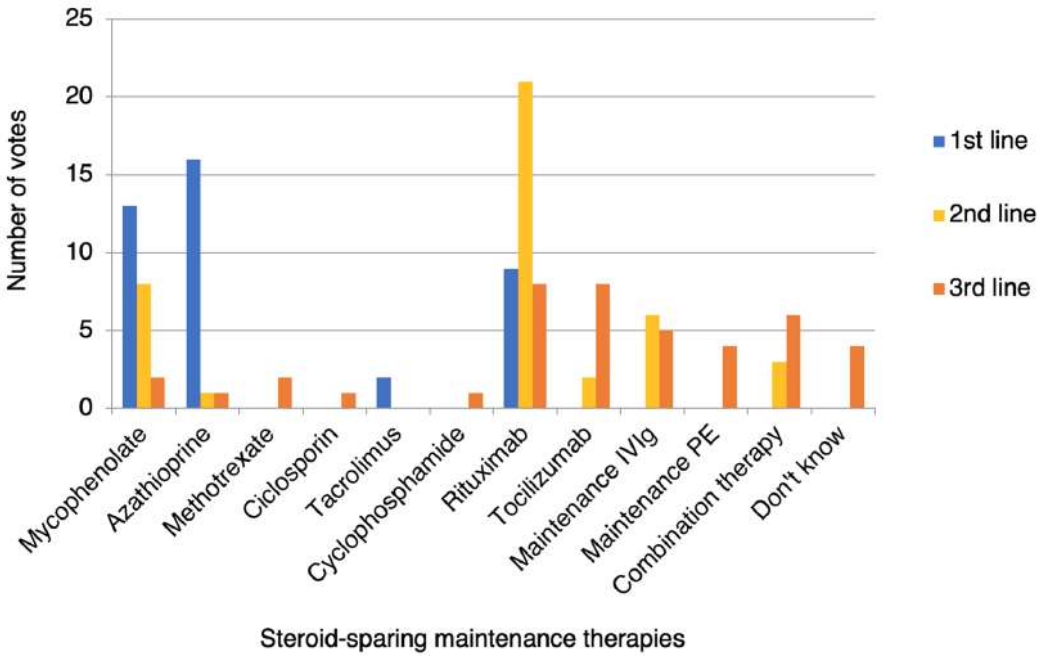
MOGAD treatment

Journal of Neurology
https://doi.org/10.1007/s00415-020-10026-y

ORIGINAL COMMUNICATION

Treatment of MOG antibody associated disorders: results of an international survey

D. H. Whittam[1] · V. Karthikeayan[1] · E. Gibbons[1] · R. Kneen[2] · S. Chandratre[3] · O. Ciccarelli[4] · Y. Hacohen[4,5] · J. de Seze[6] · K. Deiva[7] · R. Q. Hintzen[8] · B. Wildemann[9] · S. Jarius[9] · I. Kleiter[10,11] · K. Rostasy[12] · P. Huppke[13] · B. Hemmer[14,15] · F. Paul[16] · O. Aktas[17] · A. K. Pröbstel[18,19] · G. Arrambide[20] · M. Tintore[20] · M. P. Amato[21,22] · M. Nosadini[23] · M. M. Mancardi[24] · M. Capobianco[25] · Z. Illes[26] · A. Siva[27] · A. Altintas[28] · G. Akman-Demir[29] · L. Pandit[30] · M. Apiwattankul[31] · J. Y. Hor[32] · S. Viswanathan[33] · W. Qiu[34] · H. J. Kim[35] · I. Nakashima[36] · K. Fujihara[37,38] · S. Ramanathan[39,40] · R. C. Dale[39,40] · M. Boggild[41] · S. Broadley[42] · M. A. Lana-Peixoto[43] · D. K. Sato[44] · S. Tenembaum[45] · P. Cabre[46] · D. M. Wingerchuk[47] · B. G. Weinshenker[48] · B. Greenberg[49] · M. Matiello[50] · E. C. Klawiter[50] · J. L. Bennett[51] · A. I. Wallach[52] · I. Kister[52] · B. L. Banwell[53] · A. Traboulsee[54] · D. Pohl[55] · J. Palace[3] · M. I. Leite[3] · M. Levy[59] · R. Marignier[56] · T. Solomon[1,57] · M. Lim[58,59] · S. Huda[1] · A. Jacob[1,60]



Conclusion Current treatment of MOGAD is highly variable, indicating a need for consensus-based treatment guidelines, while awaiting definitive clinical trials.

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journal homepage: www.elsevier.com/locate/msard

Original article

Treatment of MOG-IgG-associated disorder with rituximab: An international study of 121 patients

Daniel H Whittam[a,b,*], Alvaro Cobo-Calvo[c], A Sebastian Lopez-Chiriboga[d], Santiago Pardo[e], Matthew Gornall[f], Silvia Cicconi[f], Alexander Brandt[g], Klaus Berek[h], Thomas Berger[i], Ilijas Jelcic[j], Grace Gombolay[e,k], Luana Micheli Oliveira[l], Dagoberto Callegaro[l], Kimihiko Kaneko[m], Tatsuro Misu[m], Marco Capobianco[n], Emily Gibbons[a,b], Venkatraman Karthikeayan[a], Bruno Brochet[o], Bertrand Audoin[p], Guillaume Mathey[q], David Laplaud[r], Eric Thouvenot[s], Mikaël Cohen[t], Ayman Tourbah[u], Elisabeth Maillart[v], Jonathan Ciron[w], Romain Deschamps[x], Damien Biotti[y], Kevin Rostasy[z], Rinze Neuteboom[aa,bb], Cheryl Hemingway[cc], Rob Forsyth[dd],

Predicted 1-year and 2-year relapse-free survival was 79% and 55% for first-line RTX therapy, and 38% and 18% for second-/third-line therapy.

Circulating CD19+B-cells were suppressed to <1% of total circulating lymphocyte population at the time of 45/57 (78.9%) relapses.

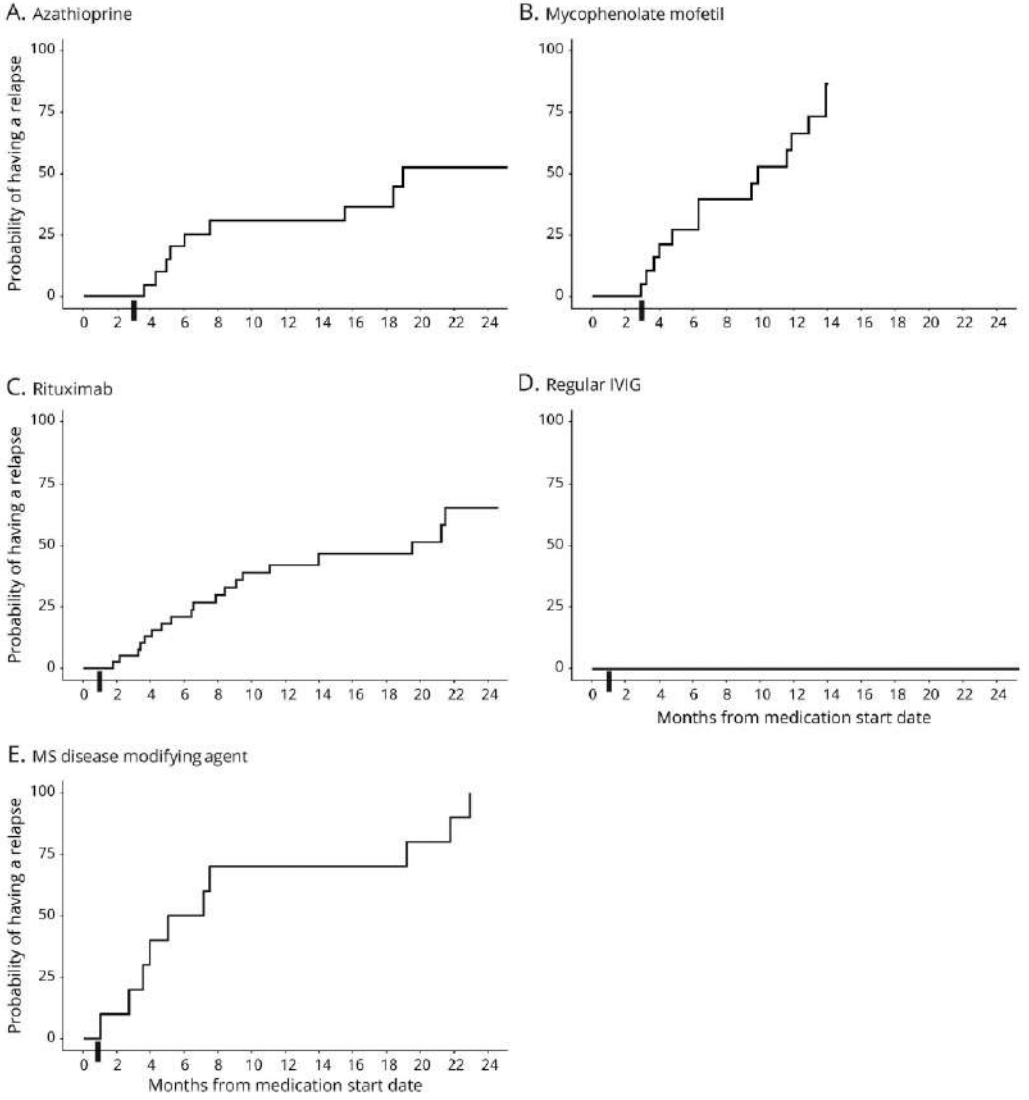
Conclusion: RTX reduced relapse rates in MOGAD. However, many patients continued to relapse despite apparent B-cell depletion. Prospective controlled studies are needed to validate these results.

