Università degli Studi della Campania *Luigi Vanvitelli*

Beyond MS…MOGAD and NMOSD

NMOSD: Therapeutic strategies

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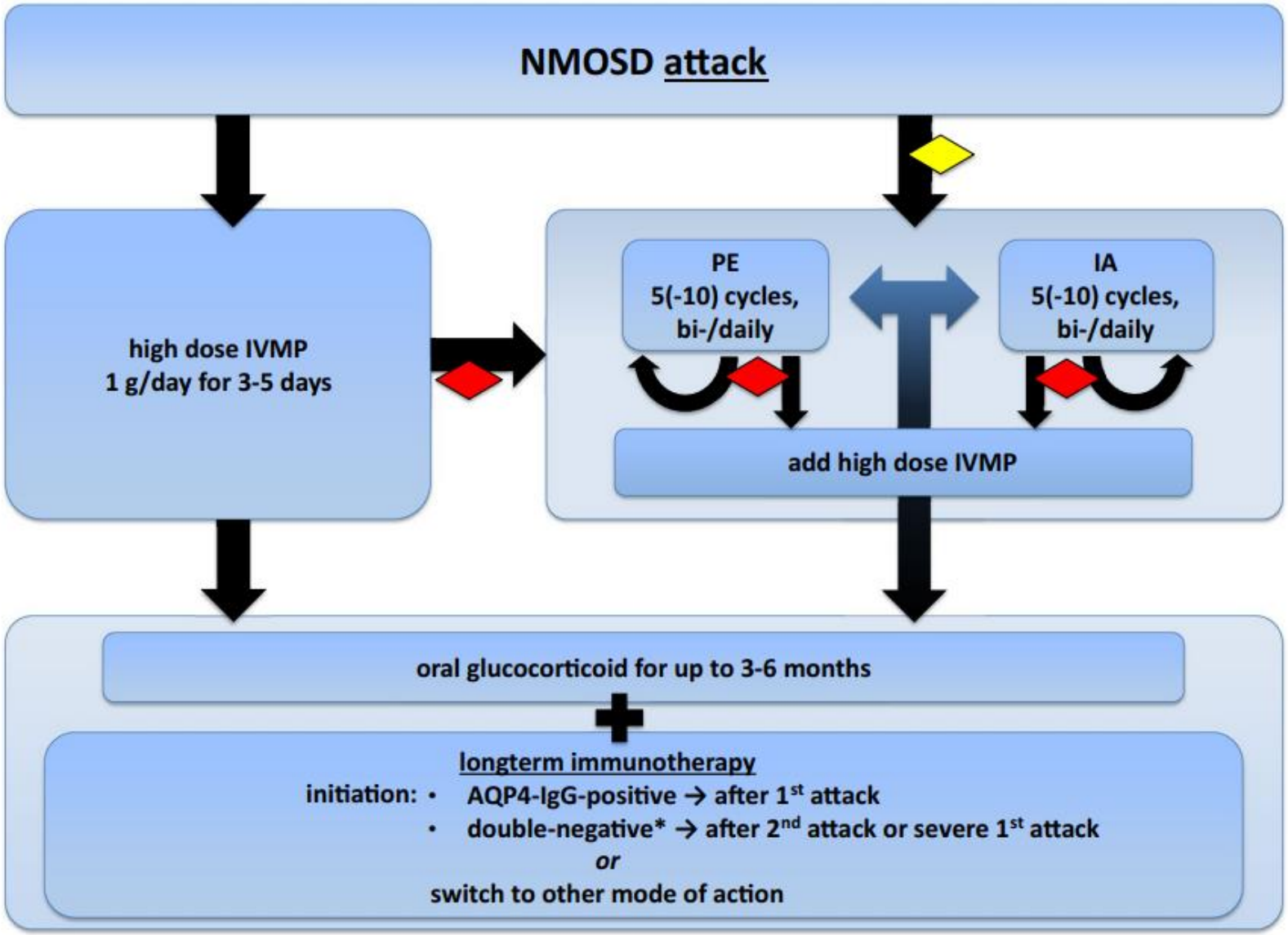
Outline

- NMOSD attack
- Long-term therapy
  - AQP4-IgG-posive NMOSD
    - principal recommendations
    - off-label therapies
    - initiation and selection criteria
    - AIFA reimbursement
  - Double-negative* NMOSD
  - Switching drugs
  - Duration
  - Family planning and pregnancy
  - Vaccinations



Abbr.: NMOSD neuromyelitis optica spectrum disorder; IVMP intravenous methylprednisolone; PE plasma exchange; IA immunoadsorption; AQP4 aquaporin-4; IgG immunoglobulin G; *AQP4-IgG and myelin-oligodendrocyte-glycoprotein(MOG)-IgG-negative

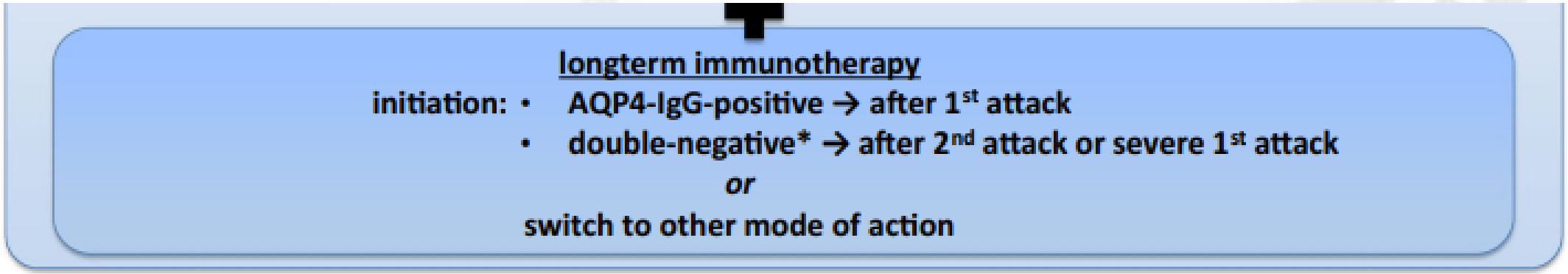
insufficient response to steroids during previous attacks or sufficient response to apheresis therapy during previous attacks or severe myelitis

no sufficient recovery

- Attack therapy must be initiated as early as possible in NMOSD attacks.
- Apheresis therapy may be the first-line treatment option for patients with:
  - ✓insufficient response to glucocorticoids during previous attacks
  - ✓sufficient response to apheresis therapy during previous attacks
  - ✓severe myelitis.
- For patients with severe attacks, concomitant treatment with high-dose glucocorticoids and apheresis may be used

Kumpfel et al, 2023

Long-term immunotherapy must be offered to patients with AQP4-IgG-positive NMOSD already after the first attack



Kumpfel et al, 2023

Pathophysiology of NMOSD

Immune tolerance is disrupted, causing B cell activation

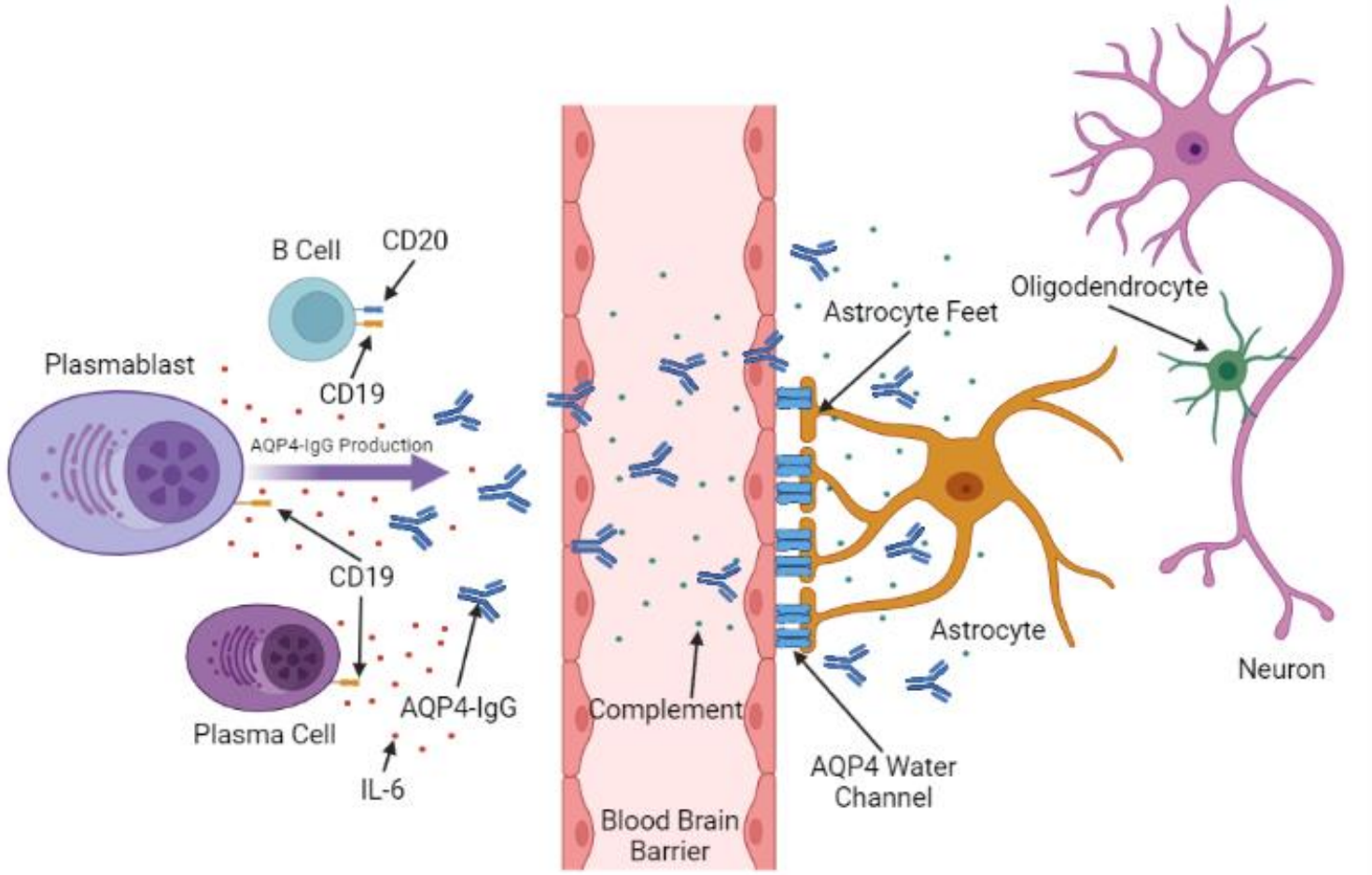
B cells mature into plasmablasts and produce AQP4-IgG

AQP4-IgG enters the CNS and selectively binds to AQP4 on astrocytes

Binding of AQP4-IgG to astrocytes leads to astrocyte cell death via complement activation and ADCC[2]

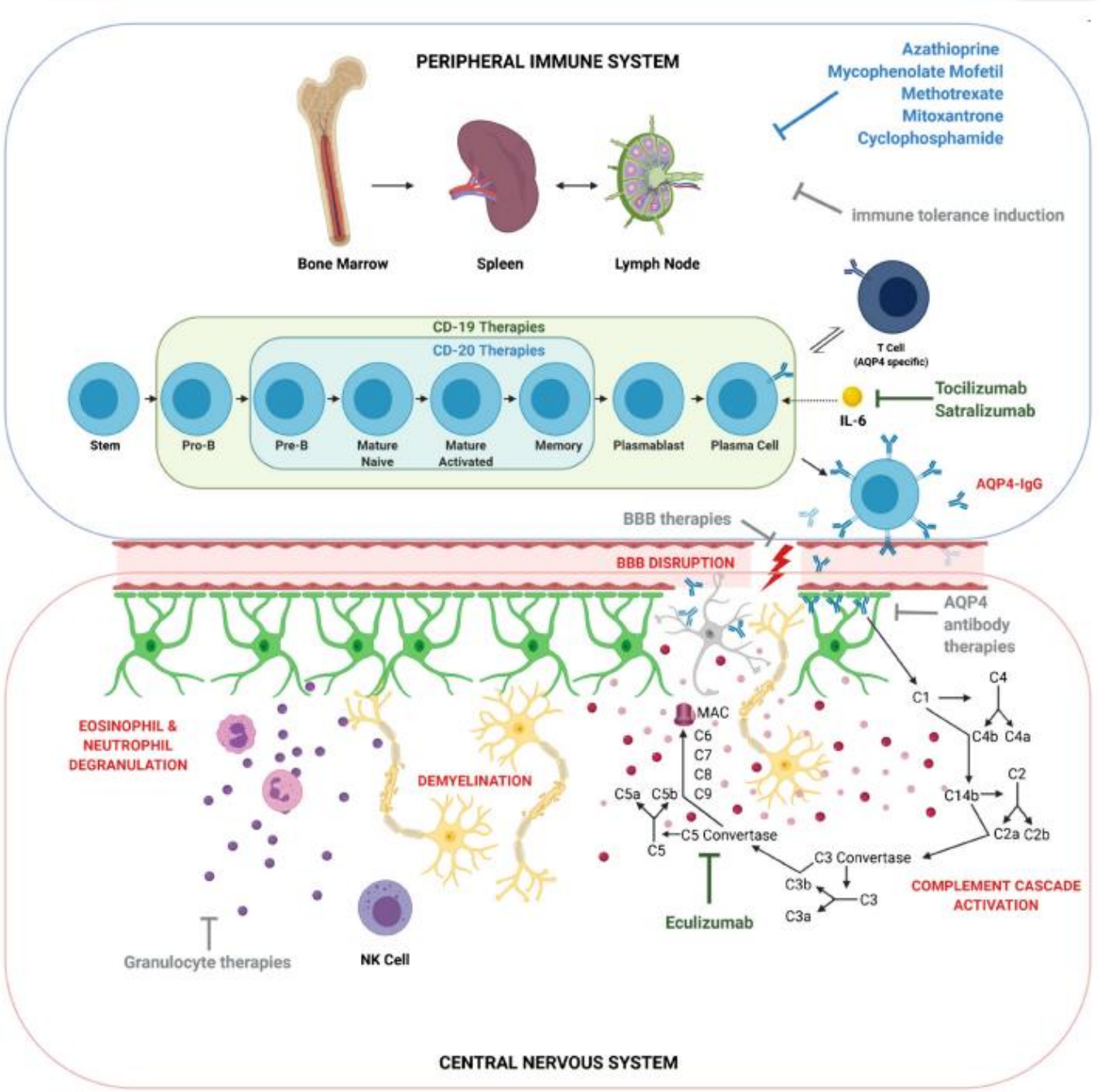
Innate immune cells are recruited in the CNS, leading to further tissue destruction

