Myasthenia Gravis and the Complement System

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What Is Myasthenia Gravis (MG)?

Rare autoimmune disease

Often due to the presence of antibodies against acetylcholine (AChR-Ab+).

Trademark: fluctuating weakness in specific muscle groups – such as bulbar weakness, limb weakness, and ocular weakness

Ocular weakness - most common initial presentation of MG

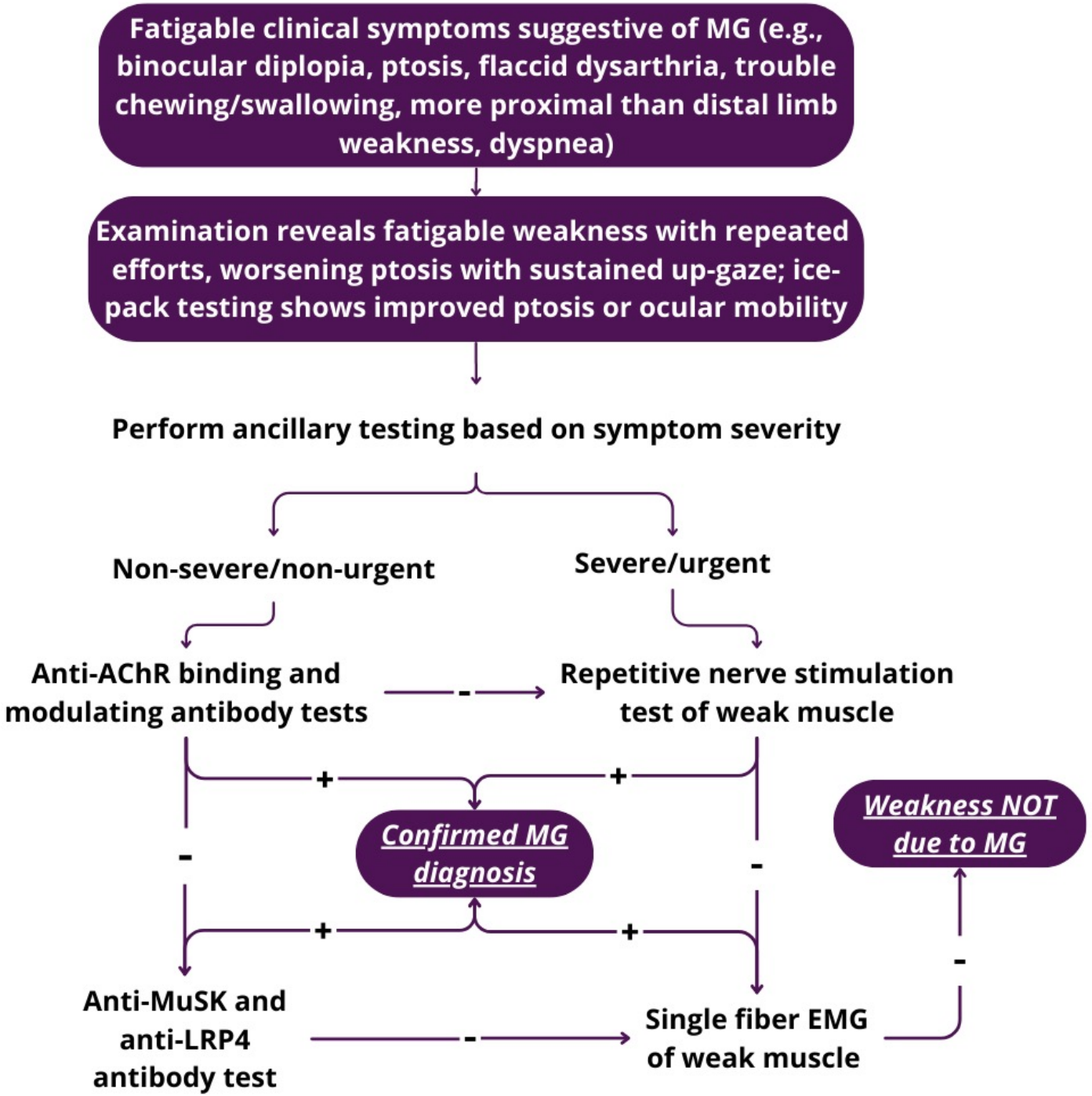
Treatment highly individualized and often includes off-label medications