MOGAD treatment

This large retrospective multicenter study of patients with MOGAD suggests that maintenance immunotherapy reduces recurrent CNS demyelinating attacks, with the lowest ARR being associated with maintenance IVIG therapy. Traditional MS disease-modifying agents appear to be ineffective.

Prospective randomized controlled studies are required to validate these conclusions.

Figure 2 Kaplan–Meier estimates of time to relapse on different maintenance therapies



Kaplan Meier curves showing time to relapse for patients treated with (A) azathioprine, (B) mycophenolate mofetil, (C) rituximab, (D) maintenance IV immunoglobulin (IVIG), and (E) multiple sclerosis (MS) disease-modifying agents. dash Along the x-axis demarks when the maintenance immunotherapy becomes fully active and a relapse is considered a failure of therapy.

[Chen, Neurology 2020]

Meeting Coverage > AAN

2019: 'The Year of NMO'

— Three different drugs report lower relapse rates in neuromyelitis optic

by Judy George, Senior Staff Writer, MedPage Today May 10, 2019

PHILADELPHIA -- Three different drugs in phase III trials demonstrated lower relapse rates in neuromyelitis optica spectrum disorder (NMOSD), especially among people with aquaporin-4 antibodies (AQP4-IgG), researchers reported at the 2019 American Academy of Neurology (AAN) annual meeting.

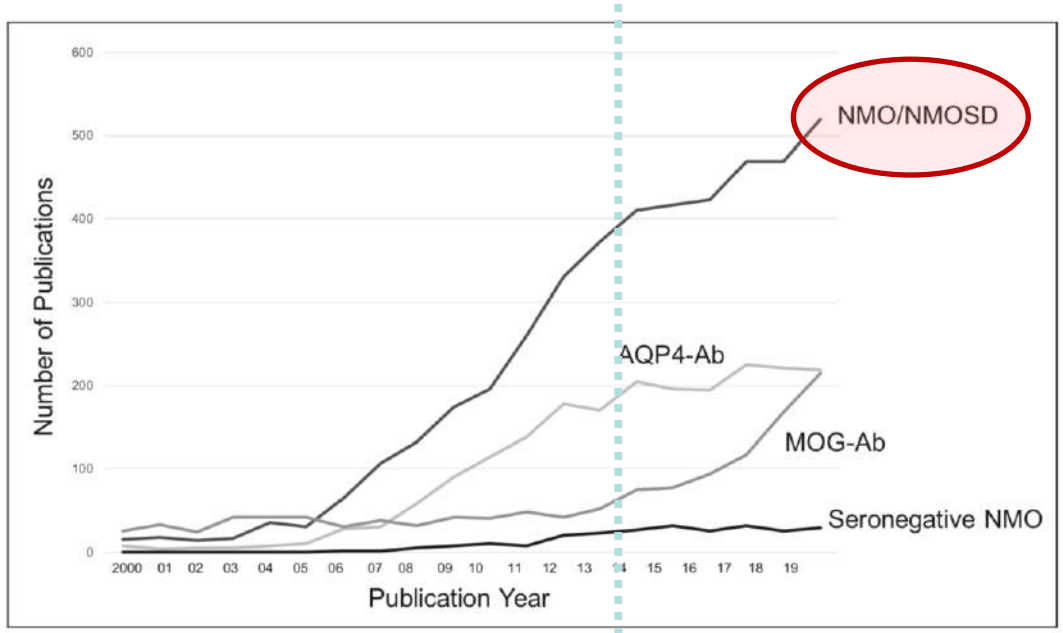


FIGURE 1. Number of yearly publications related to NMO/NMOSD, AQP4 antibody, MOG antibody, and seronegative NMO based on a PubMed search. AQP4, aquaporin 4; MOG, myelin oligodendrocyte glycoprotein; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorders.

[Fujihara et al. 2020]

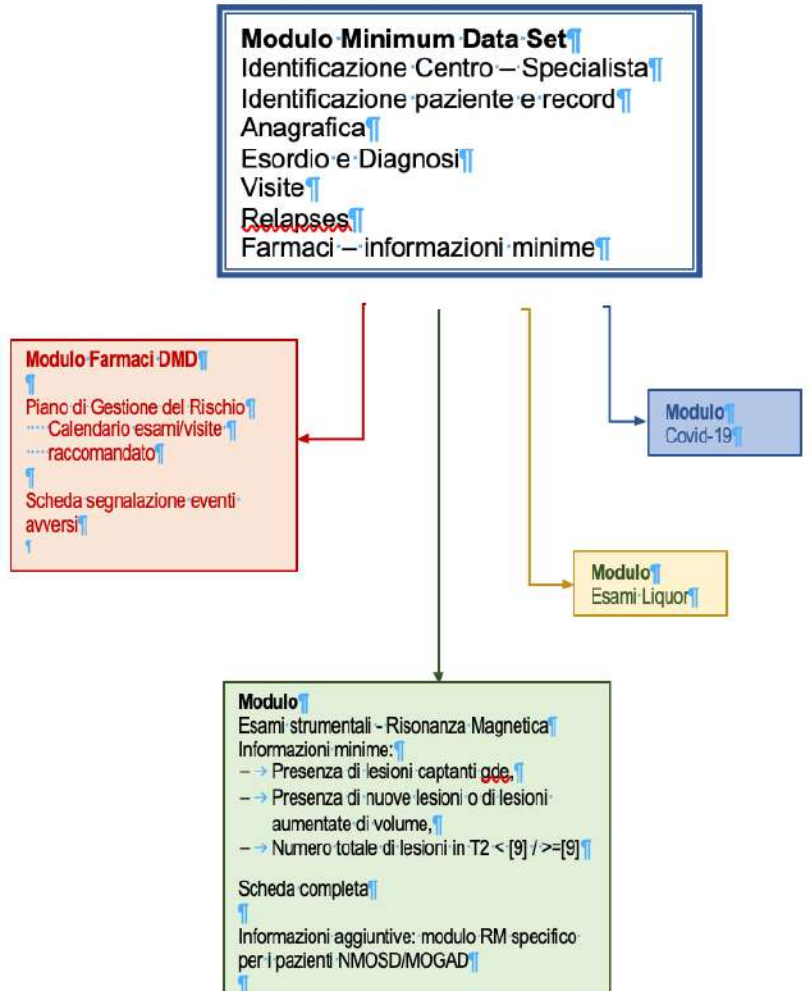
Open Issue

- **Biomarkers for diagnosis**
- **Diagnostic test standardization** (lived vs fixed assay expecially for MOGAD)
- **Presence or absence of a progressive disease**
- **Prognostic factors for disability and treatment response**
- **Protocol for treament choice** (MOGAD vs NMOSD)

...