Widespread inflammation causes secondary demyelination and bystander injury to other CNS cells

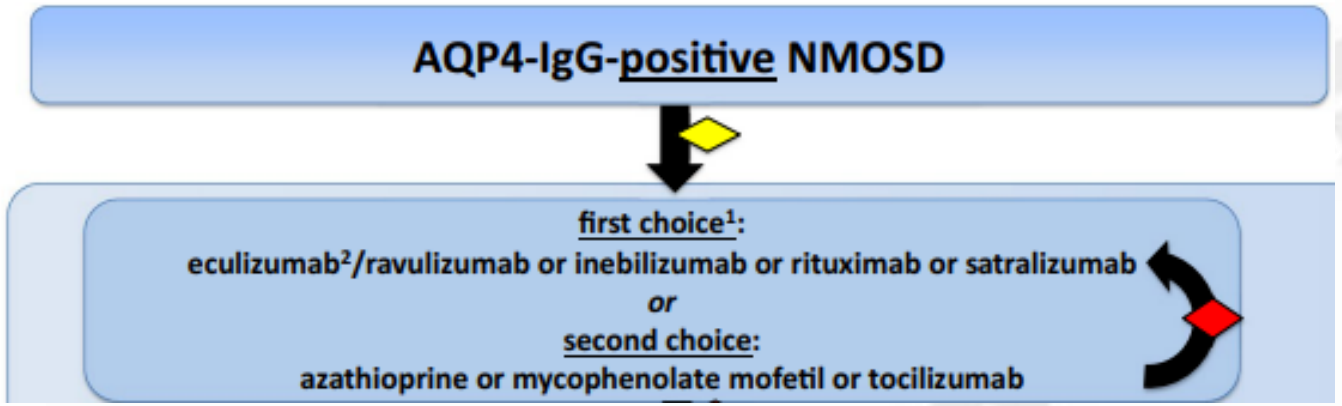


ADCC, antibody-dependent cellular cytotoxicity; APC, antigen-presenting cell; AQP4, aquaporin-4; CD19, cluster of differentiation 19; CD20, cluster of differentiation 20; CDC, complement-dependent cytotoxicity; CNS, central nervous system; EC, endothelial cells; IgG, immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder.

1. Jasiak-Zatonska M, et al. *Int J Mol Sci*. 2016;17:1-31. 2. Ratelade J, et al. *Acta Neuropathol*. 2013; 126(5):699-709.



Tugizova et al, 2021



Kumpfel et al, 2023

Long-term therapy: off-label therapies

- For patients who are stable on of-label therapies and have no signifcant side effects there is no need to be switched to other treatments
- Conventional immunosuppressive therapies (**azathioprine, mycophenolate mofetil, cyclophosphamide, oral glucocorticoids**) may be used but are considered less effective than biologicals
- Low-dose glucocorticoids should not be used as a monotherapy to prevent attacks unless no other options are available

AAR on Off-Label Therapies

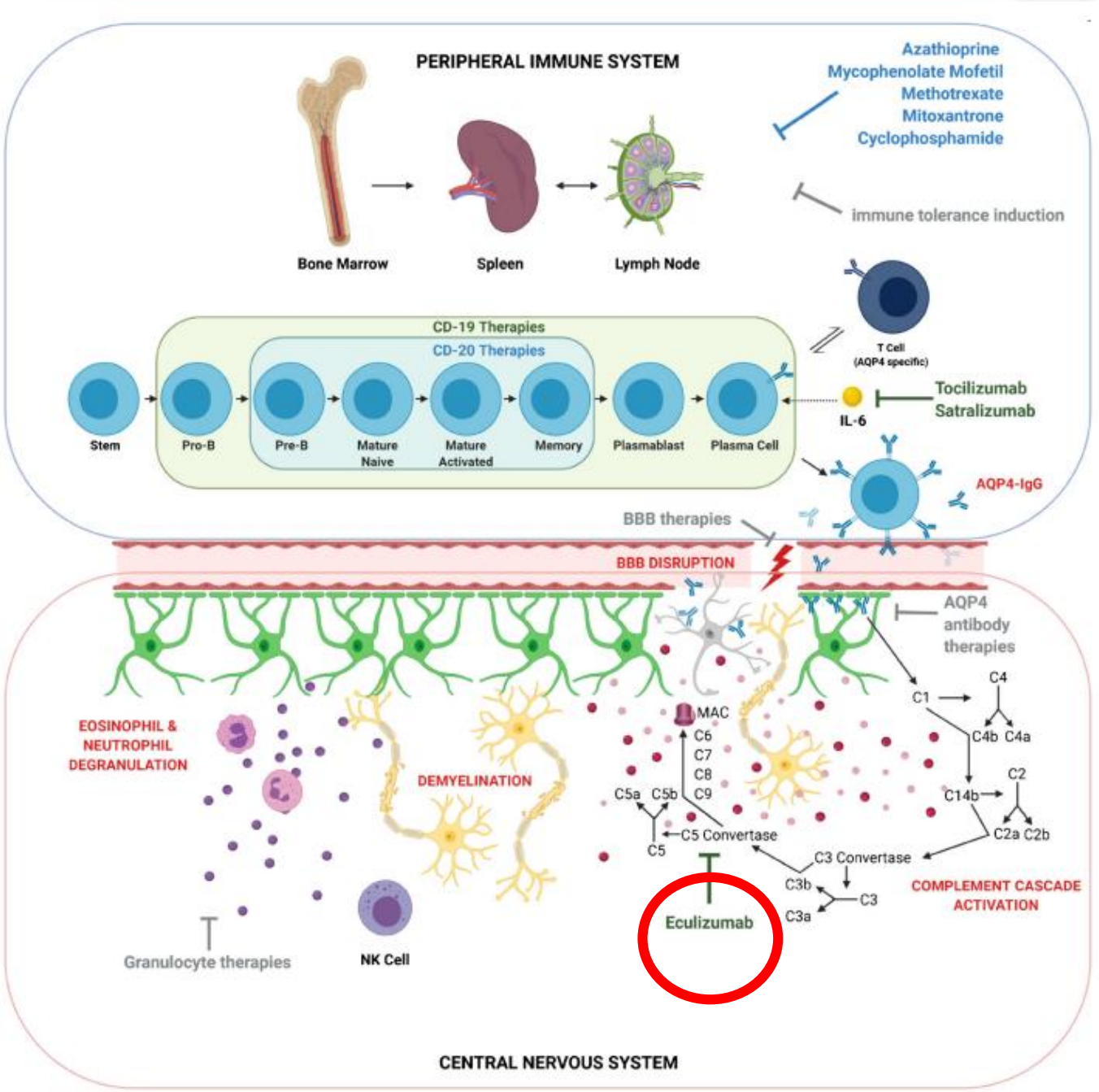
DMT	DOSAGE	PRE-TREAT AAR	POST-TREAT ARR
Azathioprine	<2 mg/Kg/d	2,09	0,82
	≥2 mg/Kg/d	2,20	0,52
	All	2,18	0,64
MMF	2 g/d	1,06	0,39
CYC	468-774 mg/m2	1,30	0,92
Rituximab	1-2 g q6 mo	1,17	0,25

Costanzi et al, 2011
Torres et al, 2015
Kumpfel et al, 2023

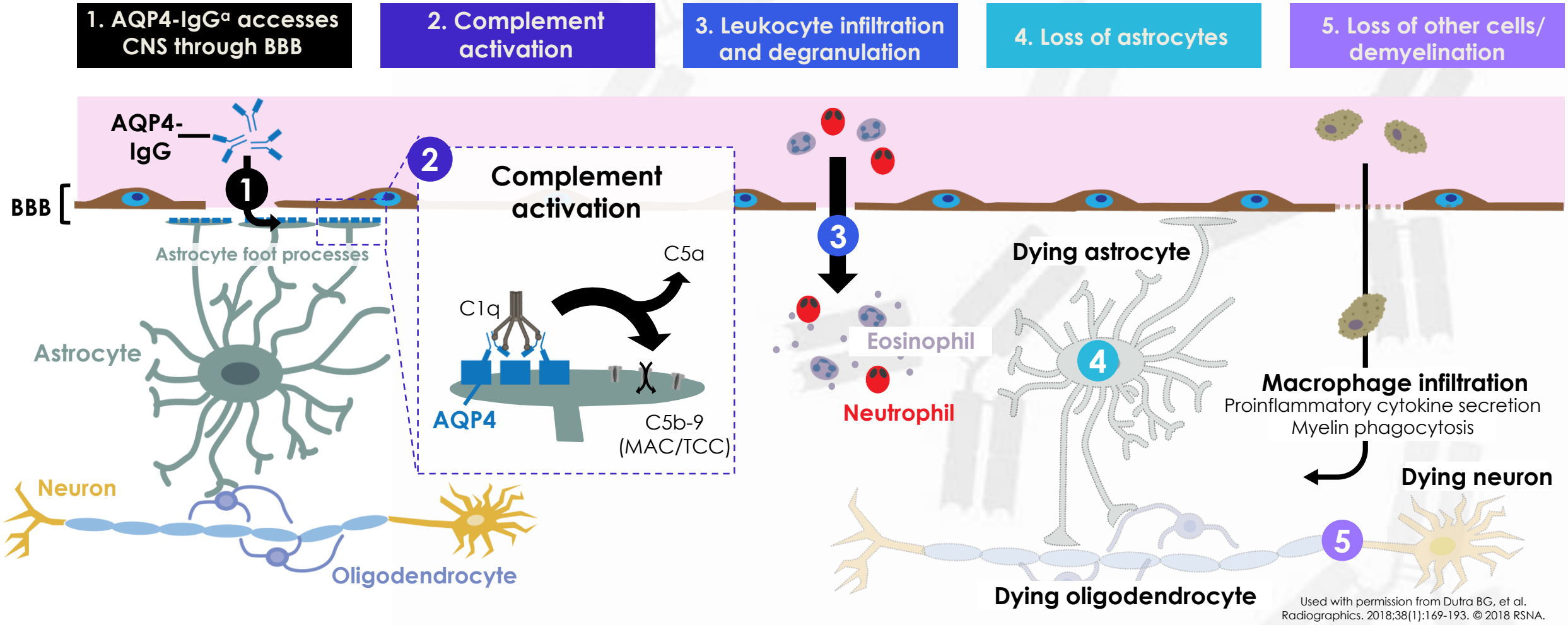
AQP4+ Key Competitor Comparison

	Eculizumab	Satralizumab	Inebilizumab
MOA	**C5 inhibitor**	**IL-6R inhibitor**	**Anti-CD-19**
ROA/Dosing	IV Q2W	SC Q4W	IV Q6M
Vaccination	Yes	No	No

Cree B et al. Lancet. 2019 Oct 12;394(10206):1352-1363.
Pittock SJ, et al. N Engl J Med. 2019;381(7):614-625.
Yamamura T, et al. N Engl J Med 2019;381:2114–2124.
Traboulsee A, et al. Lancet Neurol 2020;19(5):402–12