Five drugs approved by the FDA:

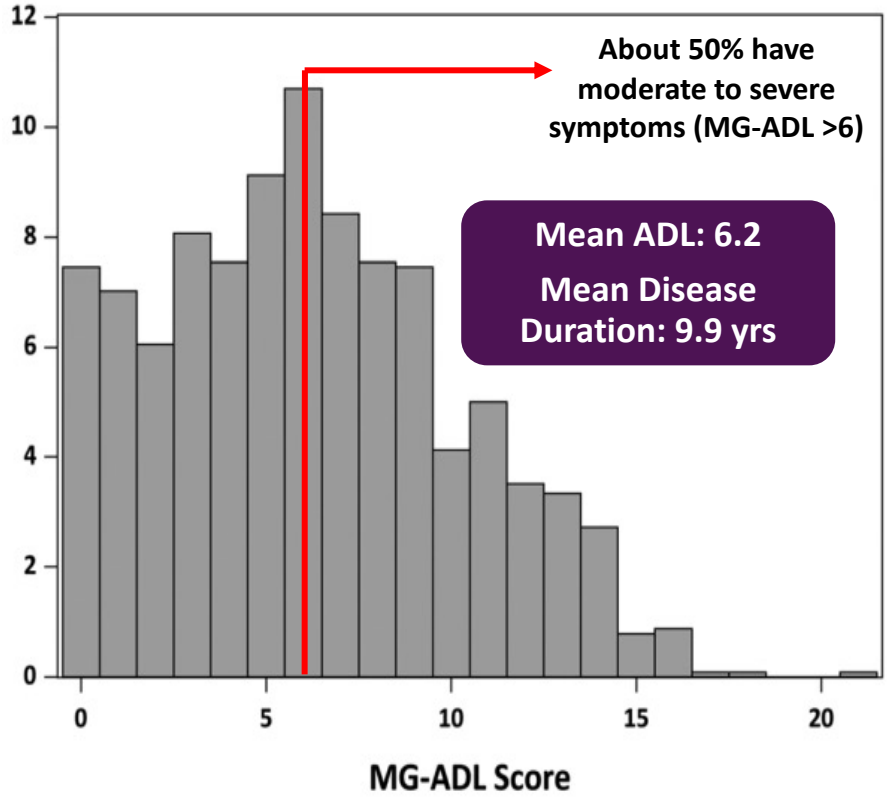
- Eculizumab
- Efgartigimod
- Ravulizumab
- Rozanolixizumab
- Zilucoplan

