Escalation therapy: MS and NMO

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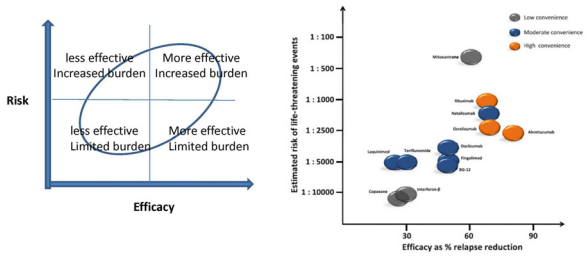
MS treatments

- Aims of DMD
  - From relapse rate reduction to No Evident Disease Activity (NEDA)
  - NEDA is based on the principle that relapse rates, disability progression and MRI activity are not independent.
- Selection of therapy
  - Efficacy, safety/ risk mitigation, cost, payer influence
- Individualized therapy
  - Complexity and heterogeneity of MS
  - Large intra-individual variability of MS courses
  - Treatments with different mechanisms & different efficacy/safety profile
  - Multiple treatment algorithms

Suboptimal response to therapy

- Standard DMDs are only modestly effective - breakthrough disease commonly occurs despite treatment.
- A significant proportion of patients will fail on first-line therapy over the longer term.
- Higher levels of MS disease activity despite current ongoing treatment, which beckons a change in management.
- Measures identify patients with suboptimal response to DMDs include clinical measures, MRI measures, and biological markers of therapy.

Selecting optimal therapy in RRMS: efficacy & risk



Currently approved DMDs for RRMS

	Trade name	DMT	Route	Dose	FDA/EMA approval	Mechanisms of action	AE/SAEs
First-line	Betaferon/Betaseron/Extavia	IFN-β1b	s.c.	3 × weekly, 250 µg	1993/1995	Modulates multitude of cell-based functions including modulation of, e.g., IL-10, IL-4, IFN-γ, IL-17, TNF-α, osteopontin and others; stabilizes BBB, modulates cell trafficking across the BBB	Mainly injection site side effects, influenza-like symptoms; SAEs rare
	Avonex	IFN-β1a	i.m.	1 × weekly, 30 µg	1996/1996		
	Rebif	IFN-β1a	s.c.	3 × weekly, usually 44 µg	2002/1998		
	Plegridy	PegIFN-β1a	s.c.	125 µg, 2 × weekly	2014/2014		
	Copaxone	GA	s.c.	20 mg daily or 40 mg 3 × weekly	1996/2001	Shifts from Th1- to Th2-driven immune response and others	Mainly injection site side effects; SAEs rare
	Tecfidera	DMF	p.o	240 mg twice daily	2013/2014	Modulates Nrf-2 and others	Bowel disorder, flushing, very rarely PML
	Aubagio	Teriflunomide	p.o.	14 mg daily	2012/2013	Inhibits proliferating lymphocytes by blocking DHODH	Nausea, hair thinning, liver enyme elevation, possibly teratogenic
Second-line	Gilenya	Fingolimod	p.o.	0.5 mg daily	2010/2011	Inhibits lymphocyte egress from lymph nodes by modulation of S1P receptors	Opportunistic infections, cardiac side effects (bradycardia, AV-node block), very rarely PML
	Tysabri	Natalizumab	i.v.	300 mg, 4-weekly	2003 (and reapproved 2006)/2006	Prevents lymphocytes from crossing BBB by blocking adhesion molecule α1β4-integrin	PML, infusion reactions
	Lemtrada	Alemtuzumab	i.v.	5 consecutive daily infusions of 12 mg; after 1 year, 3 more infusions	2014/2013	Long-term depletion of CD52-positive cells (mainly lymphocytes)	Very commonly infusion reactions, autoimmune phenomena (thyroid, kidney), opportunistic infections

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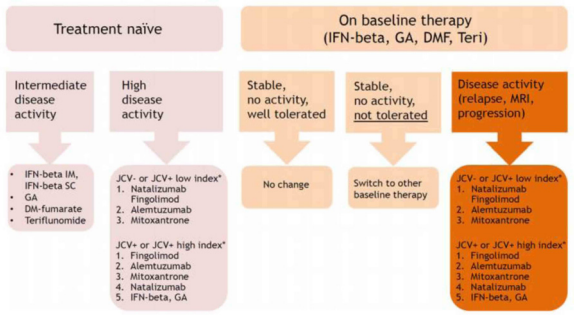
Suggested treatment algorithm in RRMS