Tugizova et al, 2021

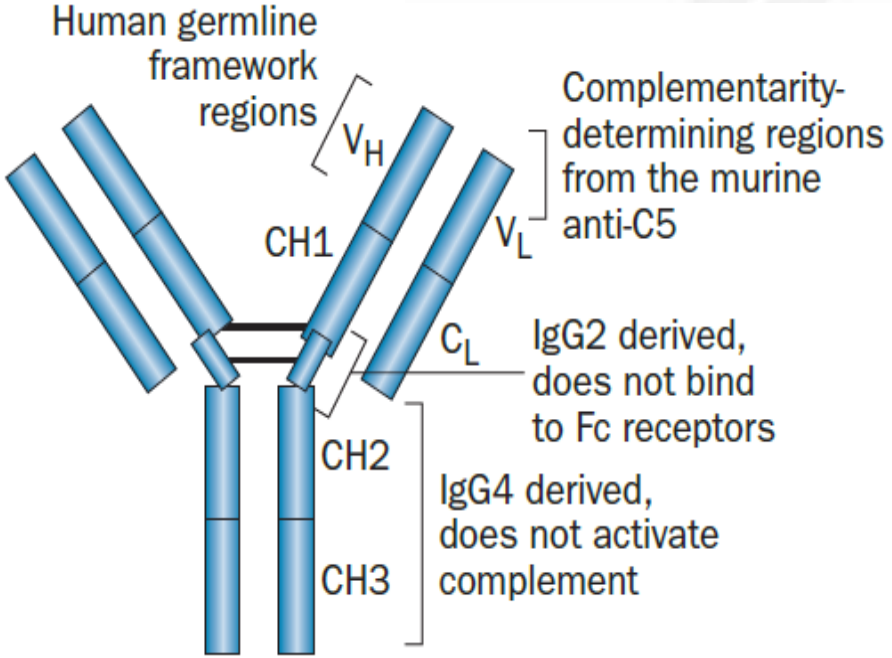


AQP4, aquaporin 4; BBB, blood brain barrier; CNS, central nervous system; ; Ig, immunoglobulin; MAC membrane attack complex; TCC, terminal complement complex.
[a]AQP4 IgG is predominantly the IgG1 subclass, which strongly activates the complement system[2]

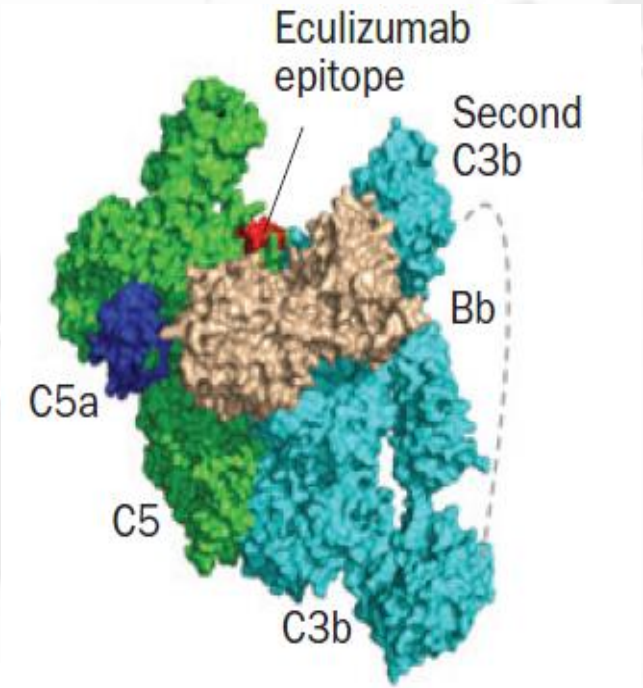
1. Dutra BG, et al. Radiographics. 2018;38(1):169-193. 2. Isobe N, et al. Mult Scler. 2012;18(11):1541-1551.

Eculizumab Is a Humanized Monoclonal Antibody That Binds C5

Eculizumab structure

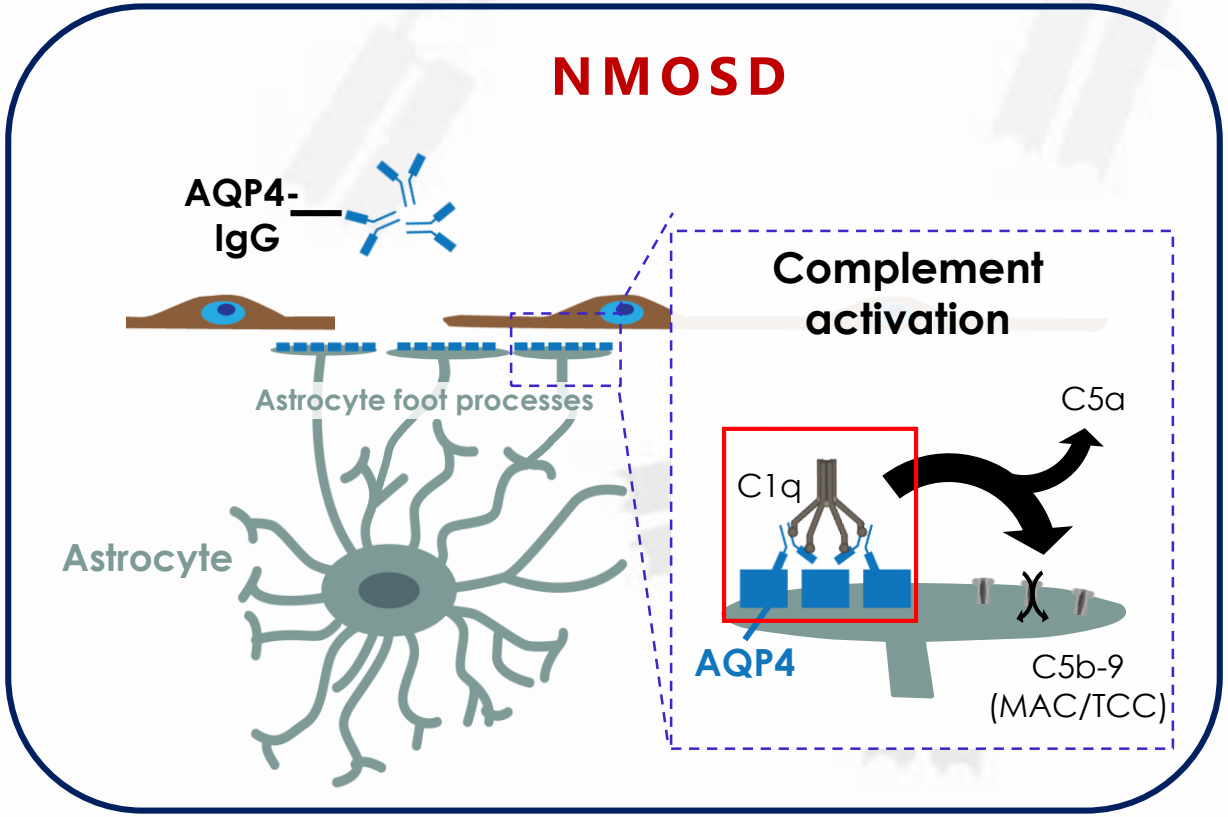


Eculizumab binds selectively to complement C5[a]



Reprinted from *Handb Clin Neurol*,133, Hinson SR et al., 377-403, © 2016, with permission from Elsevier.

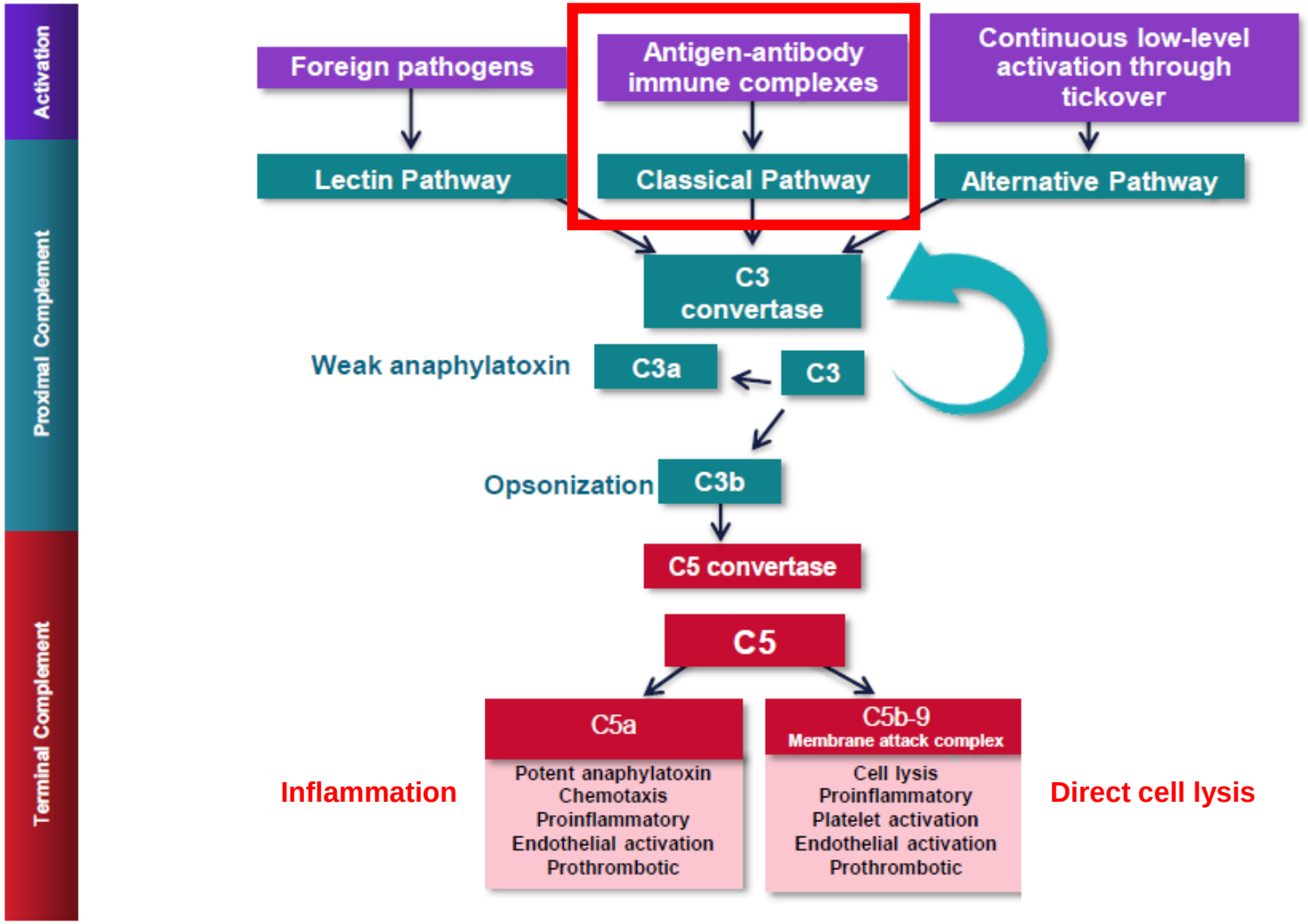
IgG, immunoglobulin G.
[a]The second C3b molecule is depicted as a dashed line because its location is still unknown.
Hinson SR, et al. *Handb Clin Neurol*. 2016;133:377-403.