Fattori prognostici clinico-radiologici nelle patologie dello spettro della Neuromielite Ottica e associate ad anticorpi anti-MOG. Analisi di coorte dal Registro Italiano Sclerosi Multipla ed implementazione di uno specifico dataset
(cod. PrReg032)

Carla Tortorella, Mariapia Amato, Marco Capobianco, Massimo Filippi, Francesco Patti



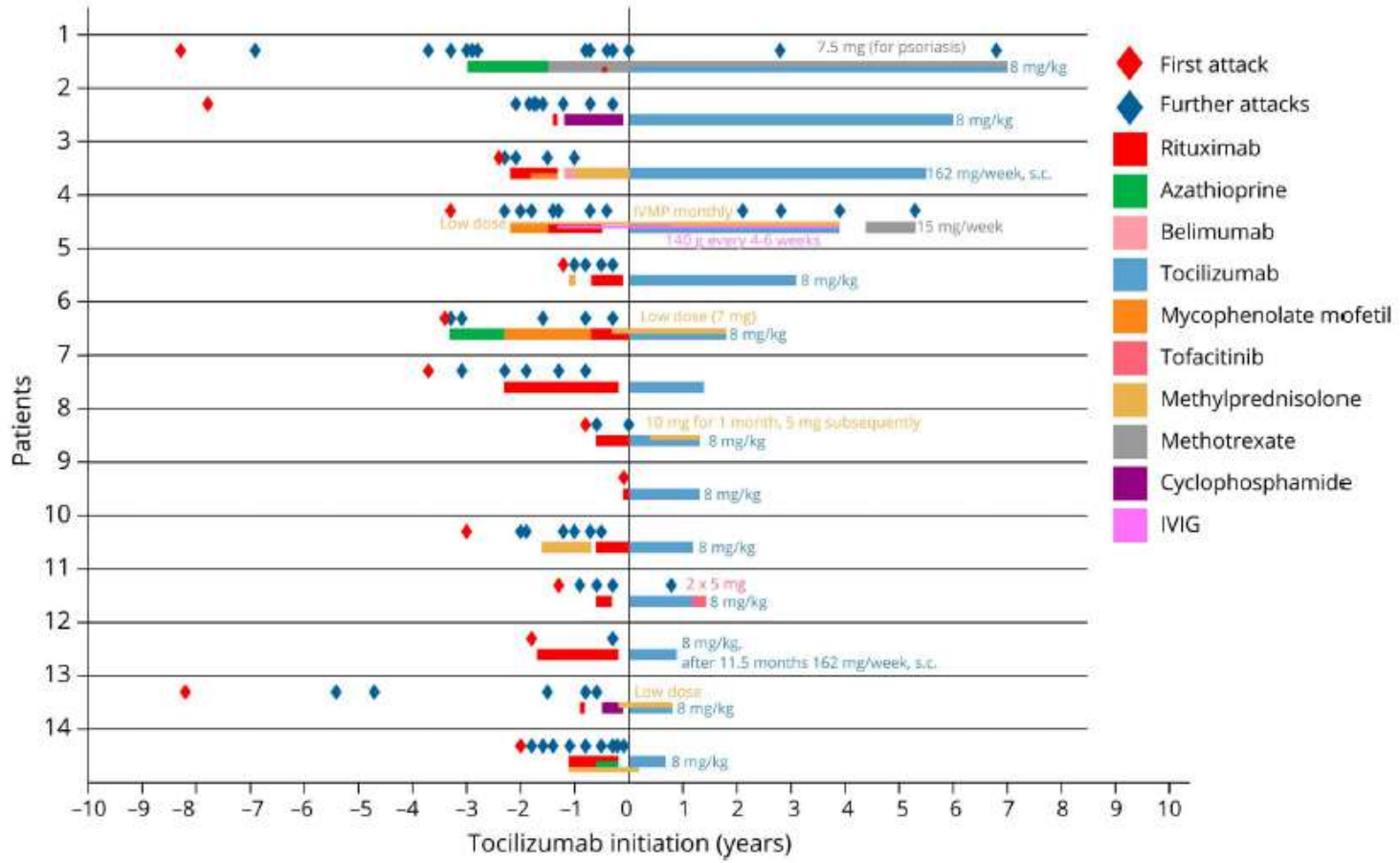
CRF SOGGETTI NMOSD/MOGAD
Registro Italiano SM e Patologie Correlate

Struttura Tecnico Operativa
Istituto Mario Negri IRCCS

Febbraio 2022

Tocilizumab as rescue treatment

Figure 1 Disease Courses and Individual Maintenance Immune Therapies of Patients With MOGAD



First attacks are indicated as red diamonds and further attacks as blue diamonds. IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; MOG = myelin oligodendrocyte glycoprotein; MOGAD = MOG-IgG–associated disease.

Ringelstein, Neurol Neuroimmunol Neuroinflamm 2022

Inebilizumab

FDA NEWS RELEASE

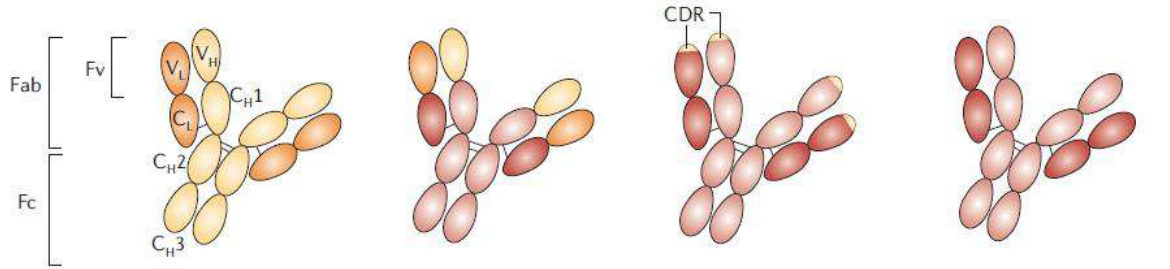
FDA Approves New Therapy for Rare Disease Affecting Optic Nerve, Spinal Cord

Second FDA Approved Therapy for Neuromyelitis Optica Spectrum Disorder Offers Patients Additional Treatment Option

Share Tweet LinkedIn Email Print

For Immediate Release: June 11, 2020

The U.S. Food and Drug Administration today approved Uplizna (inebilizumab-cdon) injection for intravenous use for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients with a particular antibody (patients who are anti-aquaporin-4 or AQP4 antibody positive). NMOSD is a rare autoimmune disease of the central nervous system that mainly affects the optic nerves and spinal cord. Uplizna is only the second approved treatment for the disorder.



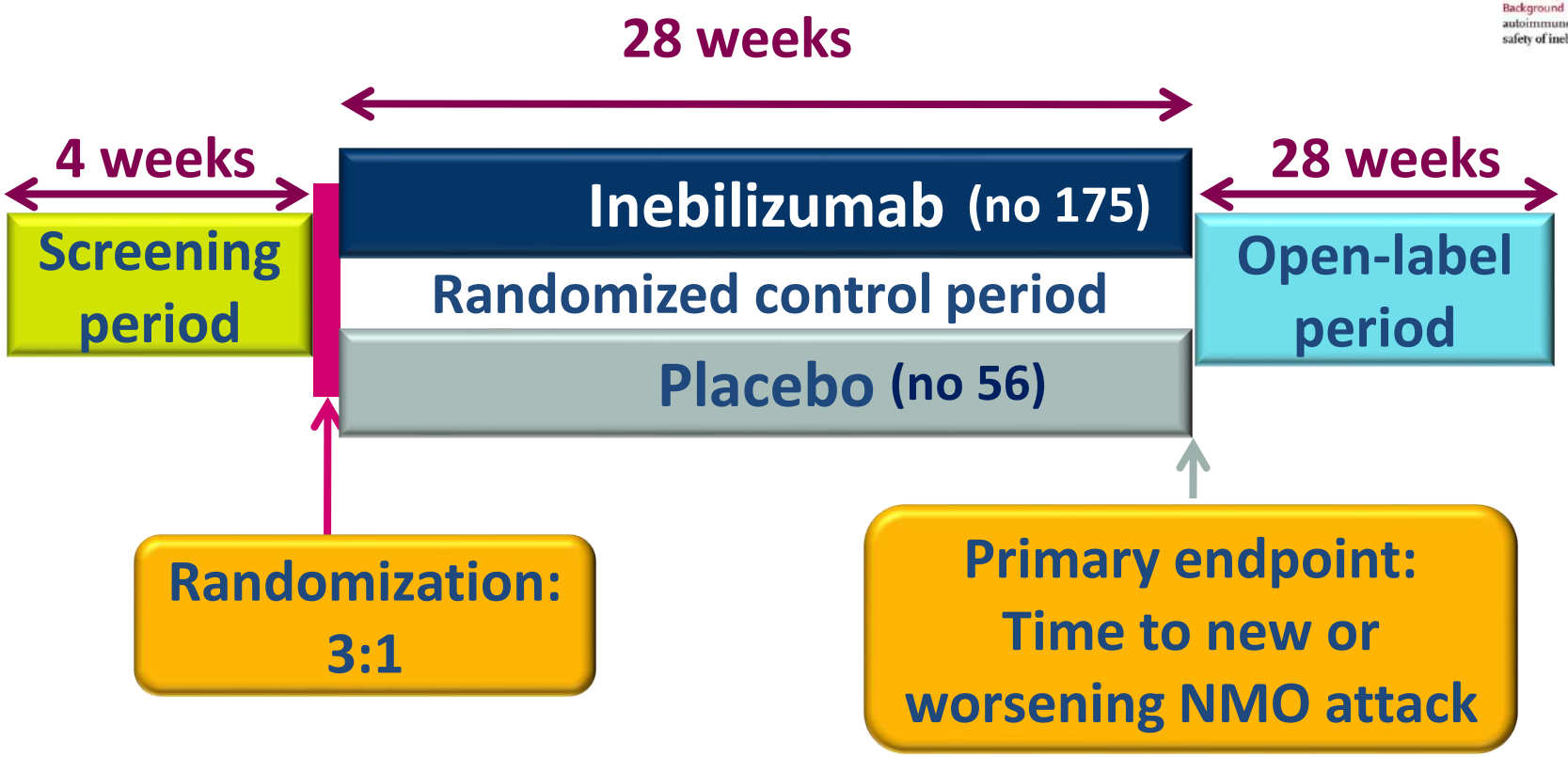
Type of mAb	Murine	Chimeric	Humanized	Human
	Ibritumomab tiuxetan (CD20); IgG1κ*	Cetuximab (EGFR); IgG1κ	Trastuzumab (ERBB2); IgG1κ	Panitumumab (EGFR); IgG2
	Tositumomab-I^{131} (CD20); IgG2aλ*	Rituximab (CD20); IgG1κ	Bevacizumab (VEGF); IgG1	
			Alemtuzumab (CD52); IgG1κ	
			Gemtuzumab ozogamicin (CD33); IgG4κ*	