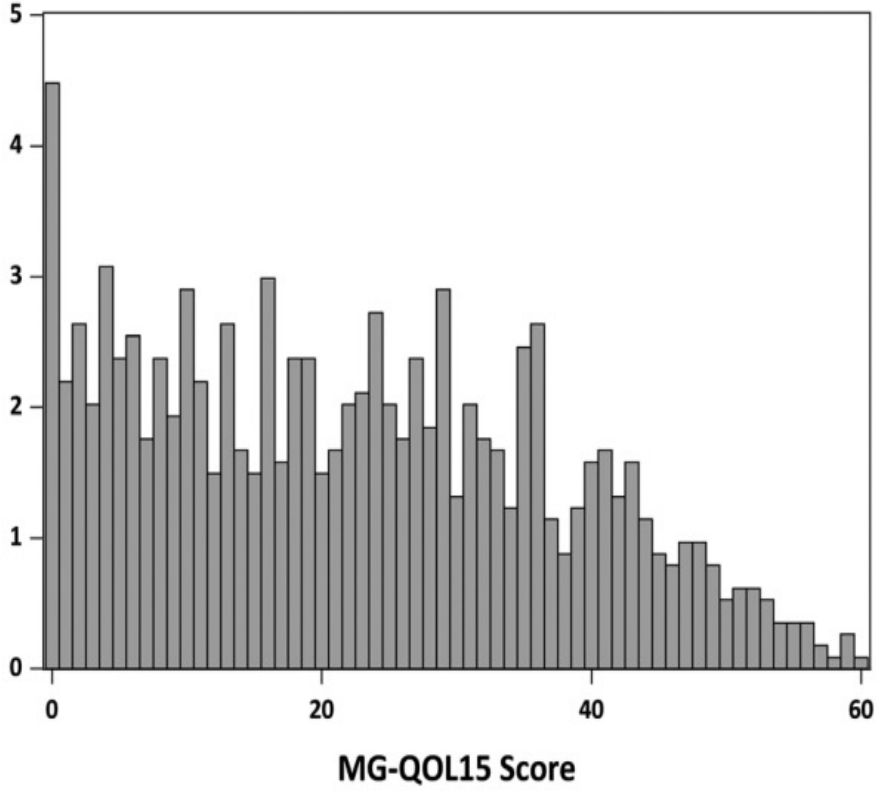
Symptoms and Diagnosis

Figure adapted from Moreen JA, Li Y. *Cleveland Clin J Med. 2023; 90: 103-13. [creative* commons]



Disease Burden

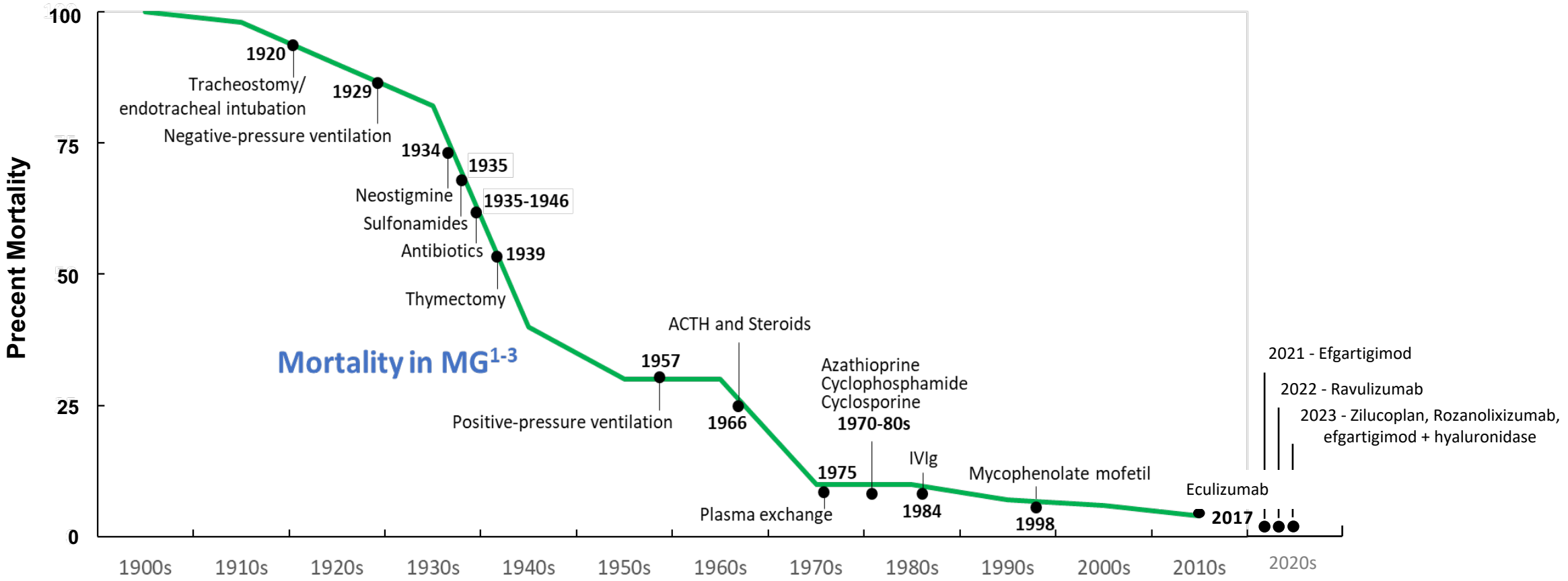




Distribution of MG-ADL (N=1138) and MG-QOL15 (N=1140) scores in patients in myasthenia gravis. The majority of patients reported moderate to severe impairment in activities of daily living.

Figures from Cutter G et al. *Muscle Nerve, 2019;* 60: 707-15. [creative commons]

History of Treatment Options



1. Mantegazza R, Antozzi C. *Ther Adv Neurol Disord.* 2018;11:1756285617749134. 2. Grob D, et al. *Muscle Nerve.* 2008;37:141-149. 3. Keesey JC. *Semin Neurol*. 2004;24(1):5-16.