Autoantibodies activate Complement

1. Dutra BG, et al. Radiographics. 2018;38(1):169-193.
2. Conti-Fine BM, et al. J Clin Invest. 2006;116(11):2843-2854.

The Complement Cascade1-6



KEY FUNCTIONS OF PROXIMAL COMPLEMENT[7]

- Immune complex clearance
- Microbial opsonization
- Inflammation

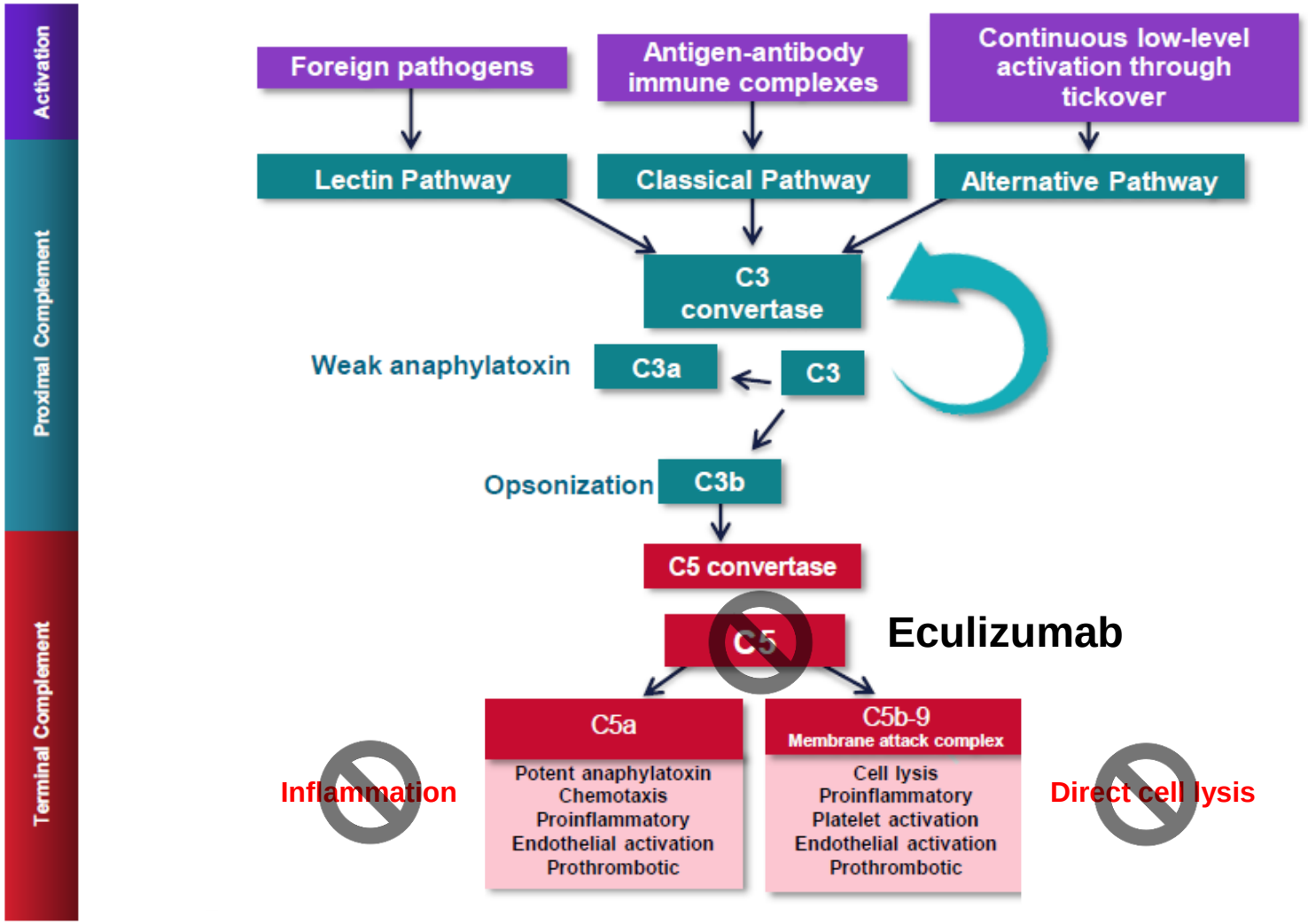
KEY FUNCTIONS OF TERMINAL COMPLEMENT[7-8]

- Inflammation
- Direct cell lysis

AQP4, aquaporin 4; BBB, blood brain barrier; NMOSD, neuromyelitis optcia spectrum disorder; WBC, white blood cell.

1. Emlen W, et al. *Semin Thromb Hemost.* 2010;36(6):660-668. 2. Dunkelberger JR, Song WC. *Cell Res.* 2010;20(1):34-50. 3. Hill A, et al.*Blood*. 2013;121(25):4985-4996. 4.Piatek P, et al. *Front Immunol.* 2018;9:1694. 5. Dutra BG, et al. *Radiographics*. 2018;38(1):169-193. 6. Noris M, et al. *Nat RevNephrol*. 2012;8:622-633. 7. Walport MJ. *N Engl J Med.* 2001;344(14):1058-1066. 8. . Rother RP, et al. *Nat Biotechnol.* 2007;25(11):1256-1264.

Eculizumab inhibits terminal complement1-6



KEY FUNCTIONS OF PROXIMAL COMPLEMENT[7]

- Immune complex clearance
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AQP4, aquaporin 4; BBB, blood brain barrier; NMOSD, neuromyelitis optcia spectrum disorder; WBC, white blood cell.

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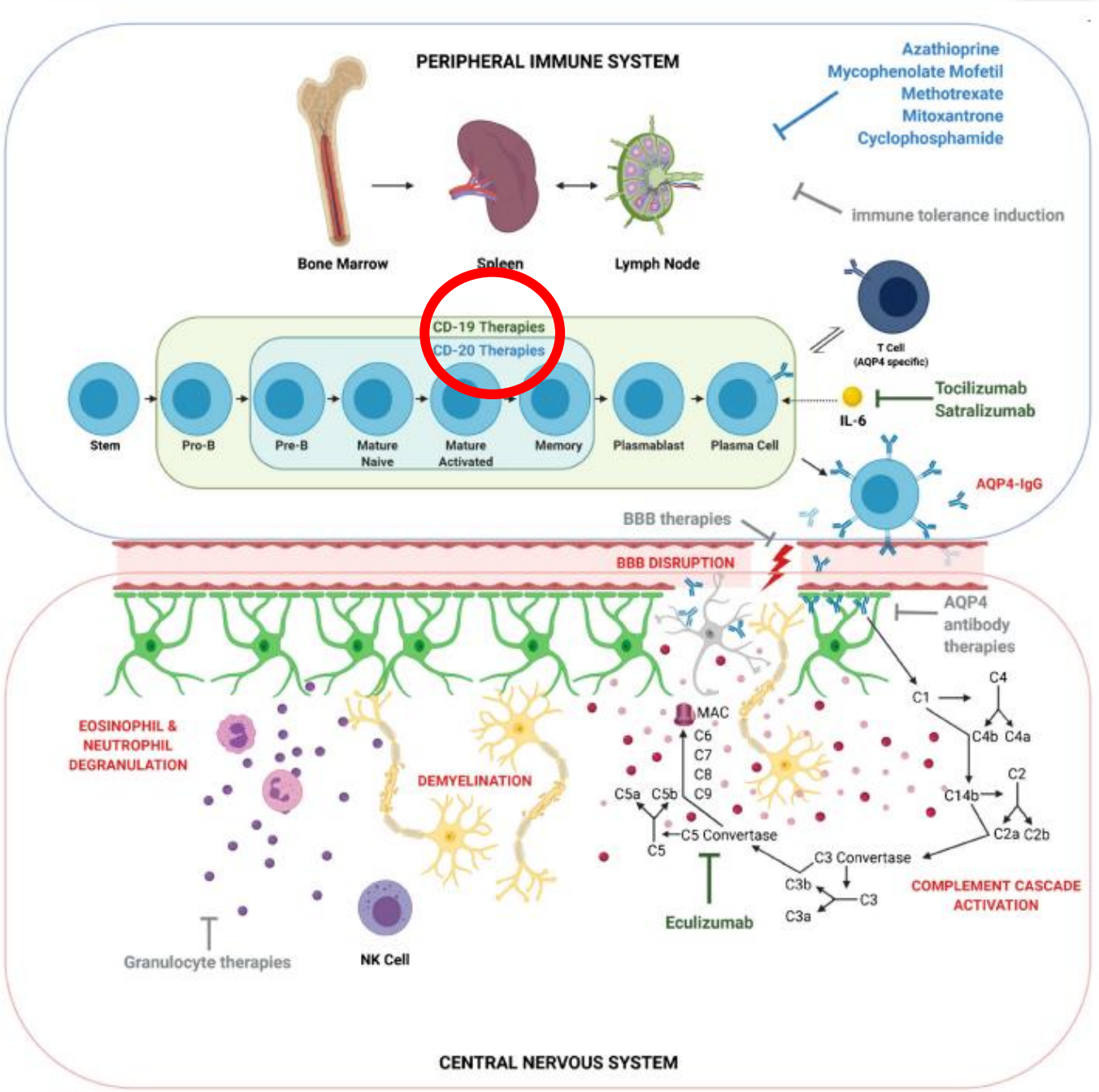
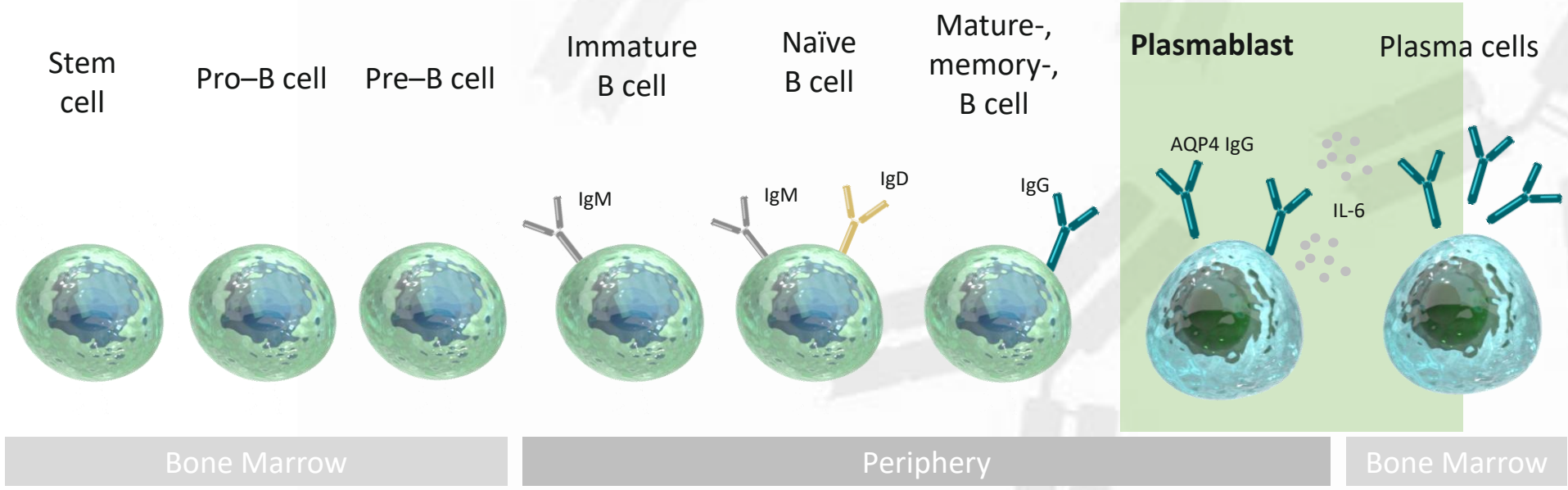


Tugizova et al, 2021

B Cell Maturation with Key Focus in Antibody-Secreting Cells

CD19 is expressed on the surfaces of B cells as they mature into plasmablasts



*3-5% of circulating T cell also express CD20[1]

Ig, immunoglobulin. CD19, cluster of differentiation 19; CD20, cluster of differentiation 20; IgD, immunoglobulin D; IgG, immunoglobulin G; IgM, immunoglobulin M.

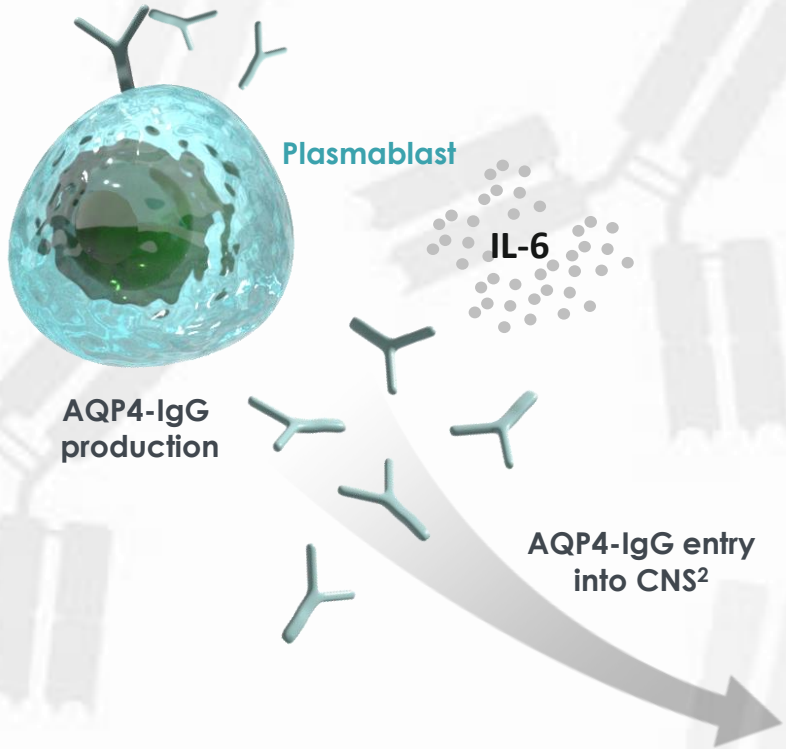
This modified image is used under a Creative Commons International CC BY 4.0 License specific to the article published by BioMed Central Ltd/Springer Nature Ltd: Blüml S et al. B-cell targeted therapeutics in clinical development. Arthritis Res Ther. 2013;15 suppl 1(suppl 1):S4. doi: 10.1186/ar3906