[Imai and Takaoaka, 2006 Nat Rev Cancer]

Inebilizumab is a **humanized** monoclonal antibody designed to target and deplete **CD19-expressing B cells**

-momab: murine
-ximab: chimeric
-zumab: humanized
-mumab: human

N-MOmentum design



Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial

Bruce A C Cree, Jeffrey L Bennett, Ho Jin Kim, Brian G Weinshenker, Sean J Pittock, Dean M Wingerchuk, Kazuo Fujihara, Friedemann Paul, Gary R Cutter, Romain Marignier, Ari J Green, Orhan Aktas, Hans-Peter Hartung, Fred D Lublin, Jorn Drappa, Gerard Boron, Soroyat Madani, John N Ratchford, Dewei She, Daniel Cimbora, Eliezer Katz, on behalf of the N-MOmentum study investigators*

Summary

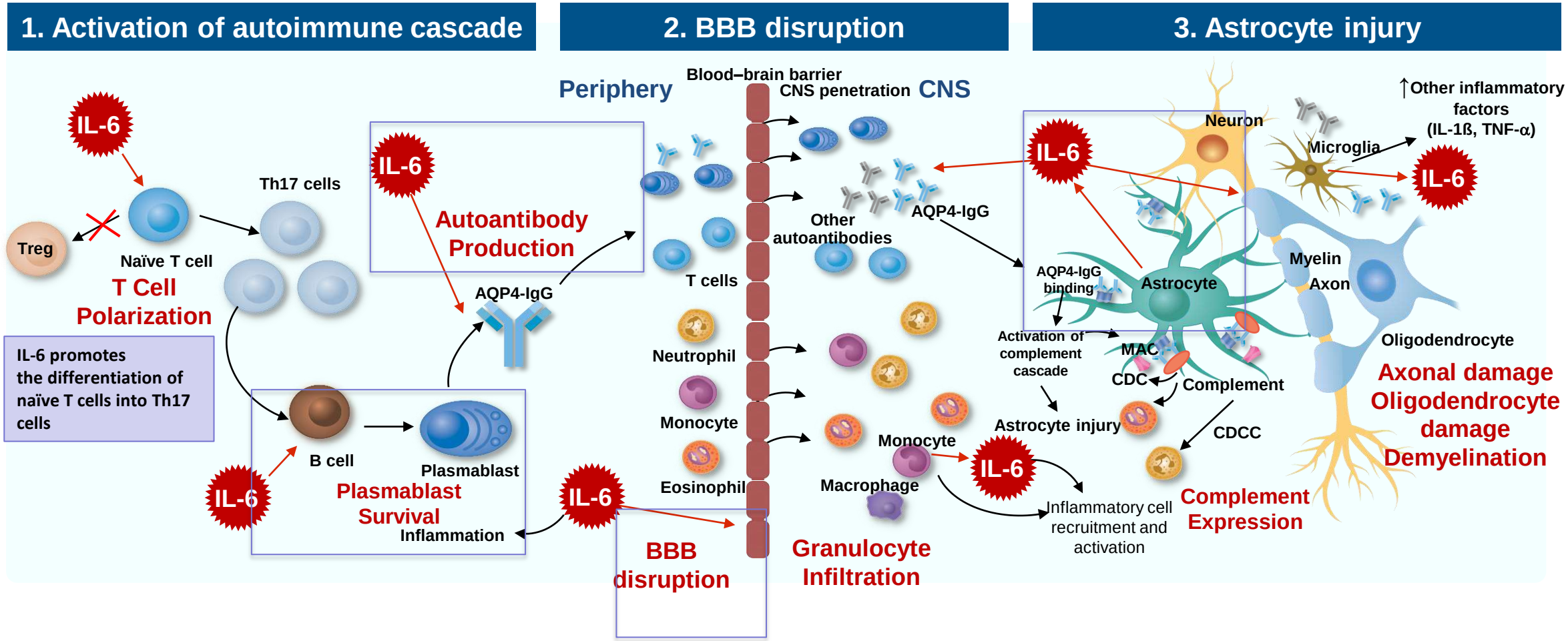
Background No approved therapies exist for neuromyelitis optica spectrum disorder (NMOSD), a rare, relapsing, autoimmune, inflammatory disease of the CNS that causes blindness and paralysis. We aimed to assess the efficacy and safety of inebilizumab, an anti-CD19, B cell-depleting antibody, in reducing the risk of attacks and disability in NMOSD.

Published Online September 5, 2019 http://dx.doi.org/10.1016/S0140-6736(19)31817-3

IV inebilizumab or placebo was administered on **days 1** and **15** *The total dose of inebilizumab in the RCT period was 600 mg, with no further doses occurring after day 15 in this study period)*.

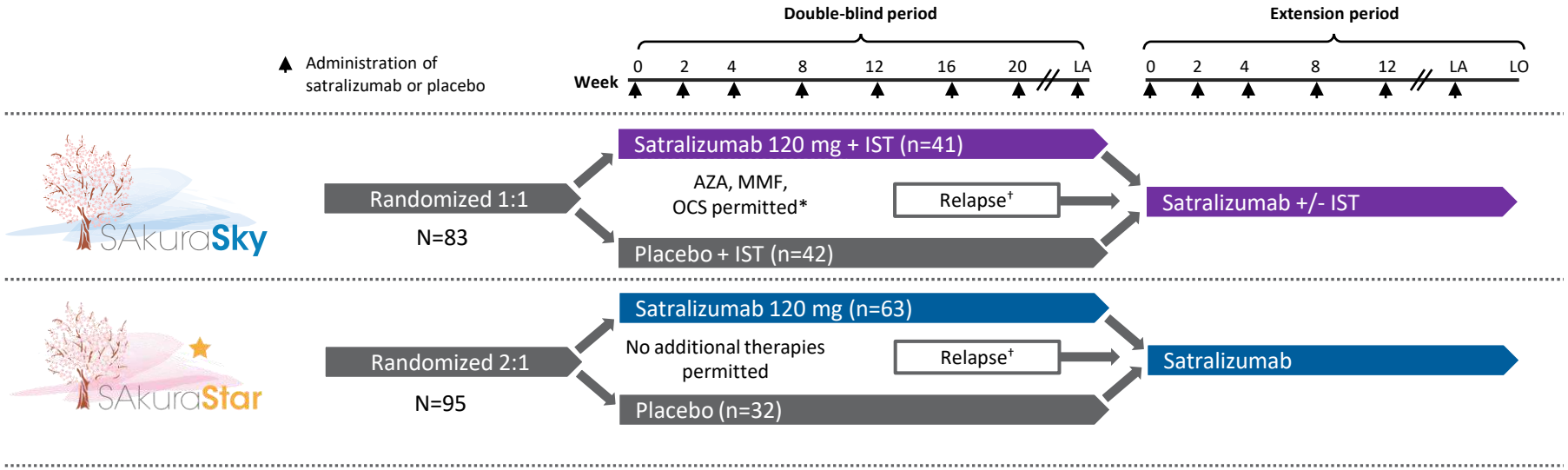
- **467** patients were screened
- **231** (49%) patients were enrolled. **175** (76%) randomly allocated to inebilizumab and 56 (24%) randomly allocated to placebo
- **93% AQP4+**
- No other use of immunosuppressants was permitted during the randomised controlled period.