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NMO treatments

- Treatment algorithms largely based on small prospective or retrospective series of various agents.
- Treatment decision
  - Cost, availability, patient choice, route of administration, side effects, physician's familiarity with the specific agent
- Recommended first-line agents
  - Prednisolone
  - Azathioprine (+ prednisolone)
  - Mycophenolate mofetil (+ prednisolone)
  - Rituximab

Recommendation levels used for NMO

Treatment	Dose/Regimen	Recommendation	Evidence level
Acute attacks			
Corticosteroid pulse (HIMP)	Methylprednisolone 1g/day for 3 to 5 days	Grade 1C	III
Plasmapheresis (PE)	2 ~ 4 liters per session, 2 to 3 sessions per week, up to 7 sessions	Grade 1C	IIb
Relapse prevention			
Oral prednisone	5 ~ 20 mg/day	Grade 1C	III
Azathioprine	2 mg/kg/day	Grade 1C	III
Mycophenolate mofetil	2 g/day	Grade 1C	III
Rituximab	375 mg/m²/week for 4 weeks or 1g repeated in 2 weeks; monitoring of CD19+ or CD27+ B cells to indicate retreatment	Grade 1C	III
Immunoglobulin (IVIG)	400 mg/kg for 5 days monthly	Grade 2C	IV
Mitoxantrone	12 mg/m²/month, maximum cumulative dose 140 mg/m²	Grade 2C	III
Cyclophosphamide	1 g/day monthly or immunoablation with 2 g/day for 4 days	Grade 2C	IV

HIMP: High-dose intravenous methylprednisolone; PE: plasmapheresis; IVIG: intravenous immunoglobulin.

Comparison of Relapse and Treatment Failure Rates

Initial Treatment	Azathioprine (n = 32)	Mycophenolate Mofetil (n = 28)	Rituximab (n = 30)
Diagnosis			
NMO	23 (72)	18 (64)	19 (63)
Seropositive NMO	16	17	15
Seronegative NMO	7	1	2
Unknown	0	0	2
NMOSD	9 (28)	10 (36)	11 (37)
Mean age at onset, y	39.1	38.5	43.7
Median age (range), y	39.5 (3-70)	36.1 (19-74)	44.9 (13-79)
Female sex	29 (91)	26 (93)	25 (83)

Table 2. Treatment-Associated Annualized Relapse Rates (ARRs) and Hazard Risks Relative to Rituximab

Medication	Pretreatment ARR	Posttreatment ARR	Change From Pretreatment to Posttreatment, %	Hazard Risk Relative to Rituximab (95% CI)	P Value
Azathioprine	2.26	0.63	72.1	2.12 (1.12- 4.01)	.02
Mycophenolate mofetil					
Total	2.61	0.33	87.4	1.48 (0.75-2.93)	.26
Optimal dosing	2.55	0.25	90.2		
Rituximab					
Total	2.89	0.33	88.6	1 [Reference]	
Optimal dosing	3.25	0.20	93.9		
Switch treatments	1.03	0.14	86.4		.054

Table 3. Failure Rates With Azathioprine, Mycophenolate Mofetil, and Rituximab

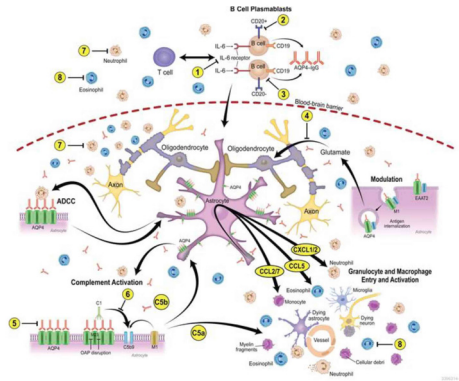
Medication	Failure Rate, %
Azathioprine	53
Mycophenolate mofetil	
Total	36
Optimal dosing	25
Rituximab	
Total	33
Optimal dosing	17
Switched treatments	22

JAMA Neurol. 2014

Breakthrough attack

- Depending on the severity of a breakthrough attack and the duration of the previous remission, every exacerbation should prompt a re-evaluation of the current treatment regimen.
- Potential reasons for treatment failure in NMO
  - suboptimal dosage
  - inadequate duration of treatment
  - in the case of rituximab, anti-chimeric antibodies to the drug
  - patient adherence
- Treatment failure should consideration of alternatives.
  - Rituximab
  - Mitoxantrone
  - Other immunosuppressive agents: methotraxate, cyclophosphamide
  - Other modalities: regular IVIG/plasma exchange
  - Emerging treatments