1. Schuh et al. J Immunol, 2016; 197(4):1111-7

Inebilizumab Depletes Biologically-Relevant B Cells

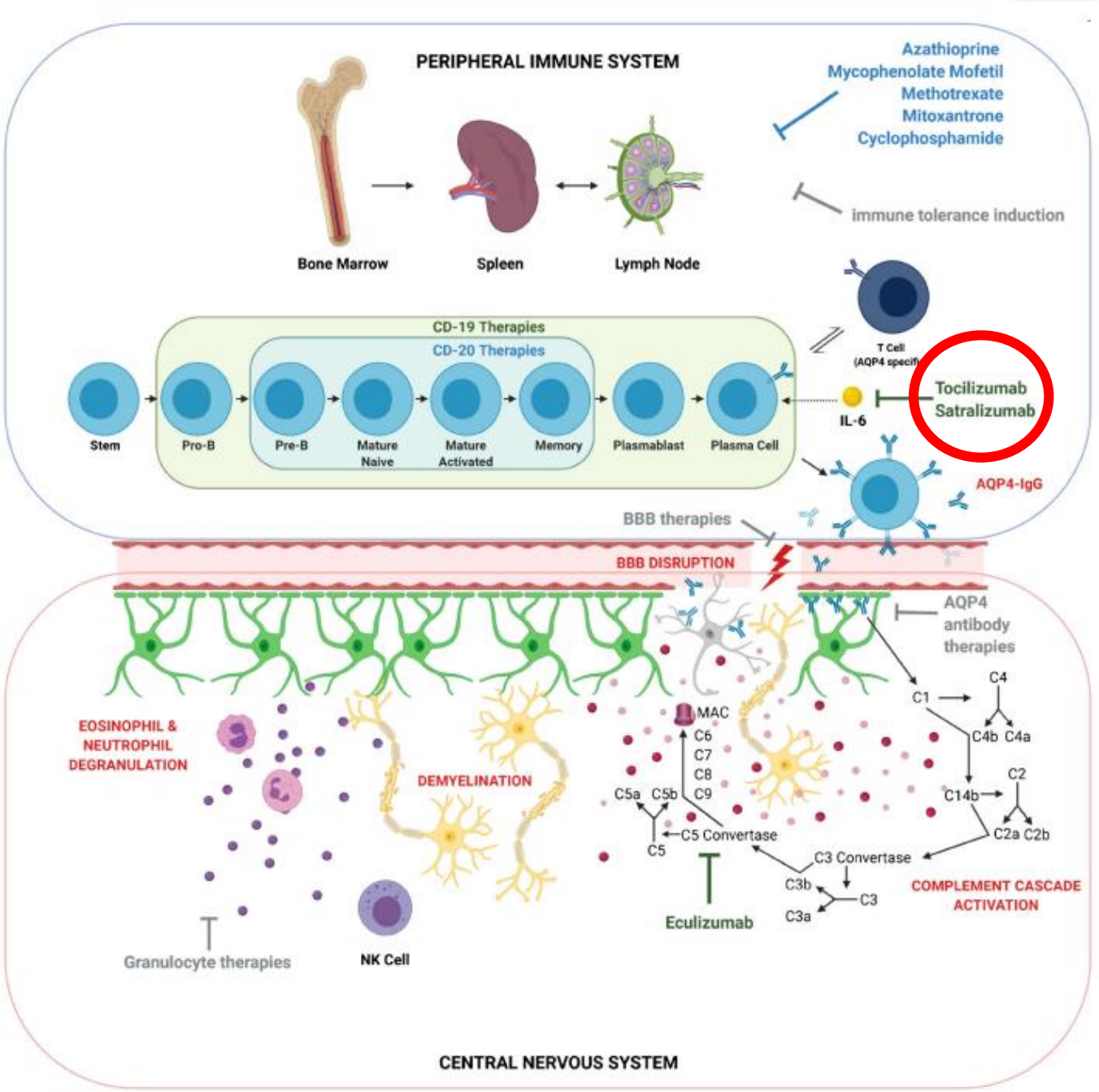
CD19-expressing plasmablasts/plasma cells:

- **Increased in the periphery in patients with NMOSD[1]**
- **Increase in frequency during NMOSD relapse[1,2]**
- **Produce AQP4 autoantibodies[1,3]**



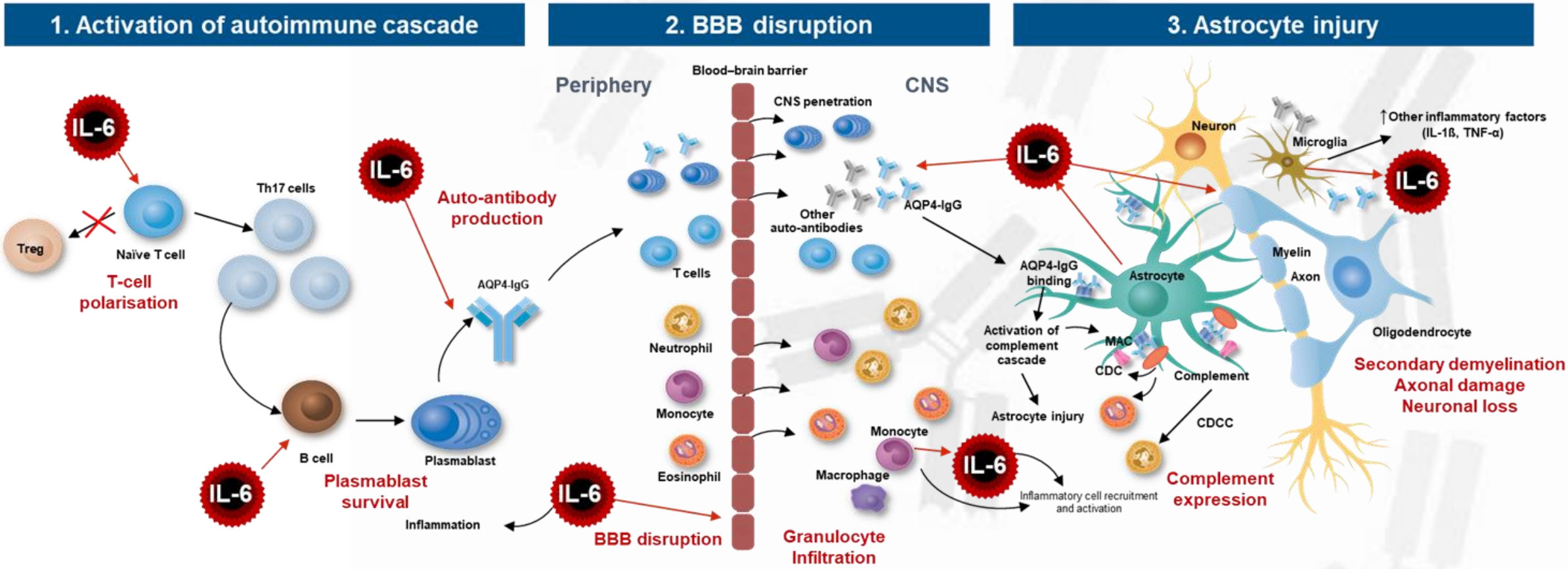
AQP4, aquaporin-4; CNS, central nervous system; IgG, immunoglobulin G; NMOSD, neuromyelitis optica spectrum disorder; IL, interleukin-6.

1. Chihara N et al. Proc Natl Acad Sci U S A. 2011 Mar 1;108(9):3701-6. 2. Chihara N et al. PLoS One. 2013 Dec 10;8(12):e83036. 3. Wilson R et al. Brain. 2018 Apr 1;141(4):1063-1074.



Tugizova et al, 2021

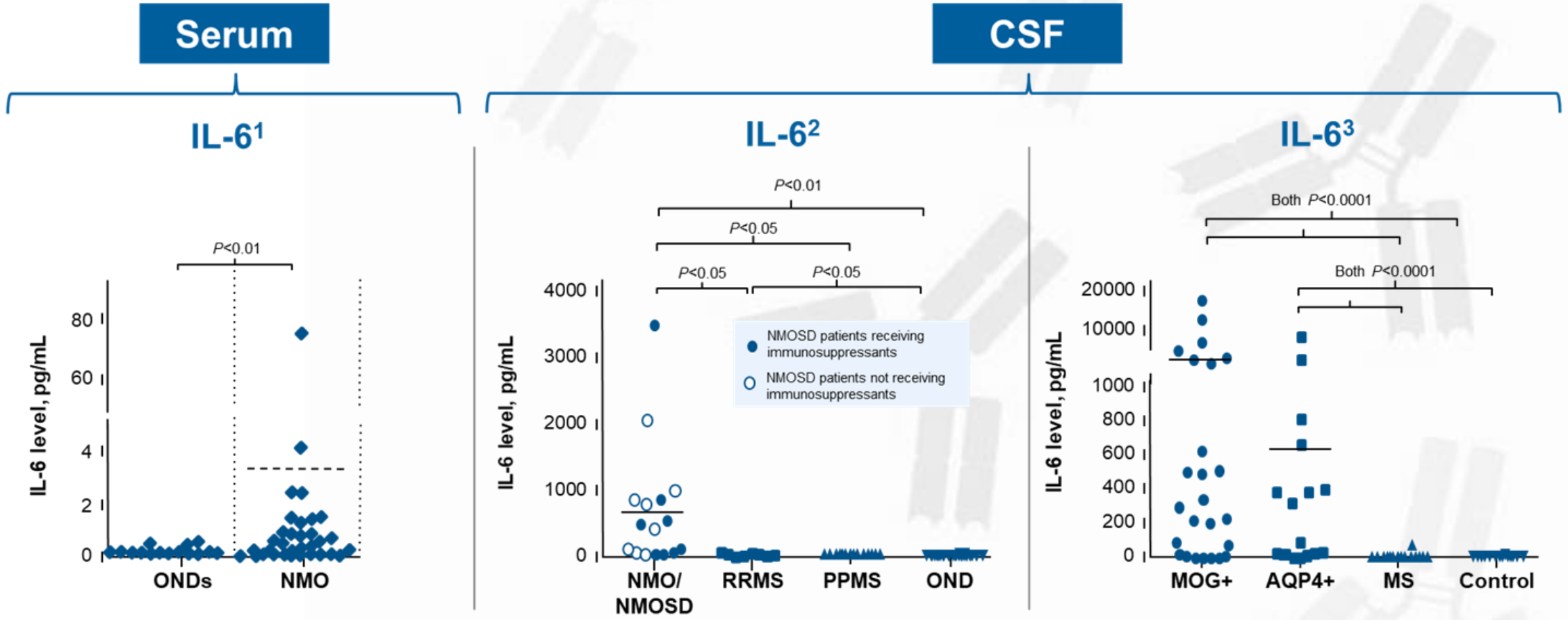
IL-6 is thought to be a central mediator in the pathogenesis of NMOSD



AQP4, aquaporin-4; BBB, blood–brain barrier; CDC, complement-dependent cytotoxicity; CDCC, complement-dependent cellular cytotoxicity; CNS, central nervous system; IgG, immunoglobulin G; IL-6/18, interleukin-6/18; MAC, membrane attack complex; NMOSD, neuromyelitis optica spectrum disorder; Th, T helper; TNF-α, tumor necrosis factor-α; Treg, regulatory T cells.

1. Kimura K, et al. *Eur J Immunol* 2010;40:1830–1835; 2. Lin J, et al. *Int J Neurosci* 2016;126:1051–1060; 3. Weinshenker BD, Wingerchuk DM. *Mayo Clin Proc* 2017;92:663–679; 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.

CSF and serum IL-6 concentrations are significantly elevated in patients with active NMOSD, but not in patients with MS



AQP4+, aquaporin-4 immunoglobulin G positive; CSF, cerebrospinal fluid; IL-6, interleukin-6; MS, multiple sclerosis; MOG +, myelin oligodendrocyte glycoprotein immunoglobulin G positive; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; OND(s), (other) non-inflammatory neurological disorders/diseases; PPMS, primary progressive multiple sclerosis; RRMS, relapsing remitting multiple sclerosis.

1. Uzawa A, et al. *Mult Scler* 2010;16:1443–1452; 2. Matsushita T, et al. PLoS One 2013;8:e61835; 3. Kaneko K, et al. *J Neurol Neurosurg Psychiatry* 2018;89:927–936.