Satralizumab



1. Kimura K, et al. Eur J Immunol 2010;40:1830–1835. 2. Lin J, et al. Int J Neurosci 2016;126(12):1051–60. 3. Weinshenker BD, Wingerchuk DM. Mayo Clin Proc. 2017;92(4):663–679. 4. Chihara N, et al. Proc Natl Acad Sci USA 2011;108:3701–3706. 5. Takeshita Y, et al. Neurol Neuroimmunol Neuroinflamm 2017;4:e311. 6. Obermeier B, et al. Nat Med 2013;19:1584–1596. 7. Uzawa A, et al. Clin Exp Neuroimmunol 2013;4:167–172. 8. Kaplin AJ, et al. J Clin Invest 2005;115:2731–2741. 9. Rothhammer V, et al. Semin Immunopathol 2015;37:625–638. 10. Papadopoulos MC, et al. Nat Rev Neurol 2014;10:493–506. 11. Erta M, et al. Int J Biol Sci 2012;8:1254–1266. 12. Barnum SR, et al. Glia 1996;18:107–117.

Satralizumab: phase III RCT (SAkuraSky and SAkuraStar)

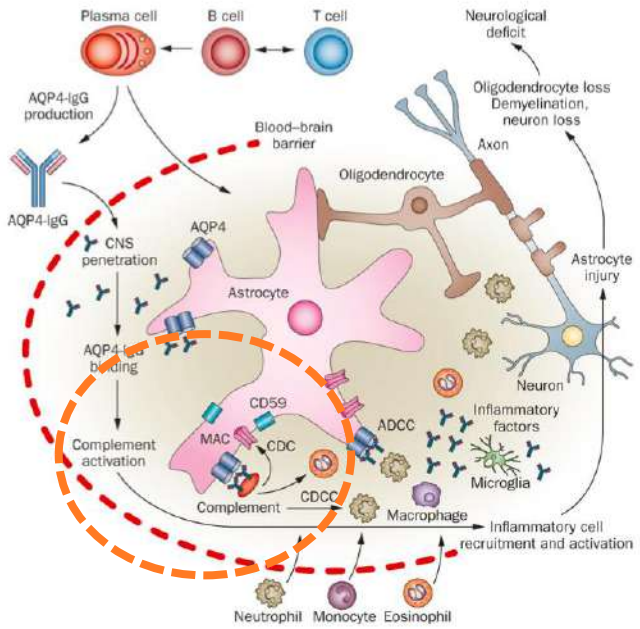


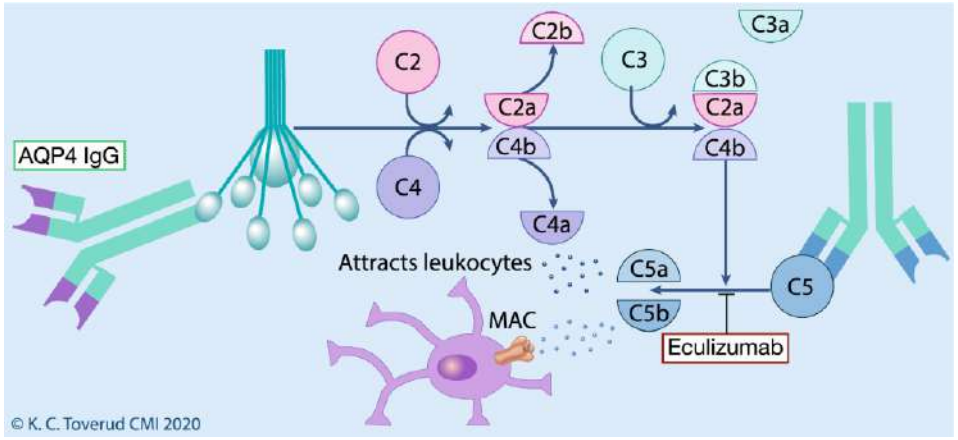
	SAkuraSky[1]	SAkuraStar[2]
Key inclusion criteria and concomitant medication	• **Aged from 12 to 74 years** • NMO‖ (AQP4-IgG+/-) or NMOSD‡ (AQP4-IgG+) patients • **≥2 relapses in last 2 years (≥1 relapse in last year)** • **In combination with baseline IST** (AZA, MMF, and/or OCs) §	• Aged from 18 to 74 years • NMO‖ (AQP4-IgG+/-) or NMOSD‡ (AQP4-IgG+) patients • **≥1 attack in last year** • **Monotherapy**
End of double-blind period	Total number of protocol-defined relapses reaches 26 (Data cut-off date Jun 2018)	Total number of protocol-defined relapses reaches 44 *or* 1.5 years after randomization of the last patient enrolled (Data cut-off date Oct 2018)

*Baseline treatment: AZA, MMF, OCs (for patients aged 12–17 years, AZA + OCs, MMF + OCs were permitted); †PDR or clinical relapse requiring rescue therapy in SAkuraSky; PDR in SAkuraStar; relapses adjudicated by CEC; ‖Defined by Wingerchuk et al 2006 criteria; ‡Defined by Wingerchuk et al with either longitudinally extensive myelitis or optic neuritis. AZA, azathioprine; BL, baseline treatment; CEC, clinical endpoint committee; LA, last administration; LO, last observation; MMF, mycophenolate mofetil; OCs, oral corticosteroids; Q4W, every 4 weeks; SC, subcutaneous.

1. Yamamura T et al. *N Engl J Med* 2019;381:2114-2124; 2. Traboulsee A, et al. *Lancet Neurol* 2020;19(5):402–12.

Eculizumab





Approved for use in *paroxysmal nocturnal haemoglobinuria* and *atypical haemolytic uraemic syndrome*

FDA approves first treatment for neuromyelitis optica spectrum disorder, a rare autoimmune disease of the central nervous system

Share Tweet LinkedIn Email Print

For Immediate Release: June 27, 2019

«On 24 April 2019 Eculizumab for treatment of NMOSD has been authorised in the EU since 26 August 2019».

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder

S.J. Pittock, A. Berthele, K. Fujihara, H.J. Kim, M. Levy, J. Palace, I. Nakashima, M. Terzi, N. Totolyan, S. Viswanathan, K.-C. Wang, A. Pace, K.P. Fujita, R. Armstrong, and D.M. Wingerchuk

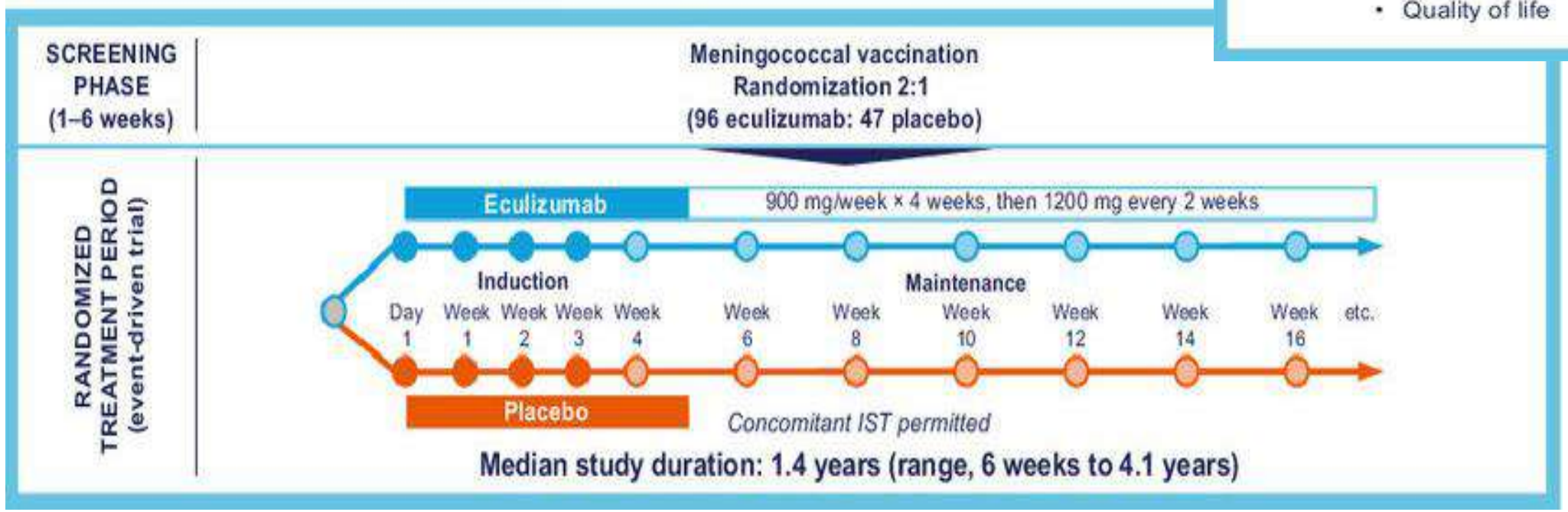
PREVENT STUDY DESIGN

143 patients with AQP4+ NMOSD

Event-driven, phase 3 trial completed after **23** confirmed relapses

Primary endpoint
- Time to first adjudicated relapse

Secondary endpoints
- Safety and tolerability
- Relapse rate
- Disability
- Quality of life