Pharmacologic targets in NMO



Pittock. Annals of the New York Academy of Sciences 2015

Current randomized controlled trials in NMO

Study number	Compound (company)	Target structure	Trial design	Regimen	Patients	Estimated recruitment (n)	Study duration	End point, comments
NCT01892345	Eculizumab (Alexion)	C5	Phase III, placebo-controlled, double blind, add-on to immunosuppressive therapy OR as monotherapy	900 mg IV every week for 4 weeks, followed by 1200 mg IV every 2 weeks	AQP4-pos. NMO/NMOSD, age≥18 years, EDSS≤7.0	132	104 weeks	Time to first attack, randomization 2:1, study followed by open-label extension, completion of double-blind part of study estimated 2016
NCT02028884	SA237 (Chugai)	IL-6R	Phase III, placebo-controlled, double blind, add-on to oral corticosteroids or AZA, or MMF (EU, Japan, Taiwan)	120 mg SC at weeks 0, 2, and 4; thereafter, every 4 weeks	NMO or AQP4-pos. NMOSD, age 12–74 years	70	Up to 30 months	Time to first attack, randomization 1:1, double blind followed by open-label extension, completion of double-blind part of study estimated 2017
NCT02073279	SA237 (Chugai)	IL-6R	Phase III, placebo-controlled, double blind, monotherapy (North America)	120 mg SC at weeks 0, 2, and 4; thereafter, every 4 weeks	NMO or AQP4-pos. NMOSD, age 18–74 years	70	Up to 30 months	Time to first attack, randomization 1:2, double blind followed by open-label extension, completion of double-blind part of study estimated 2017
NCT02200770	MEDI-551 (MedImmune)	CD19	Phase II/III placebo-controlled, double blind, monotherapy	300 mg IV on days 1 and 15, and then every 6 months	NMO or AQP4-pos. NMOSD, age≥18 years, EDSS≤7.5	212	3 years	Time to first attack, randomization 3:1, maximum 197 days placebo, followed by open-label period, completion estimated 2019

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Novel treatments

- Eculizumab: anti-complement (C5) monoclonal antibody
- Tocilizumab: anti-IL-6 receptor monoclonal antibody
- Aquaporumab: non-pathogenic antibody blocker of AQP4-IgG binding
- Sivelestat: neutrophil elastase inhibitor
- CD19-targeted therapies

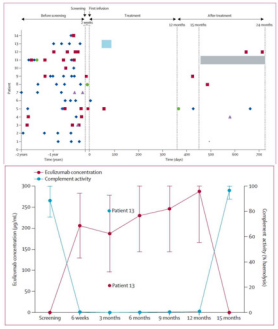
Eculizumab in AQP4-IgG-positive relapsing neuromyelitis optica spectrum disorders: an open-label pilot study

Sean J Pittock, Vanda A Lennon, Andrew McKeon, Jay Mandrekar, Brian G Weinshenker, Claudia F Lucchinetti, Orna O'Toole, Dean M Wingerchuk

	Patients enrolled (n=14)*
Ethnic origin	
African American	2
Hispanic	3
White	9
Age at enrolment (years)	43·1 (18·4–67·6)
Duration of disease (years)	4·3 (0·4–20·5)
Diagnosis	
Neuromyelitis optica	8
Relapsing optic neuritis	2
Relapsing transverse myelitis	4
Coexisting autoimmune diseases	4
Myasthenia gravis	2
Idiopathic thrombocytopenic purpura	1
Mixed connective tissue disease	1
Total number of previous attacks at enrolment	86
Optic neuritis	28
Transverse myelitis	57
Brainstem	1
Multifocal optic neuritis and transverse myelitis	3
Other multifocal	2
Number of previous attacks per patient	5·5 (2·0–10·0)
Expanded disability status scale score	4·8 (2·0–8·0)†

Data are median (range) or n. *All patients were women. †At enrolment; median score at first infusion was 4·3 (range 1·0–8·0).