Satralizumab overview: A humanised, IgG2, monoclonal recycling antibody that targets the IL-6 receptor

Satralizumab binds to both **membrane-bound** and **soluble forms** of the **IL-6 receptor**, preventing IL-6 from binding and **inhibiting the inflammatory IL-6 signalling pathways**[5,6]

By inhibiting IL-6 activity, satralizumab reduces pro-inflammatory signalling processes associated with many autoimmune disorders[5–7]

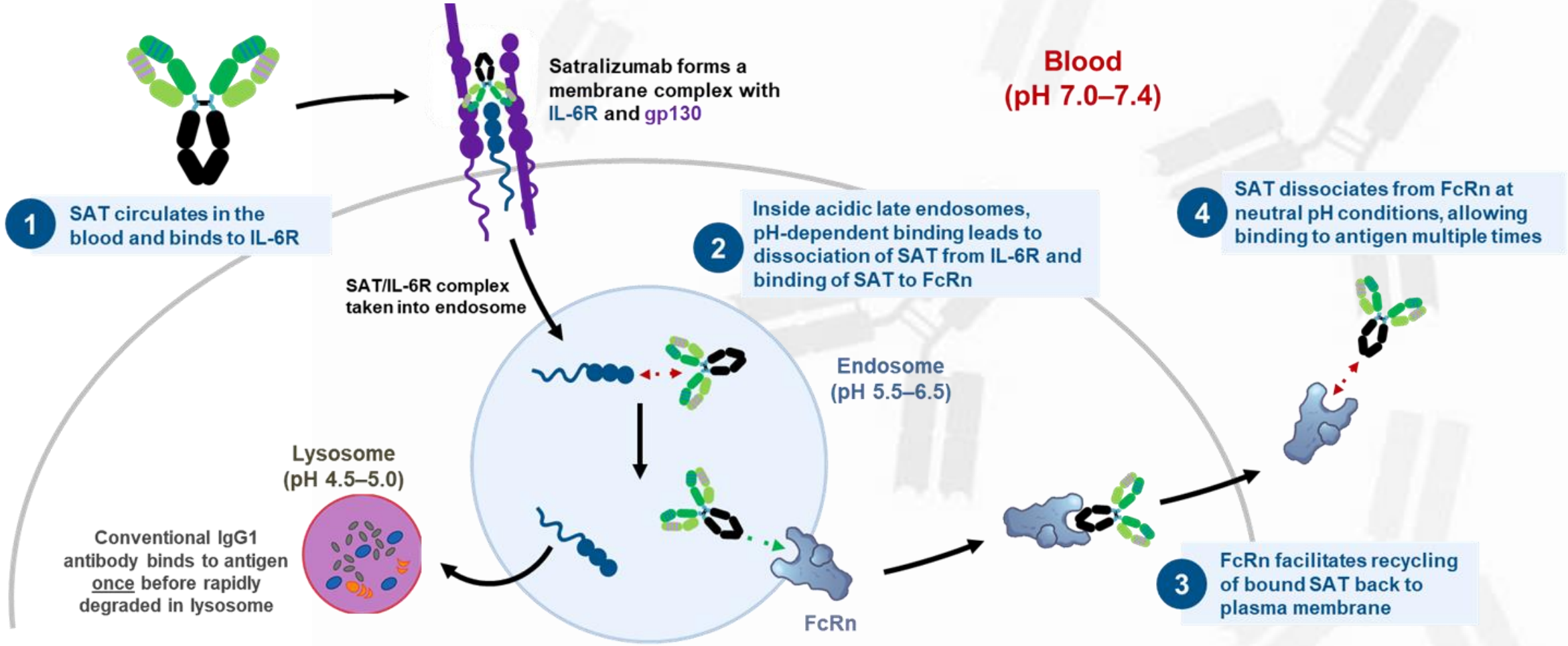
Satralizumab was engineered with **Recycling Antibody™** technology to ensure maximal sustained IL-6 suppression[1]

Satralizumab binds to the IL-6 receptor in a pH-dependent manner, which prolongs its plasma persistence and facilitates antibody binding to antigen multiple times[1,2,8]

EMA, European Medicines Agency; FDA, Food and Drug Administration; IgG, immunoglobulin G; IL-6, interleukin-6; SC, subcutaneous.

1. Chugai. Proprietary Innovative Antibody Engineering Technologies in Chugai Pharmaceutical. Available at: https://www.chugai-pharm.co.jp/cont_file_dl.php?f=FILE_1_36.pdf&src=[%0],[%1]&rep=139,36. Accessed September 2022; 2. Reichert JM. *Mabs* 2017;9:167–181; 3. FDA satralizumab Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761149s002lbl.pdf. Accessed September 2022; 4. EMA satralizumab Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/enspryng-epar-product-information_en.pdf. Accessed September 2022; 5. Traboulsee A, et al. *Lancet Neurol* 2020;19:402–412; 6. Yamamura T, et al. *N Engl J Med* 2019;381:2114–2124; 7. Schett G. *Rheumatology* 2018;57:ii43–ii50; 8. Igawa T, et al. *Nat Biotechnol* 2010;28:1203–1207.

Satralizumab binds to IL-6R in a pH-dependent manner, which prolongs its plasma persistence and facilitates antibody binding to antigen multiple times



FcRn, neonatal Fc receptor; gp, glycoprotein; IgG, immunoglobulin G; IL-6, interleukin-6; IL-6R, IL-6 receptor; SAT, satralizumab.

1. Igawa T, et al. *Nat Biotechnol* 2010;28:1203–1207.

PHASE 3 BASELINE CHARACTERISTICS

	Soliris Ph3 PREVENT trial (+/- IST)		Inebilizumab Ph3 N-MOmentum trial (Monotherapy)		Satralizumab			
					Ph3 SAkuraSky trial (+IST)		Ph3 SAkuraStar trial (Monotherapy)	
Dose	900 mg every week for 4 weeks. At week 5, 1200 mg every 2 weeks	Placebo	300 mg, Least frequent (every 6 months) Day 1, 15, and every 6 months (+corticosteroid for first 3 weeks)	Placebo	120 mg + IST; Week 0, 2, 4, and Q4W after	Placebo + IST	120 mg; Week 0, 2, 4, and Q4W after	Placebo
Number of patients	96	47	175	56	41	42	63	32
Trial Design	Randomized,, double-blind, placebo-controlled, time-to-event trial		Randomized; parallel assignment; quadruple masked; placebo-controlled		Randomized; parallel assignment; double blinded; placebo-controlled			
Inclusion Criteria	• NMO or NMOSD diagnosis (2006 or 2007 criteria, respectively) • Relapses: – ≥ 2 relapses during previous 12 months – 3 during previous 24 months (with ≥ 1 within previous 12 months) • EDSS ≤7 • Age ≥18 years • Patients receiving ISTs for relapse prevention eligible if receiving stable-dose regimens		• AQP4-IgG+/- NMOSD/NMO • ≥1 attack requiring rescue therapy in the last year or 2 attacks requiring rescue therapy in the last 2 years • EDSS ≤7.5 (8 in special circumstances) • Age ≥18 years		• AQP4-IgG+/- NMOSD/NMO • ≥2 relapses in last 2 years, including first attack (at least 1 relapse in last year) • EDSS ≤6.5 • Age 12-74 years • Stable dose for 8 weeks prior to baseline of AZA/MMF/OCS for 18+ years, or AZ+OCS/ MMF+OCS for 12-17 years.		• AQP4-IgG+/- NMOSD/NMO • ≥1 relapse in previous 12 months, including first attack • EDSS ≤6.5 • Age 18-74 years	
ARR	1.94	2.07	1.7	1.6	1.5	1.4	1.4	1.5
EDSS	4	4	3.8	4.2	3.83	3.63	3.9	3.7
AQP4+	100%	100%	92%	93%	66%	67%	65%	72%

Cree B et al. Lancet. 2019 Oct 12;394(10206):1352-1363.
Pittock SJ, et al. N Engl J Med. 2019;381(7):614-625.
Yamamura T, et al. N Engl J Med 2019;381:2114–2124.
Traboulsee A, et al. Lancet Neurol 2020;19(5):402–12

PHASE 3 RESULTS EFFICACY COMPARISON

	Soliris Ph3 PREVENT trial (+/- IST)		Inebilizumab Ph3 N-MOmentum trial (Monotherapy)		Satralizumab			
					Ph3 SAkuraSky trial (+IST)		Ph3 SAkuraStar trial (Monotherapy)	
Dose	900 mg every week for 4 weeks. At week 5, 1200 mg every 2 weeks	Placebo	300 mg, Least frequent (every 6 months) Day 1, 15, and every 6 months (+corticosteroid for first 3 weeks)	Placebo	120 mg + IST; Week 0, 2, 4, and Q4W after	Placebo + IST	120 mg; Week 0, 2, 4, and Q4W after	Placebo
Primary Endpoint	Time To First Adjudicated On-Trial Relapse		Time to determined NMOSD attack during RCP [(Day 1 (Baseline) through Day 197]		Time to 1st protocol-defined relapse in the DB period (up to approx. 30 months)			
Key Secondary Endpoints	Safety endpoints; Adjudicated On-Trial ARR; Changes in scores between baseline and trial end: EDSS score, -mRS score, HAI index, EQ-5D-3L index; VAS scale		EDSS score; Visual Acuity; MRI Lesions; NMOSD-related hospitalizations; NMOSD Attack Rate; Safety and PK endpoints; Participants with ADA		VAS Pain; FACIT; Relapse-free rate; ARR; EQ-5D Index; SF-36 domain scores; mRS Score; ZBI Score; EDSS Score; Visual Acuity; Safety and PK/PD endpoints; Participants with ADA; T25W (SAkuraStar)			
Efficacy in AQP4+ pts								
Relapse risk reduction	94,2%		77%		79%		74%	
% relapse free	48 weeks – 97,8% 72 weeks – 96,4% 96 weeks – 96,4%	48 weeks – 63.2% 72 weeks – 56.2% 96 weeks – 51.9%	28 weeks – 89% 52 weeks – 87% 208 weeks – 83%	28 weeks – 58%	48 weeks – 92% 96 weeks – 92% 144 weeks – 85%	48 weeks – 60% 96 weeks – 53% 144 weeks – 53%	48 weeks – 83% 96 weeks – 77% 144 weeks – 77%	48 weeks – 55% 96 weeks – 41% 144 weeks – 41%

Cree B et al. Lancet. 2019 Oct 12;394(10206):1352-1363.
Pittock SJ, et al. N Engl J Med. 2019;381(7):614-625.
Yamamura T, et al. N Engl J Med 2019;381:2114–2124.
Traboulsee A, et al. Lancet Neurol 2020;19(5):402–12

PHASE 3 RESULTS SAFETY COMPARISON

	Soliris Ph3 PREVENT trial (+/- IST)		Inebilizumab Ph3 N-MOmentum trial (Monotherapy)		Satralizumab			
					Ph3 SAkuraSky trial (+IST)		Ph3 SAkuraStar trial (Monotherapy)	
Safety								
Dose	900 mg every week for 4 weeks. At week 5, 1200 mg every 2 weeks	Placebo	300 mg, Least frequent (every 6 months) Day 1, 15, and every 6 months (+corticosteroid for first 3 weeks)	Placebo	120 mg + IST; Week 0, 2, 4, and Q4W after	Placebo + IST	120 mg; Week 0, 2, 4, and Q4W after	Placebo
Any AE	92%	91%	72%	73%	90%	95%	92%	75%
Any SAE	26%	28%	5%	9%	17%	21%	19%	16%
Urinary tract infection	14%	21%	12%	9%	17%	17%	18%	25%
Headache	23%	23%	8%	7%	24%	10%	16%	13%
Overall Safety[1]	Meningococcal infection (Black box) Systemic infection risk Infusion reactions		Infusion reactions Infection risk Hypogammaglobinemia Fetal risk		Infection risk[2] Elevated ALT/AST levels Decreased neutrophil counts			

Cree B et al. Lancet. 2019 Oct 12;394(10206):1352-1363.
Pittock SJ, et al. N Engl J Med. 2019;381(7):614-625.
Yamamura T, et al. N Engl J Med 2019;381:2114–2124.
Traboulsee A, et al. Lancet Neurol 2020;19(5):402–12

Table 2 Main data of randomized, double-blind, placebo-controlled, time-to-event trials in NMOSD