Eculizumab: Inclusion Criteria PREVENT

	PREVENT
Key inclusion criteria and concomitant medication	•**Aged >18 years** •Recurrent NMO (AQP4-IgG+) or NMOSD‡ (AQP4-IgG+) patients •**≥2 relapses in last 12 months or 3 relapses in the last 24 months (≥1 relapse in last year)** •**EDSS score <7** •**Baseline IST if stable-dose regimen**(AZA, MMF, and/or OCs) §
End of double-blind period	Total number of protocol-defined relapses reaches 23

*Baseline treatment: AZA, MMF, OCs (for patients aged 12–17 years, AZA + OCs, MMF + OCs were permitted); †PDR or clinical relapse requiring rescue therapy in SAkuraSky; PDR in SAkuraStar; relapses adjudicated by CEC; ‖Defined by Wingerchuk et al 2006 criteria; ‡Defined by Wingerchuk et al with either longitudinally extensive myelitis or optic neuritis.
AZA, azathioprine; BL, baseline treatment; CEC, clinical endpoint committee; LA, last administration; LO, last observation; MMF, m
1. Yamamura T et al. *N Engl J Med* 2019;381:2114-2124; 2. Traboulsee A, et al. *Lancet Neurol* 2020;19(5):402–12.

Roche

Unmet need in NMOSD treatment

No RCT
Approved for 648 use in Italy
G.U. 05/03/2018 n. 53

- **Controlled data driven by RCT**
- **Treatment of patients with AE to Rituximab (26%)**
  - patients Infusion-related reactions (CDC) (10%)
  - Infections
  - Hypogammaglobulinemia, late onset neutropenia
- **Rituximab non responders**

[Damato et al 2016, Marracinò et al, Neurol Neuroimmunol Neuroinflamm 2018; Kim et al, 2013 Eur J Neurol]

ECULIZUMAB

E	*Campo obbligatorio ai fini dell'eleggibilità*	SOLIRIS (eculizumab) - NMOSD
O	*Campo obbligatorio*	

Indicazione autorizzata: *Disturbo dello spettro della neuromielite ottica (NMOSD) in pazienti positivi agli anticorpi anti-acquaporina 4 (AQP4) con decorso recidivante della malattia*

Indicazione rimborsata SSN: Soliris è indicato per il trattamento di seconda linea, dopo rituximab, del disturbo dello spettro della neuromielite ottica (NMOSD) in pazienti adulti positivi agli anticorpi anti-acquaporina 4 (AQP4) con storia clinica di almeno 1 recidiva negli ultimi 12 mesi e un punteggio alla scala EDSS (Expanded Disability Status Scale) ≤ 7.

Attribuzione del requisito dell'innovazione terapeutica, in relazione all'indicazione terapeutica negoziata «Trattamento di adulti affetti da disturbo dello spettro della neuromielite ottica (NMOSD) in pazienti positivi agli anticorpi anti-acquaporina 4 (AQP4) con decorso recidivante della malattia», da cui conseguono:

l'inserimento nel Fondo dei farmaci innovativi di cui all'art. 1, comma 401, della legge n. 232/2016 (legge di bilancio 2017), come modificato dal decreto-legge 25 maggio 2021, n. 73, convertito con modificazioni dalla legge 23 luglio 2021, n. 106, (art. 35-*ter*);

il beneficio economico della sospensione delle riduzioni di legge, di cui alle determine AIFA del 3 luglio 2006 e del 27 settembre 2006, derivante dal riconoscimento dell'innovatività;

Gazzetta Ufficiale Repubblica Italiana 07.09.22

O	Il paziente ha ricevuto una precedente terapia con Rituximab per il trattamento della NMOSD?	Si	
		No	
E	*Se risposto "No alla domanda precedente:* Sono presenti delle chiare controindicazioni (reazioni avverse e/o intolleranza) all'uso di Rituximab?	Si	
		No	*blocca*
O	*Se risposto "Si"alla domanda precedente:* Indicare che tipo di controindicazione è presente all'uso di Rituximab	Controindicazioni ad ogni trattamento immunosoppressivo (storia di neoplasie, infezioni croniche latenti, epatite B, ecc)	*Combobox scelta multipla*
		Ipersensibilità verso rituximab	
		Elevato rischio connesso alla grave deplezione linfocitaria B (es. ipogammaglobulinemia)	
		Altro	
O	Specificare *Se risposto "Altro" alla domanda precedente "Indicare che tipo di controindicazione è presente all'uso di Rituximab"*	.....	*Testo libero*
O	Il paziente è attualmentein in trattamenro con farmaci immunosoppressori?	Si	
		No	
O	*Se risposto "Si" alla domanda precedente:* Indicare i farmaci immunosoppressori	Aziatropina	*Combobox scelta multipla*
		Ciclofosfamide	
		Metotressato	
		Micofenolato mofetil	
		Prednisolone	
		Altro	

SATRALIZUMAB

E	*Campo obbligatorio ai fini dell'eleggibilità*
O	*Campo obbligatorio*

ENSPRYNG_(satralizumab) - NMOSD

Indicazione autorizzata: Enspryng è indicato in monoterapia o in associazione a terapia immunosoppressiva (TIS), per il trattamento dei disturbi dello spettro della neuromielite ottica (NMOSD), in pazienti adulti e adolescenti a partire dai 12 anni di età con sieropositività per le IgG anti-acquaporina-4 (AQP4-IgG)

Indicazione autorizzata e rimborsata SSN:

- Negli adolescenti dai 12 ai <18 anni di età: Enspryng è rimborsato , in monoterapia o in associazione a terapia immunosoppressiva (TIS) per il trattamento dei disturbi dello spettro della neuromielite ottica (NMOSD),in presenza di sieropositività per le IgG anti-acquaporina-4 (AQP4-IgG) (come da indicazione autorizzata) e con punteggio di EDSS basale ≤6.5.

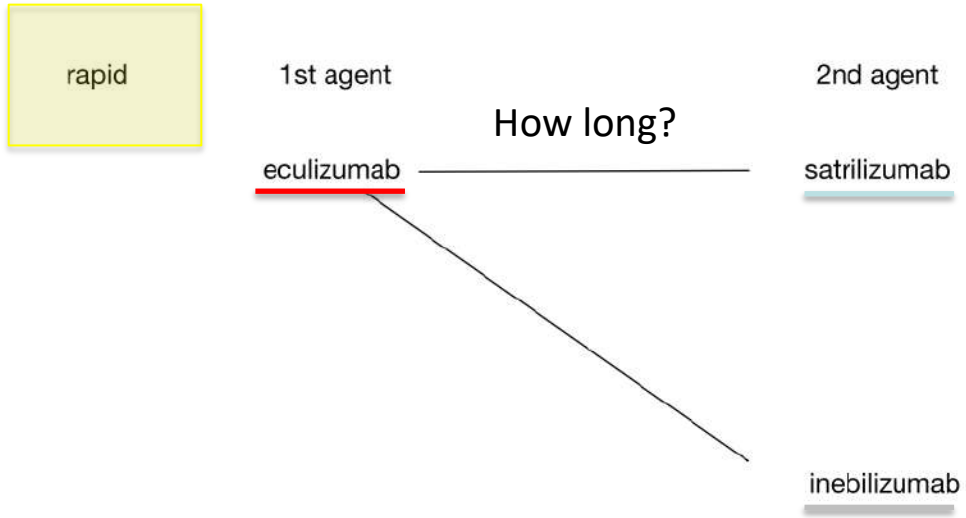
- Nei pazienti che iniziano il trattamento in età adulta: Enspryng è rimborsato come trattamento di seconda linea dopo rituximab, o in caso di controindicazioni all'utilizzo di rituximab, in monoterapia o in associazione a terapia immunosoppressiva per il trattamento dei disturbi dello spettro della neuromielite ottica (NMOSD) in presenza di sieropositività per le IgG anti-acquaporina 4 (AQP4), storia clinica di almeno una recidiva negli ultimi 12 mesi e un punteggio alla scala EDSS (Expanded Disability Status Scale) ≤ 6.5.