Complement System

Complement activation represents one pathogenic mechanism in AChR+ myasthenia gravis.

AChR antibodies are of class IgG1 and IgG3 that activate the complement cascade via the classical pathway which terminates with the formation of the terminal complement complex (TCC/MAC).

End result is formation of C6 thru C9 which form a lytic pore (TCC/MAC) on the postsynaptic membrane leading to its disruption.

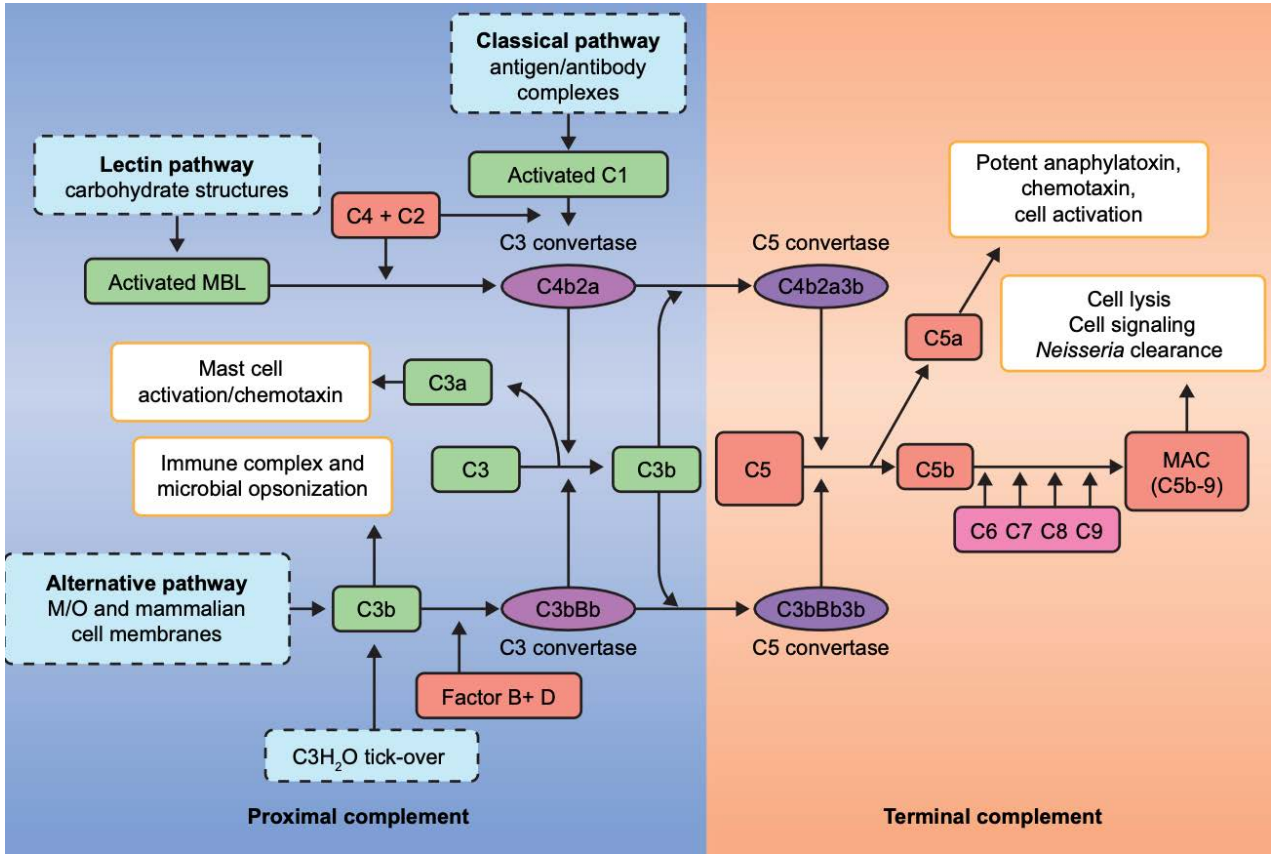


Figure from Howard JF Jr. *Ann NY Acad Sci.* 2018; 1412: 113-28. [creative commons]