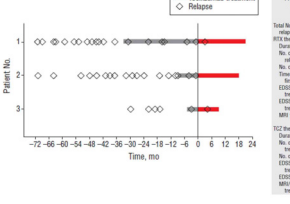
Table 1: Baseline characteristics



Lancet Neurol 2013; 12: 554–62

Interleukin 6 Receptor Blockade in Patients With Neuromyelitis Optica Nonresponsive to Anti-CD20 Therapy

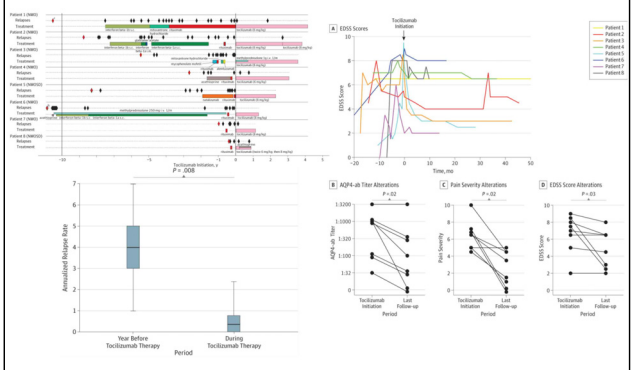
Ilya Ayzenberg, MD; Ingo Kleiter, MD; Alexandra Schröder, MD; Kerstin Hellwig, MD; Andrew Chan, MD; Takashi Yamamura, MD; Ralf Gold, MD



	Patient No. 1	Patient No. 2	Patient No. 3
Baseline characteristics at start of RTX treatment			
Sex	F	F	F
Age, y[a]	40	26	39
Disease duration, y[a]	9.4	8.2	2.5
AQP4 Abs	Positive	Positive	Positive
Previous treatments (duration/relapses)[b]	IFN beta-1b (2002-2006/10); mitoxantrone hydrochloride, 52 mg/m² (2006-2007/3)	IFN beta-1b (2004-2005/3); IFN beta-1a (2005-2006/1); glatiramer acetate (2006/3); IFN beta-1a (2006-2008/9)	No therapy (2009-2010/2); azathioprine (2010-2011/2)
Total No. of previous relapses/estimated ARR[a]	13/2.6	19/2.7	4/1.7
RTX therapy			
Duration, mo	32	8	4
No. of CD19 cells during the first relapse, /µL	0	1	2
No. of relapses/estimated ARR	6/2.3	2/1.0	1/1.0
Time from first application to the first relapse, d	18	137	40
EDSS score at start of RTX treatment	5.0	4.5	7.0
EDSS score at end of RTX treatment	6.5	5.0	7.0
MRI findings	Enlargement of spinal cord lesions with contrast enhancement	ND	Enlargement of spinal cord lesions with contrast enhancement
TCZ therapy			
Duration, mo	21	18	9
No. of CD19 cells at start of TCZ treatment, /µL	44	4	2
No. of relapses/estimated ARR	1/0.6	0	1/1.3
EDSS score at start of TCZ treatment	6.5	5.0	7.0
EDSS score at the last visit	6.5	4.0	7.0
MRI/time since start of TCZ treatment, mo	No new lesions, no contrast enhancement/12	No new lesions, no contrast enhancement/9	No new lesions, no contrast enhancement/7

JAMA Neurol. 2013;70(3):394-397

Long-term Therapy With IL-6 Receptor Blockade



JAMA Neurol. 2015

AQP4-IgG blocking and inactivation strategies for NMO therapy

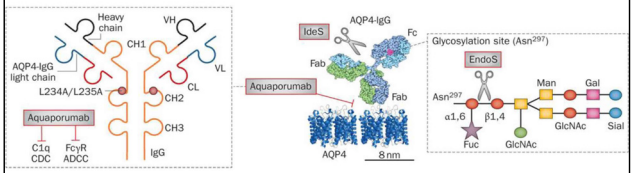


Table 3 | Compounds in the pipeline

Compound	Target molecule	Mechanism of action
Anti-CD19[34,118]	B-cell surface marker	Depletion of naive and memory B cells, plasmablasts, and some plasma cells
Anti-IL-17[54,183]	Cytokine	Blocks IL-17 signal transduction
Aquaporumab[144]	AQP4	Binds to AQP4 on CNS astrocytes and blocks AQP4-IgG binding
IdeS[153]	AQP4-IgG	Cleaves circulating AQP4-IgG
EndoS[152]	AQP4-IgG	Deglycosylates AQP4-IgG to eliminate CDC and ADCC function
Small-molecule blockers[145]	AQP4-IgG	Competitive inhibition of AQP4-IgG binding
Peptoid inhibitors[184]	AQP4-IgG	Competitive inhibition of AQP4-IgG binding

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; AQP4, aquaporin-4; CDC, complement-dependent cytotoxicity; NMO, neuromyelitis optica.

Papadopoulos, M. C. *et al.* (2014) *Nat. Rev. Neurol.*