Drug	Trial/Randomization	Number of patients / AQP4-IgG serostatus	Inclusion criteria		Concomitant immunosuppression	Attacks n (%) (HR, 95% CI, and/or p)	previous immunotherapies	Duration of treatment in core study/open-label extension
			Previous disease activity	Age [years]				
Rituximab	RIN-1[1]/1:1	38 / all positive; including 11 AQP4-IgG negative patients who previously tested positive	Any history of optic neuritis or myelitis	16–80	No, but oral glucocorticoids, tapered during initiation period	0 vs. 7 (37%); (p = 0.0058)	0% with rituximab, other n.a	Median 72.1 weeks/mean 20.5 months (SD 10.1)[7]
Inebilizumab	N-MOmentum[2]/3:1	230 / 213-positive, 17-negative	≥ 1 attack in 12 months or ≥ 2 attacks in 24 months	> 18	No, but oral glucocorticoids during initiation period (20 mg/d until d14, then tapered to d21)	21 (12%) vs. 22 (39%);(0.272, 0.15–0.496, $p < 0.0001$)	Inebilizumab group: 66% (mostly azathioprine and glucocorticoids, including 7% with rituximab)	Up to 28 weeks/mean 3.2 years, up to 4.5 years (median)[8]
Eculizumab	PREVENT[3]/2:1	143 / all-positive	≥ 2 attacks in 12 months or ≥ 3 attacks in 24 months with 1 attack in the last 12 months	> 18	Yes	3 (3%) vs. 20 (43%); (0.06, 0.02–0.20, $p < 0.001$)	Eculizumab group: 78% IS at baseline; (27% with previous rituximab)	Median 89.4 weeks/median 132 weeks, up to 277 weeks[9]
Ravulizumab	CHAMPION–NMOSD[4]/ Placebo group of PREVENT as external comparator	58 / all-positive	≥ 2 attacks in 12 months or ≥ 3 attacks in 24 months with 1 attack in the last 12 months	> 18	Yes	0 vs. 29 (43%) in PREVENT (0.014, 0.000–0.103, $p < 0.0001$)	Ravulizumab group: 48% IS at baseline; 86% previos IS (including 36% with previous rituximab)	Median 73.5 weeks (range 11.0–117.7)/OLE ongoing
Satralizumab	SAkuraSky[5]/1:1	83 /55 -positive, 28-negative	≥ 2 attacks in 24 months with 1 attack in the last 12 months	12–74	Yes	8 (20%) vs. 18 (43%); (0.38, 0.16–0.88, $p = 0.02$)	Satralizumab group: 78% with previous IS before add-on IS at baseline (including 4,9% with rituximab);	Median 107.4 weeks/ median 4.4 years (range 0.1–7.0)[10]
	SAkuraStar[6]/2:1	95/63-positive, 31-negative	≥ 1 attack in 12 months	18–74	No	19 (30%) vs. 16 (50%); (0.45, 0.23–0.89, $p = 0.018$)	Satralizumab group: 87% with previous IS or other; 13% with previous B-cell depleting therapies	Median 92.3 weeks/ median 4.0 years (range 0.1–6.1)[10]

n.a. not available, *HR* hazard ratio, *CI* confidence interval, *d* day, *OLE* open-label extension, *SD* standard deviation, *IS* immunosuppressive therapy

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Table 3 Summary of the criteria for treatment decision-making in long-term immunotherapy in AQP4-IgG-positive NMOSD

Drug	Application	Full onset of action[1]	Availability[2]	Costs	Additional effects on concomitant rheumatological autoimmune disease	Recommended management/blood monitoring[3]	Effectiveness[4]	Family planning/pregnancy
Azathioprine	Oral, easy and independent	Delayed	+++	Low	Yes	Blood examinations every 1–4 weeks for the first 3 months, followed by three monthly examinations	+	Treatment possible during pregnancy[5]
Mycophenolate Mofetil	Oral, easy and independent	Intermediate	+++	Low	Yes	Blood examinations every 2–4 weeks for the first 3 months, followed by three monthly examinations	+	Teratogenic, must not be used 3 months prior to and during pregnancy
Rituximab	Infusion with premedication and monitoring every 6 months	Intermediate	++	Low (biosimilars), reimbursement issues	Yes	Blood examinations every 4 weeks for the first 3 months, followed by three monthly examinations	+++	Some data for NMOSD available, treatment possible during pregnancy[5]
Inebilizumab	Infusion with premedication and monitoring every 6 months	Intermediate	+	High	n. k	Blood examinations every 4 weeks for the first 3 months, followed by three monthly examinations	+++	No data[5]
Eculizumab	Infusion with monitoring: initially 1x/week, then every 2 weeks; meningococcal vaccination and/or antibiotic prophylaxis before start mandatory**	Rapid	+	Very high	No	Blood examinations after 4 weeks of treatment, followed by three to six monthly examinations; standardized query of meningococcal infection symptoms before each infusion	++++	Limited data, treatment possible during pregnancy after careful risk–benefit evaluation[5]

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Table 3 (continued)

Drug	Application	Full onset of action[1]	Availability[2]	Costs	Additional effects on concomitant rheumatological autoimmune disease	Recommended management/blood monitoring[3]	Effectiveness[4]	Family planning/pregnancy
Ravulizumab	Infusion with monitoring: initially on day 1 and 15, then every 8 weeks; meningococcal vaccination and/or antibiotic prophylaxis before start mandatory**	Rapid	+	Very high	No	Blood examinations after 4 weeks of treatment, followed by three to six monthly examinations; standardized query of meningococcal infection symptoms before each infusion	++++	no data[5]
Tocilizumab	Infusion every 4–6 weeks*	Intermediate	++	Low, reimbursemen issues	Yes	Blood examinations every 4 weeks for the first 3 months, followed by three monthly examinations	++	Limited data, treatment possible during pregnancy[5]
Satralizumab	Initial infusion and titration with monitoring, followed by independent self-infusions every 4 weeks	Intermediate	+	High	n. k	Blood examinations every 4 weeks for the first 3 months, followed by three monthly examinations	+++	No data[5]

[1]Full onset of action: delayed: ≥ 6 months, intermediate: 3–6 months, rapid: within 1–3 months

[2]Accessibility: +++ worldwide, ++ in most industrialized countries, + only in specific countries

[3]Please refer to Table 2 for specific laboratory tests to be performed during treatment with the respective substances

[4]Estimates of effectiveness compared to each other, based on the decrease in relapse rates observed in controlled trials (no comparative data), comparative retrospective analyses and meta-analyses: ++++ very high, +++ high, ++ intermediate, + low, n. k. = not known

[5]Considering data availability and limitations, consult the section of the manuscript "Pregnancy and NMOSD"

*Most data are available for intravenous mode of administration, and some data are available for weekly subcutaneous self-administration

**See text for details

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RISK OF HBV INFECTION REACTIVATION

Agents	Increased risk of overall infection	Risk of VZV/HBV infection	Risk of active TB	Observations and recommendations
Mepolizumab, reslizumab	None	No/no	No	• Age-appropriate antiviral vaccinations • No apparent increase in the risk of infection
Tocilizumab, siltuxumab	Modest	Yes/yes	Yes	• Risk comparable to that observed for anti-TNF-α agents (probably lower for TB) • Screening for chronic HBV infection before starting therapy • Antiviral prophylaxis while on therapy on HBsAg-positive patients • Monitoring for HBV viral load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection • Screening for LTBI before starting treatment (followed by appropriate therapy if needed)
Eculizumab	Major (only for neisserial infections)	No /no	No	• Markedly increased risk of infection due to *Neisseria* spp. • Meningococcal vaccination (MenACWY and MenB) at least 2 –4 weeks before starting eculizumab, with booster doses of MenACWY every 5 years if therapy is maintained • Meningococcal chemoprophylaxis (penicillin V or ciprofloxacin) at least 4 weeks since completion of vaccination or until protective antibody titres are documented • Continuation of chemoprophylaxis for immunocompromised patients, with discontinuation after 4 weeks from the last dose of eculizumab • Monitoring of serum bactericidal antibody may help to guide the requirements for vaccine booster and prolongation of chemoprophylaxis • Screening for gonococcal infection in patients at high-risk for STD and their sexual partners • Pneumococcal and Hib vaccination before starting eculizumab

HBV, hepatitis B virus; Hib, *Haemophilus influenzae* type b; IL, interleukin; Ig, immunoglobulin; LTBI, latent tuberculosis infection; MenACWY, meningococcal (serogroups A, C, W-135 and Y) conjugate vaccine; MenB, meningococcal serogroup B vaccine; STD, sexually transmitted disease; TB, tuberculosis; TNF-α, tumor necrosis factor-α; VZV, varicella zoster virus.

Winthrop et al. Clin Microbiol Infect. 2018 Jun;24 Suppl 2:S21-S40.

RISK OF HBV REACTIVATIONS

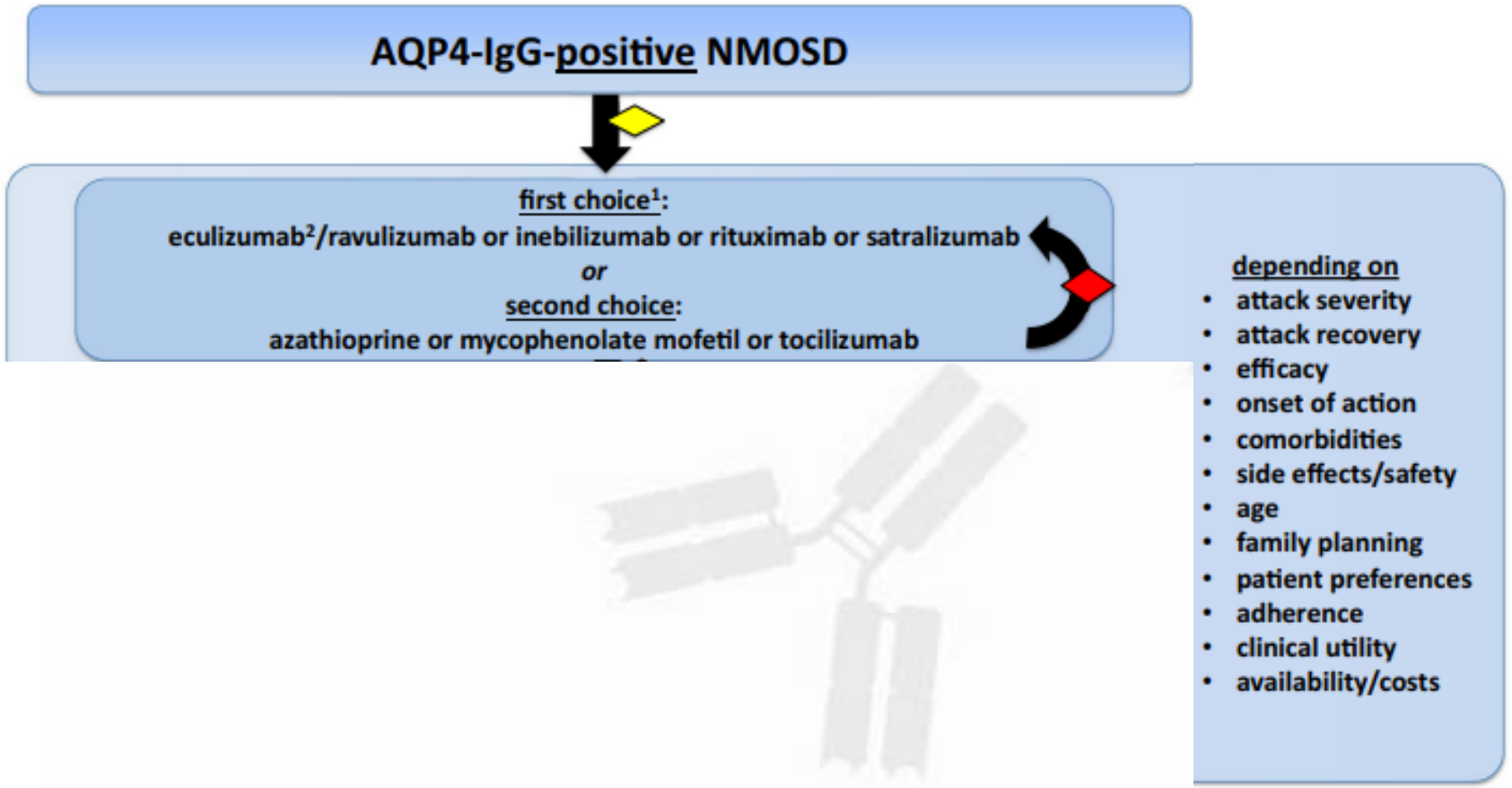
Table 1
Risk of HBV reactivation associated with biologics for hepatitis B surface antigen–positive patients

Biologics, grouped by mechanism of action	Reactivation Risk: Low (<1%) or Unknown (Probable Low Risk)	Moderate (1 to <10%)	High (≥10%)
Agents targeting B cells Anti-CD20 Anti-CD38 Anti-CD30 Inhibit B-cell activating factor			Rituximab Ofatumumab Ocrelizumab Obinutuzumab Ibritumomab Daratumumab Brentuximab Belimumab
Interleukin inhibitors IL-1 inhibitors IL-6 inhibitors		Anakinra Canakinumab Rilonacept Tocilizumab Sarilumab	
Targeting JAK-STAT signaling and complement pathway JAK inhibitors C5 inhibitors	Eculizumab Ravulizumab	Ruxolitinib Tofacitinib Baricitinib	

Table 2
Risk of HBV reactivation associated with biologics for hepatitis B surface antigen–negative/ anti-HBc-positive patients

	Reactivation Risk: Low (<1%) or Unknown (Probable Low Risk)	Moderate (1 to <10%)	High (≥10%)
Agents targeting B cells Anti-CD20 Anti-CD38 Anti-CD30 Inhibit B-cell activating factor		Daratumumab Brentuximab Belimumab	Rituximab Ofatumumab Ocrelizumab Obinutuzumab Ibritumomab
Interleukin inhibitors IL-1 inhibitors IL-6 inhibitors		Anakinra Canakinumab Rilonacept Tocilizumab	
Targeting JAK-STAT signaling and complement pathway JAK inhibitors C5 inhibitors	Eculizumab Ravulizumab	Ruxolitinib Tofacitinib Baricitinib	

Adapted from Ogawa et al. Infect Dis Clin North Am. 2020 Jun;34(2):341-358.