Pathophysiology

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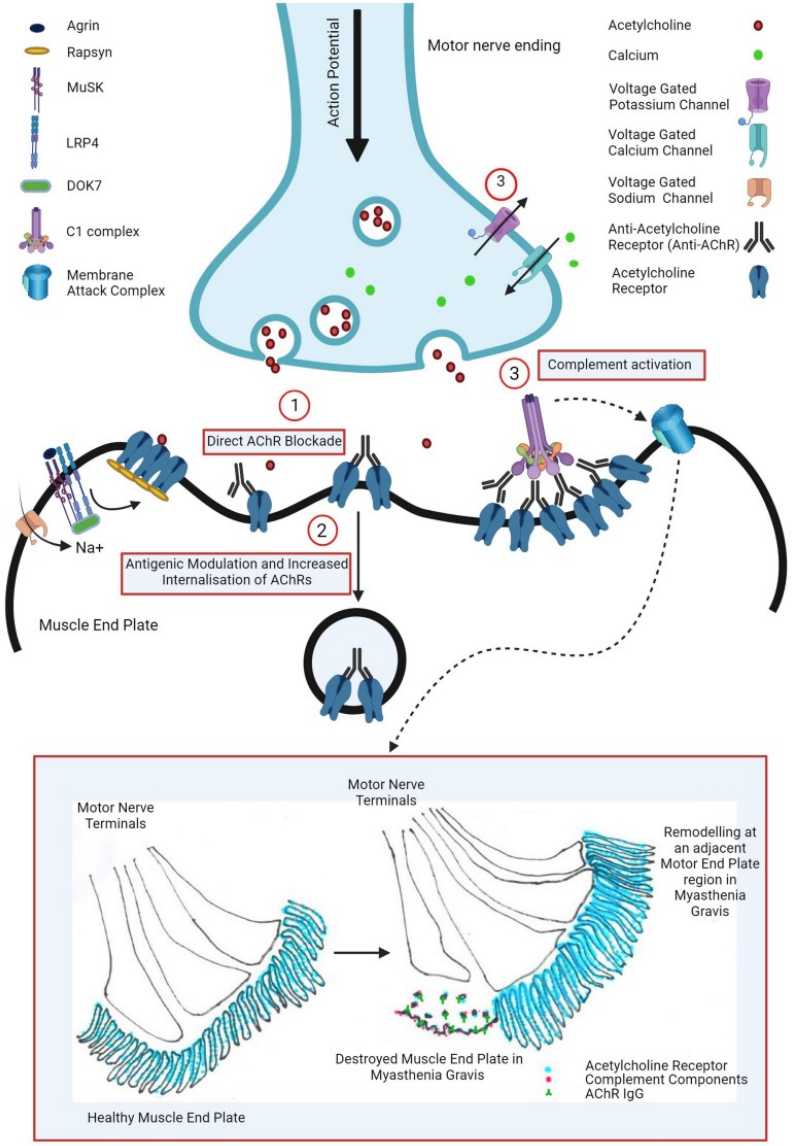
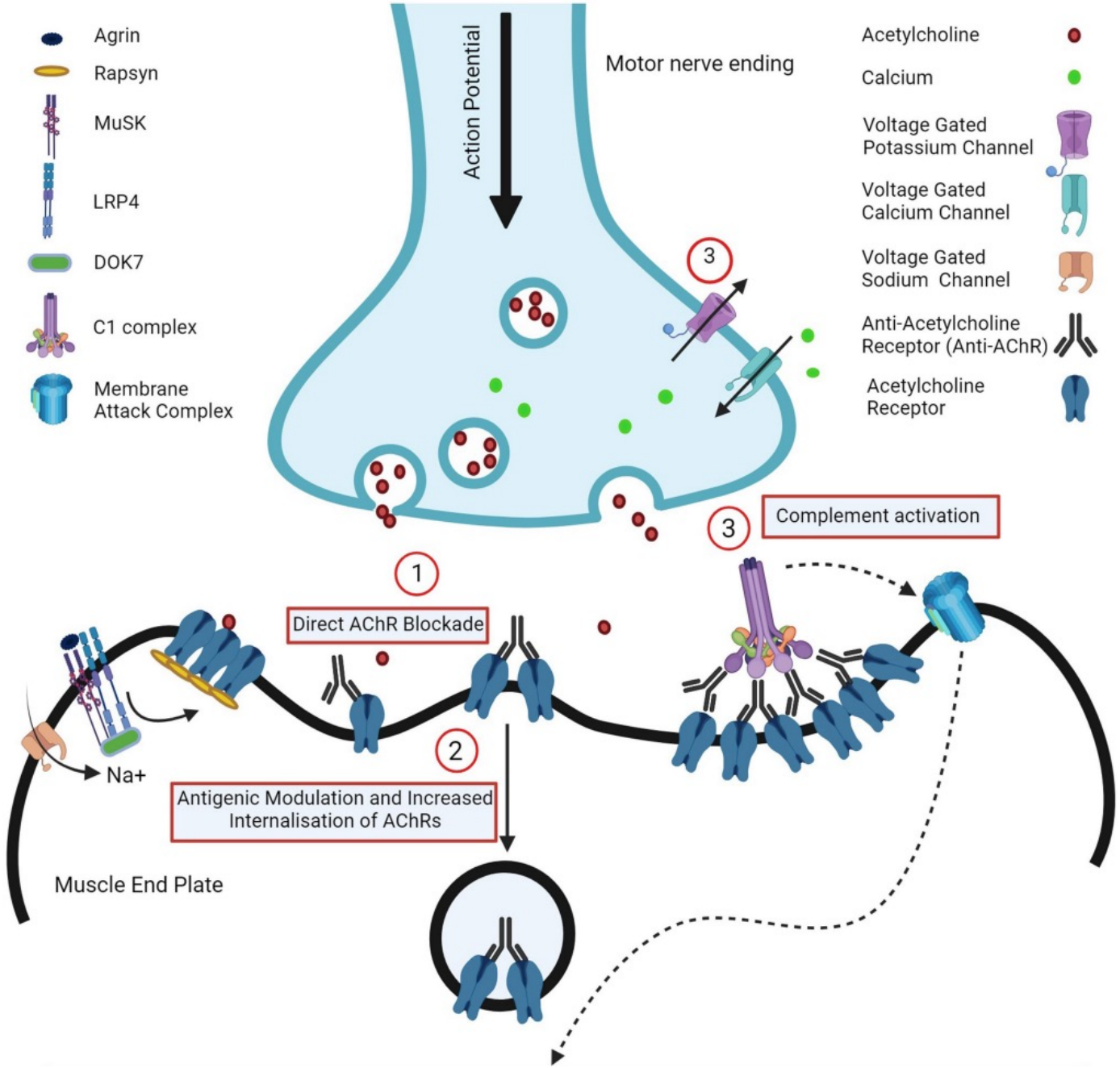