I medici devono discutere con i pazienti dei benefici e dei rischi della terapia con Enspryng e fornire ai pazienti l'opuscolo informativo e la sche
sicurezza del paziente" (RCP, paragr.4.4)

O	Il paziente ha ricevuto una precedente terapia con Rituximab per il trattamento della NMOSD?	Si	
		No	
E	*Se risposto "No alla domanda precedente:* Sono presenti delle chiare controindicazioni (reazioni avverse e/o intolleranza) all'uso di Rituximab?	Si	
		No	*blocca*
O	*Se risposto "Si"alla domanda precedente:* Indicare che tipo di controindicazione è presente all'uso di Rituximab	Controindicazioni ad ogni trattamento immunosoppressivo (storia di neoplasie, infezioni croniche latenti, epatite B, ecc)	*Combobox scelta multipla*
		Ipersensibilità verso rituximab	
		Elevato rischio connesso alla grave deplezione linfocitaria B (es. ipogammaglobulinemia)	
		Altro	
O	Specificare *Se risposto "Altro" alla domanda precedente "Indicare che tipo di controindicazione è presente all'uso di Rituximab"*	.....	*Testo libero*
O	Il paziente è attualmentein in trattamenro con farmaci immunosoppressori?	Si	
		No	
O	*Se risposto "Si" alla domanda precedente:* Indicare i farmaci immunosoppressori	Azlatropina	*Combobox scelta multipla*
		Ciclofosfamide	
		Metotressato	
		Micofenolato mofetil	
		Prednisolone	
		Altro	

NMOSD & MoA: positioning consideration

Onset of action



advantages	disadvantages
eculizumab -no effect acquired immunity -rapid AOA -long term efficacy	eculizumab -cost -freq administration
satrilizumab -convenience -long term modulation	satrilizumab ~110 week overlap with eculizumab to maintain relapse free
inebilizumab -eliminates AQP4	inebilizumab ~48 week overlap with eculizumab to maintain relapse free immunosuppressive

[Bord SA 2020]

NMOSD & MoA: positioning consideration

onset of action intermediate

When?

inebilizumab — satrilizumab ?

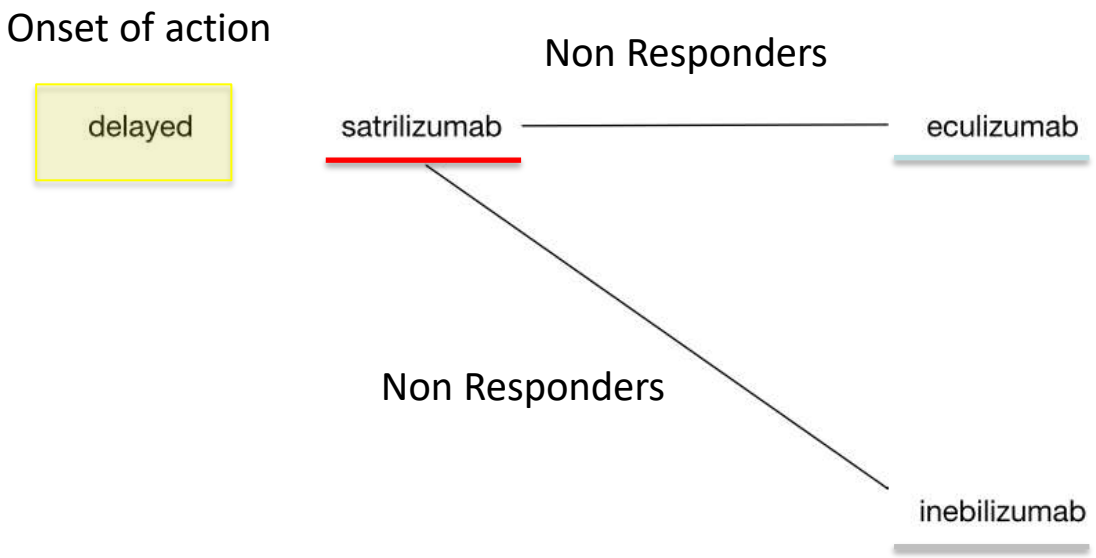
Non responders

eculizumab

	Advantages	Disadvantages
inebilizumab	-eliminates AQP4	-delayed AOA
satrilizumab	-convenience -long term modulation	-needs B cells for AOA
eculizumab	-rapid AOA	-cost -freq administration -long term switch to satralizumab

[Bord SA 2020]

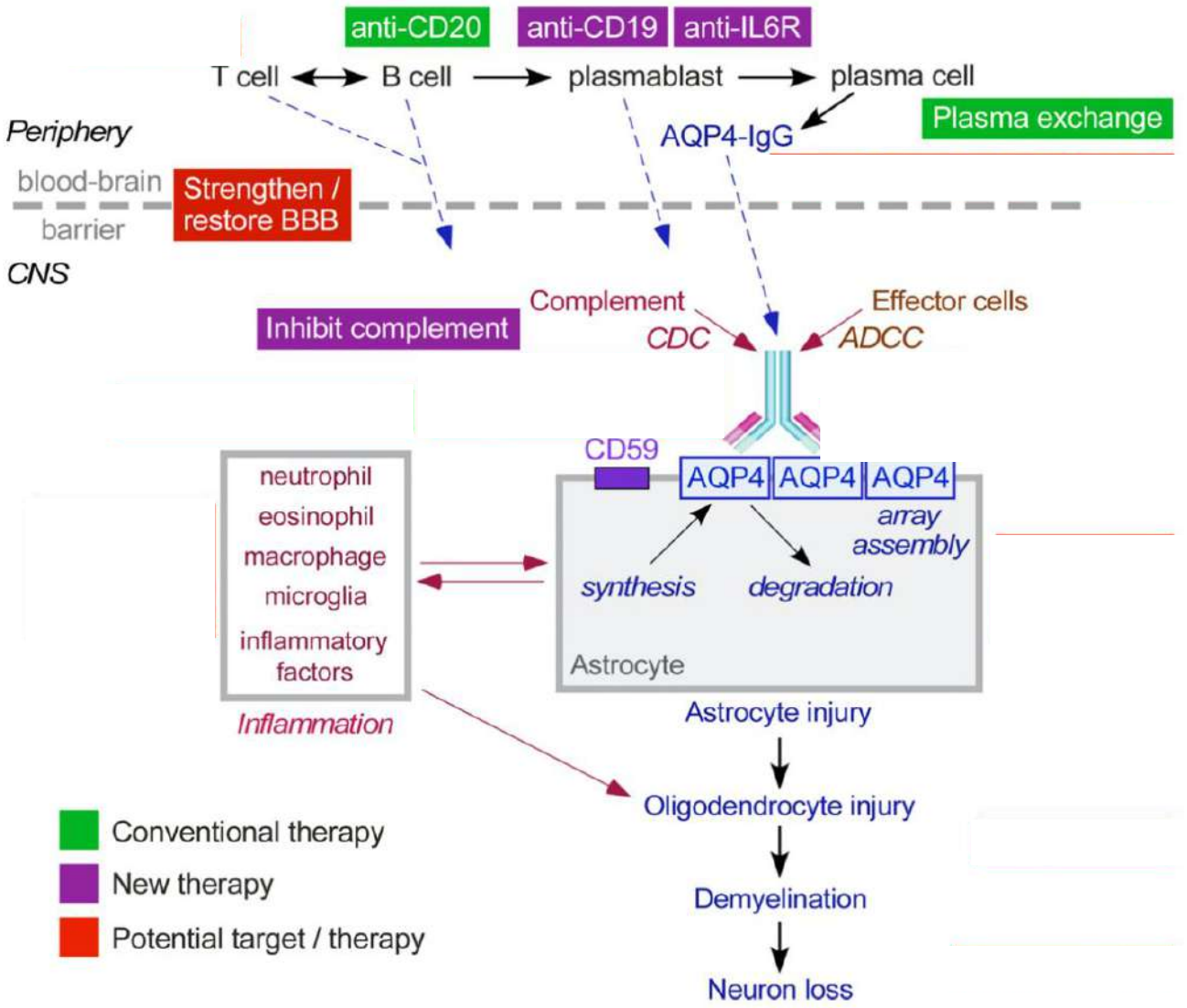
NMOSD & MoA: positioning consideration



Advantages	Disadvantages
satrilizumab -convenience from outset -long term modulation	satrilizumab -breakthrough disease from outset to ~110 weeks
eculizumab -rapid AOA	eculizumab -cost -freq administration
inebilizumab -eliminates AQP4	inebilizumab ~48 week overlap to maintain relapse free immunosuppressive