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LONG-TERM IMMUNOTHERAPY: SWITCHING AND DURATION

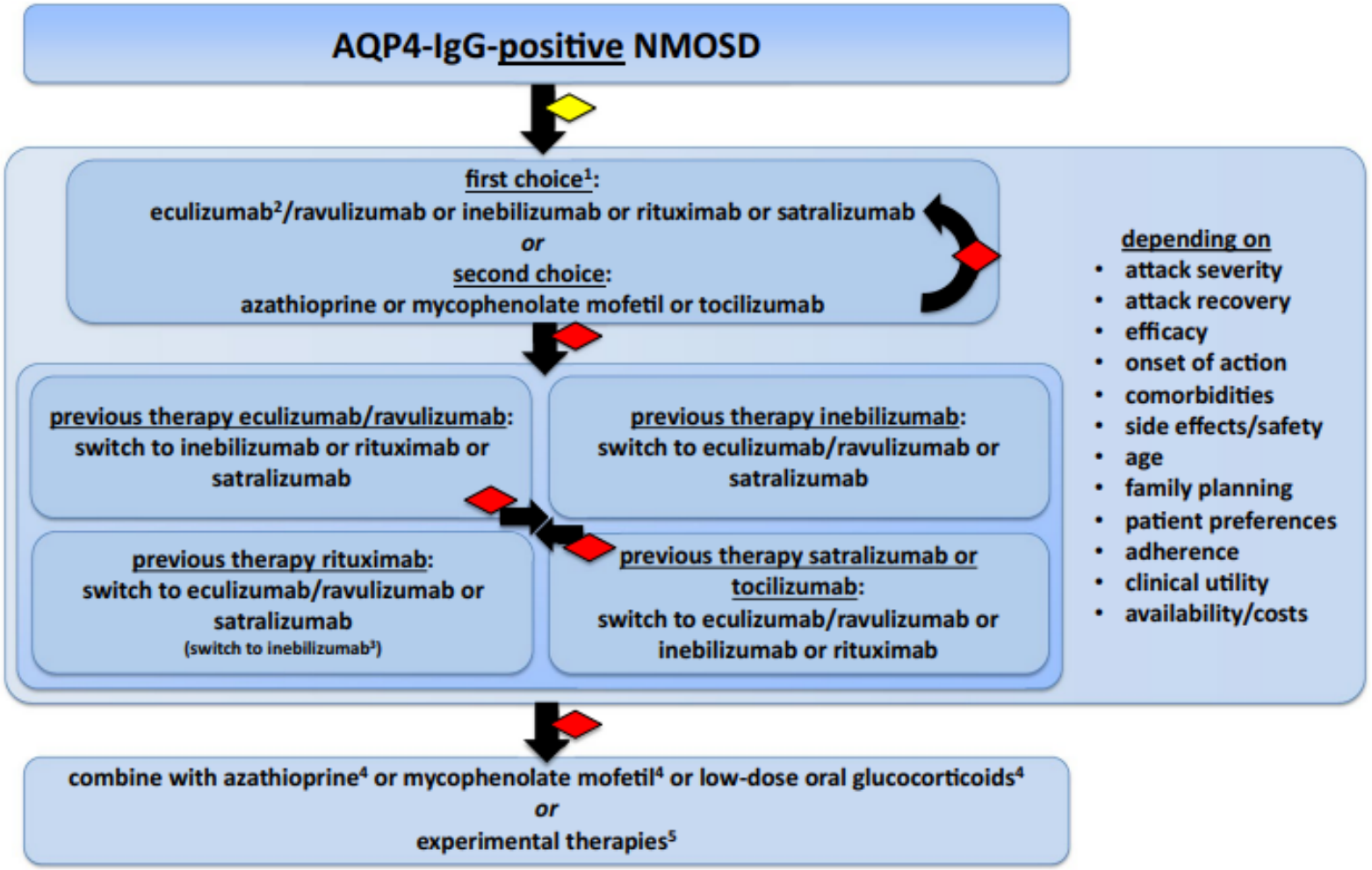
Switching drugs:

- In case of treatment failure with classical immunosuppressive therapies, therapy should be switched to a monoclonal antibody.
- In case of treatment failure with a monoclonal antibody, therapy should be switched to another monoclonal antibody, preferably with a diferent mode of action
- The interval between therapies should be as short as possible
- When switching immunotherapy, bridging therapy with low-dose oral glucocorticoids should be performed for up to 3–6 months, depending on the mode and onset of action of the subsequent therapy, duration of action of the previous therapy, disease activity, comorbidities, and side effects

Duration

- Immunotherapy should be continued in stable AQP4-IgG-positive NMOSD patients and patients must be closely monitored if treatment is temporarily or permanently discontinued due to side effects or patient choice.
- In double-negative NMOSD patients who have been stable for over 5 years, re-evaluation of immunotherapy may be considered (expert opinion).
- Research studies should focus on investigating the signifcance of seroreversion to seronegativity, which remains unknown to date

LONG-TERM IMMUNOTHERAPY



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Legge 648/1996

La Legge 648/1996 consente di erogare un farmaco a carico del Servizio Sanitario Nazionale (SSN), previo parere della Commissione Tecnico-Scientifica (CTS) di AIFA:

Quando non esiste un'alternativa terapeutica valida:

- per medicinali innovativi autorizzati in altri Stati, ma non in Italia
- per medicinali non ancora autorizzati, ma in corso di sperimentazione clinica
- per medicinali da impiegare per una indicazione terapeutica diversa da quella autorizzata

In tutti questi casi è necessaria l'esistenza di studi conclusi, almeno di fase II, che dimostrino un'efficacia adeguata con un profilo di rischio accettabile a supporto dell'indicazione richiesta.

In presenza di una alternativa terapeutica valida (Art. 3 Legge 79/2014):

- per medicinali da impiegare per una indicazione terapeutica diversa da quella autorizzata, purché tale indicazione sia nota e conforme a ricerche condotte nell'ambito della comunità medico-scientifica nazionale e internazionale, secondo parametri di economicità e appropriatezza.

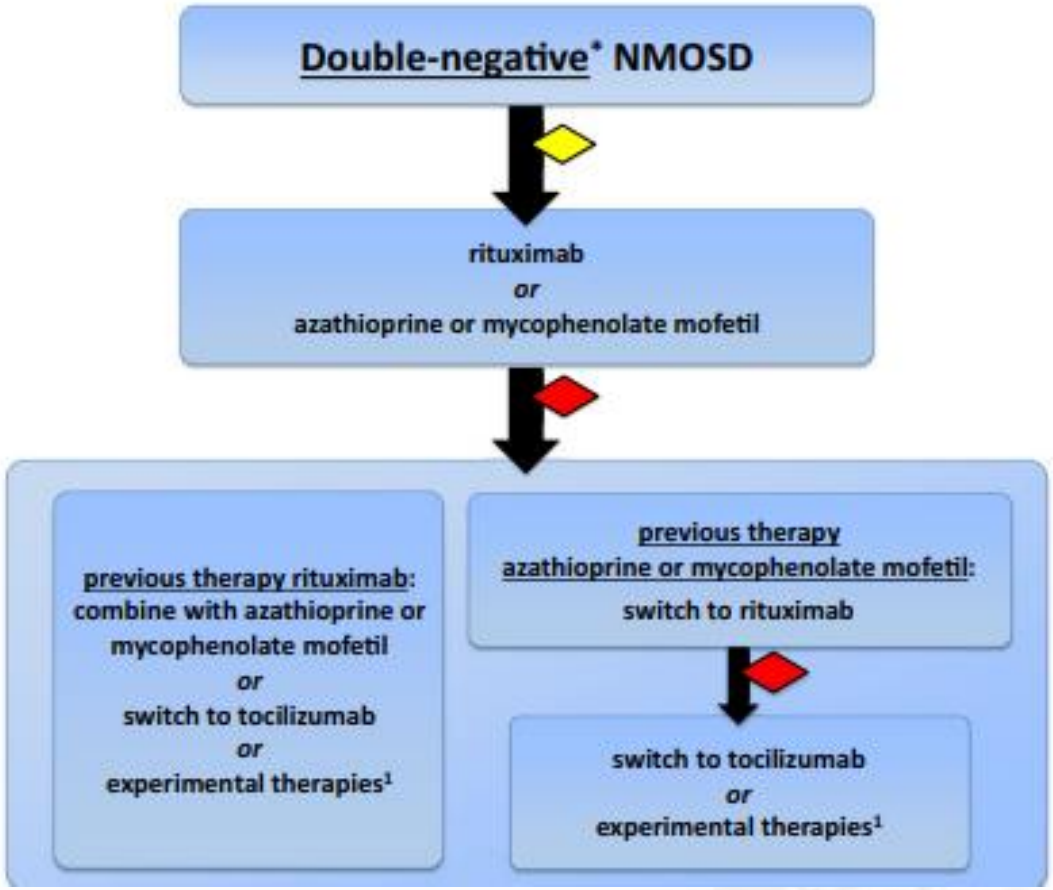
Indicazione aut
Uplizna (inebilizumab) è indicato in monoterapia per il trattamento di pazienti adulti affetti da disturbi dello spettro della neuromielite ottica (NMOSD) sieropositivi per le immunoglobuline G anti-aquaporina-4 (IgG AQP4), in seconda linea rispetto a rituximab, limitatamente ai pazienti che abbiano riportato almeno un attacco acuto di NMODS nell'anno precedente, che hanno richiesto una terapia dui salvataggio (ad esempio steroidi, plasmaferesi, somministrazione endovenosa di immunoglobuline) e che presentino un punteggio alla scala EDSS (Expanded Disability Severity Scale) ≤ 8,0

Long-term immunotherapy in Double-negative NMOSD patients

- Research studies should focus on unveiling the significance of **“true” double-negative NMOSD,** which remains unknown to date.
- Long-term immunotherapy in double-negative NMOSD should be initiated **after a second attack or after a severe first attack**.
- In case of therapy failure with rituximab, a combination therapy, tocilizumab, or other experimental therapies may be considered

AARs in AQP4+ and AQP4− participants.

	AQP4+	AQP4− All	MOG+	MOG−
During the 24 months before first dose of study treatment				
Participants, *n*	214	16	7	9
Mean AAR	1.35	1.70	1.93	1.60
Total person-years	335.56	23.30	8.28	15.02
95% CI	1.15–1.54	0.74–2.66	1.10–3.14	1.02–2.38
With inebilizumab exposure[a]				
Participants, *n*	208	16	7	9
Mean AAR	0.097	0.048	0.043	0.051
Total person-years	667.6	62.8	23.5	39.3
95% CI	0.07–0.136	0.015–0.148	0.006–0.302	0.013–0.204



Kumpfel et al, 2023; Marignier et al 2021

Long-term immunotherapy: family planning and pregnancy

- Pregnancy should be planned during a **stable phase** of the disease
- **Teratogenic drugs** such as mycophenolate mofetil or methotrexate should be avoided in patients of childbearing age and must be replaced with safer options prior to pregnancy
- **Long-term immunotherapy** should not be discontinued or postponed for the desire to become pregnant
- **Monoclonal antibodies** (eculizumab/ravulizumab, rituximab, tocilizumab) or **azathioprine** should be **continued** during pregnancy
- If exposure to **anti-B-cell-directed drugs** occurs during pregnancy, **lymphocyte and B-cell count testing in the newborn** (umbilical cord blood) should be performed
- If **monoclonal antibodies** are continued during pregnancy, the timing of **live attenuated vaccinations** must be discussed with pediatricians and carefully planned
- In case of treatment interruption during pregnancy, long-term immunotherapy should be resumed shortly after delivery

Conclusions

- Four therapies, **eculizumab, inebilizumab, and satralizumab** and most recently **ravulizumab** have been approved for use in AQP4-IgG-positive NMOSD since 2019. **Rituximab was also approved for NMOSD in Japan** in 2022 following the positive results of the placebo-controlled RIN-1 trial .

- **The order of preference for these therapies is yet unclear**, and further comparative trials and real-world data are needed

- **The efficacy of therapeutic antibodies in treating AQP4-IgGpositive NMOSD is superior to classical immunosuppressants and makes them the drugs of choice**

- **No head-to-head studies between monoclonal antibodies**, including rituximab, have been conducted to date.

- **A network meta-analysis on the RCT data** of eculizumab, inebilizumab and satralizumab, with time to a first attack as the efficacy outcome, suggests that **complement inhibition with eculizumab may be more effective in preventing NMOSD attacks** than treatment with inebilizumab or satralizumab.

Conclusions

- The choice of first-line treatments for NMOSD has to rely on several factors, which include **disease activity and severity, mode and onset of action, possibility to combine it with immunosuppressive drugs, effect on autoimmune and other comorbidities, gender (“family planning”), frequency and route of drug administration (intravenous vs. s. c.), side effects and safety profile**, as well as drug availability and regulatory approval status

- Age is another important factor to consider. **Satralizumab is the only drug that is approved for adolescents (≥12 years).**

- When choosing immunotherapy in elderly NMOSD patients, immunosenescence and the higher risk of comorbidities and infections should be considered.