Figure from San PP, Jacob S. *Front Neurol.* 2033; 14: 1277596. [creative commons]



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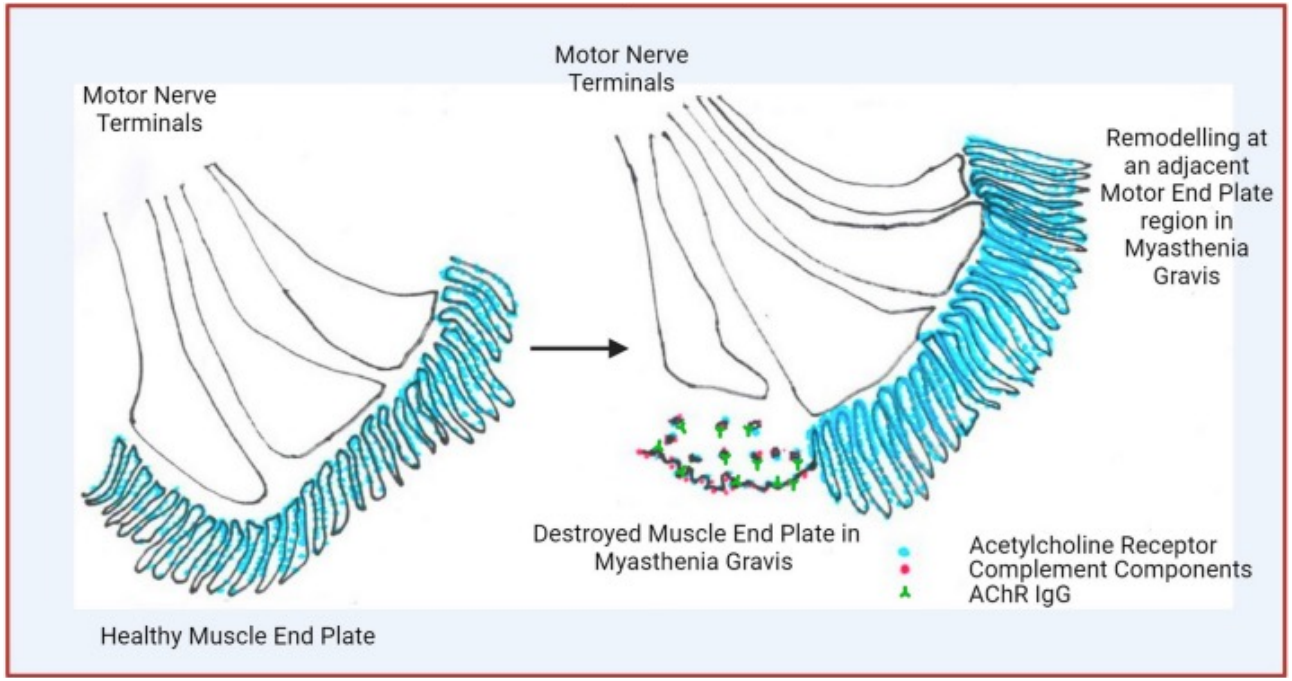