[Bord SA 2020]

Immunosuppression



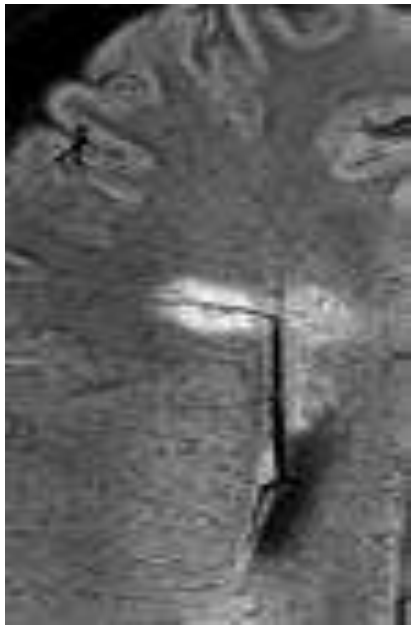
Biomarkers di RISPOSTA

AQP4-Ab levels?

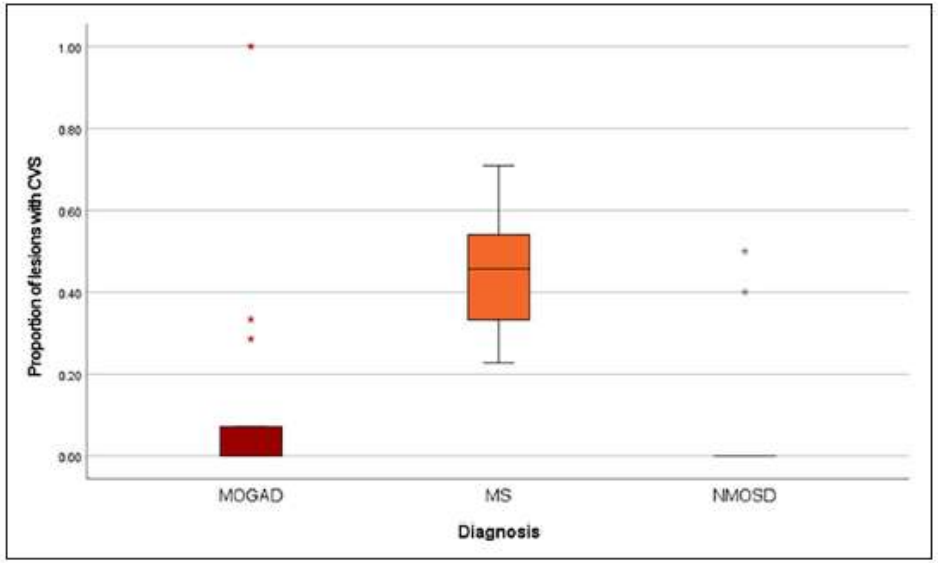
Modified from Tradtrantip L et al. 2020

ADCC, antibody-dependent cellular cytotoxicity; AQP4, aquaporin-4; AQP4-IgG, aquaporin-4-immunoglobulin G; IL6R, CDC, complement-dependent cytotoxicity; CNS, central nervous system; interleukin-6 receptor.

Central vein sign: MS vs MOGAD vs NMOSD

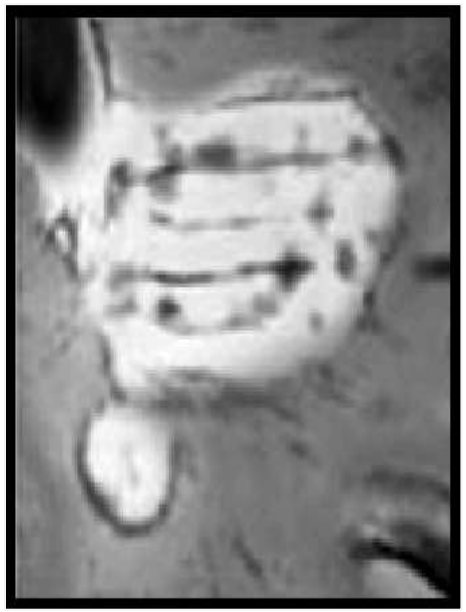


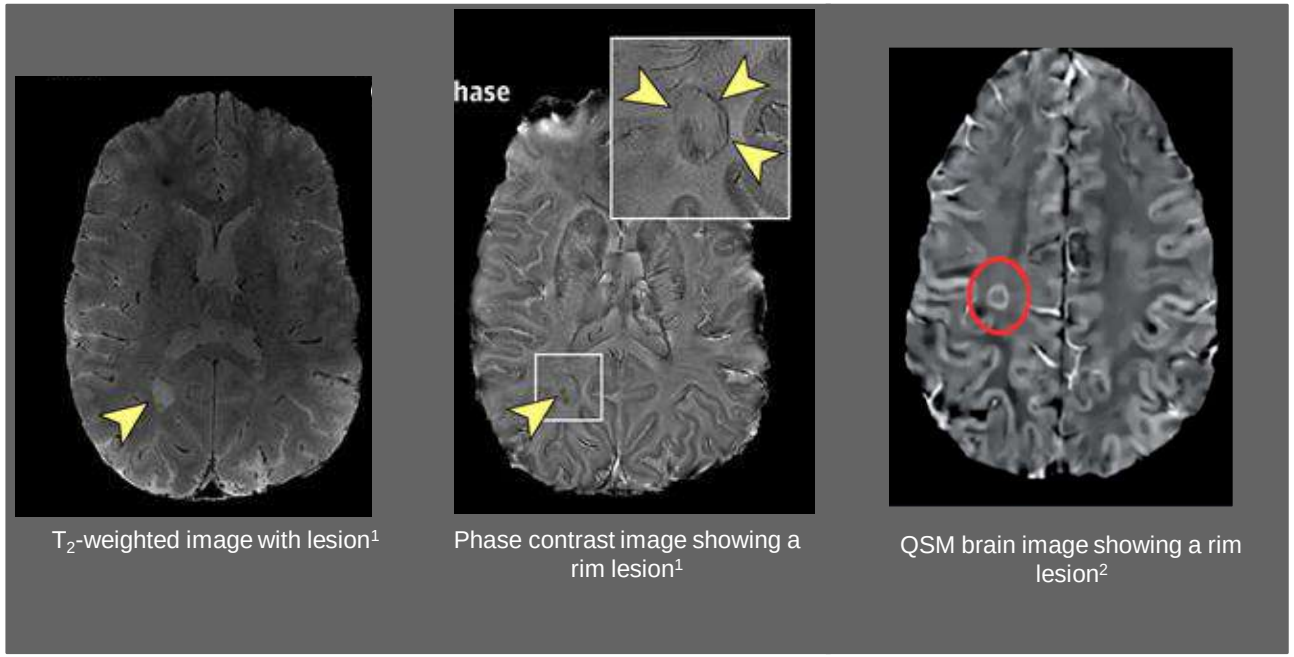
	MOGAD	MS	*p*-value	NMOSD	*p*-value
Brain MRIs assessed for CVS—no. (%)[c]	14 (56%)	19 (76%)		15 (60%)	
Lesions assessed for CVS—no.[d,e]	36	244		31	
CVS+ rate (%)	14.1%	44.5%	**0.006**	16.1%	0.816
Average CVS+ rate (per individual patient) (%)	12.1%	44.4%	**0.0008**	6.0%	0.481
Number of patients with >50% lesions CVS+—no. (%)	1 (7.1%)	7 (36.8%)	0.100	0	0.483



[Ciotti et al. Mult scler 2021]

Smoldering lesions: MS vs MOGAD





T_2-weighted image with lesion[1]

Phase contrast image showing a rim lesion[1]

QSM brain image showing a rim lesion[2]

Chronic active lesions

- Are less likely to remyelinate
- More likely to leave behind black holes (axonal loss) and increased brain atrophy[1,3-5]
- Associated with increased disability[1,6]
- Increase transition to progressive disease[1]

AUROOM Special edition 2021

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