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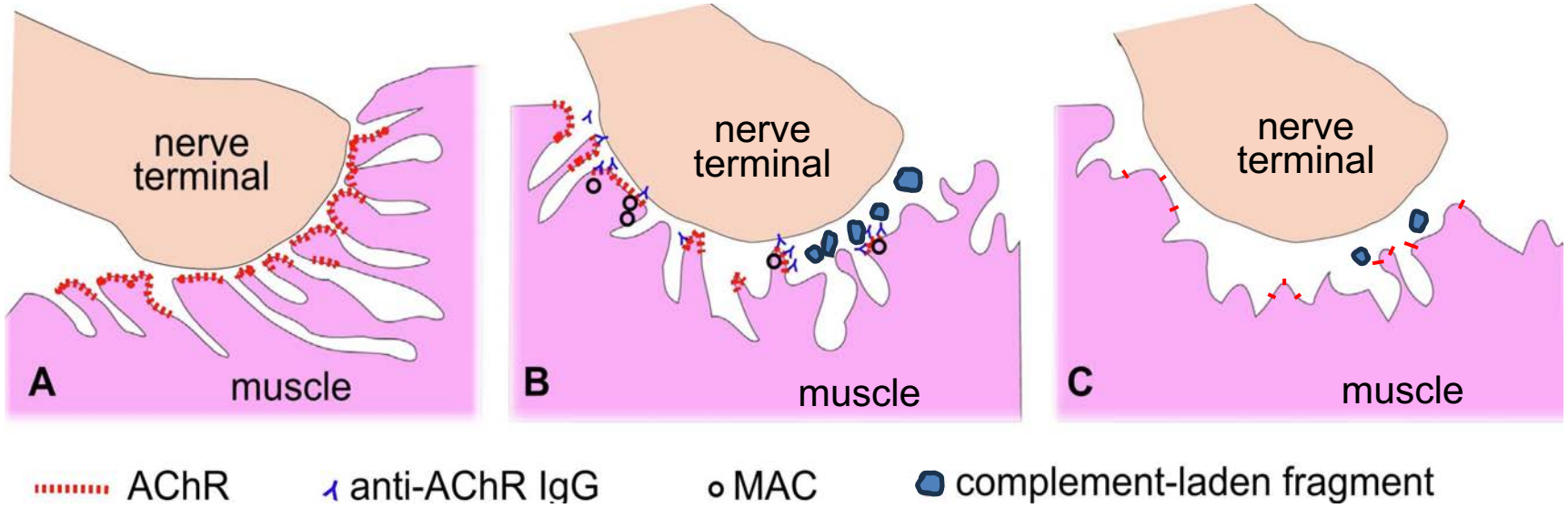
Pathophysiology



Normal neuromuscular junction.

Autoantibodies bind to AChR that initiates activation of complement that forms terminal complement complex (TCC) or membrane attack complex (MAC).

Loss of postsynaptic folds, widening of synaptic cleft as a result of TCC / MAC lesioning.

Figure from Sanderson NSR. *Mol Immunol* 2023; 151: 22-8. [creative commons]

Weak Correlation Between C3 and QMG

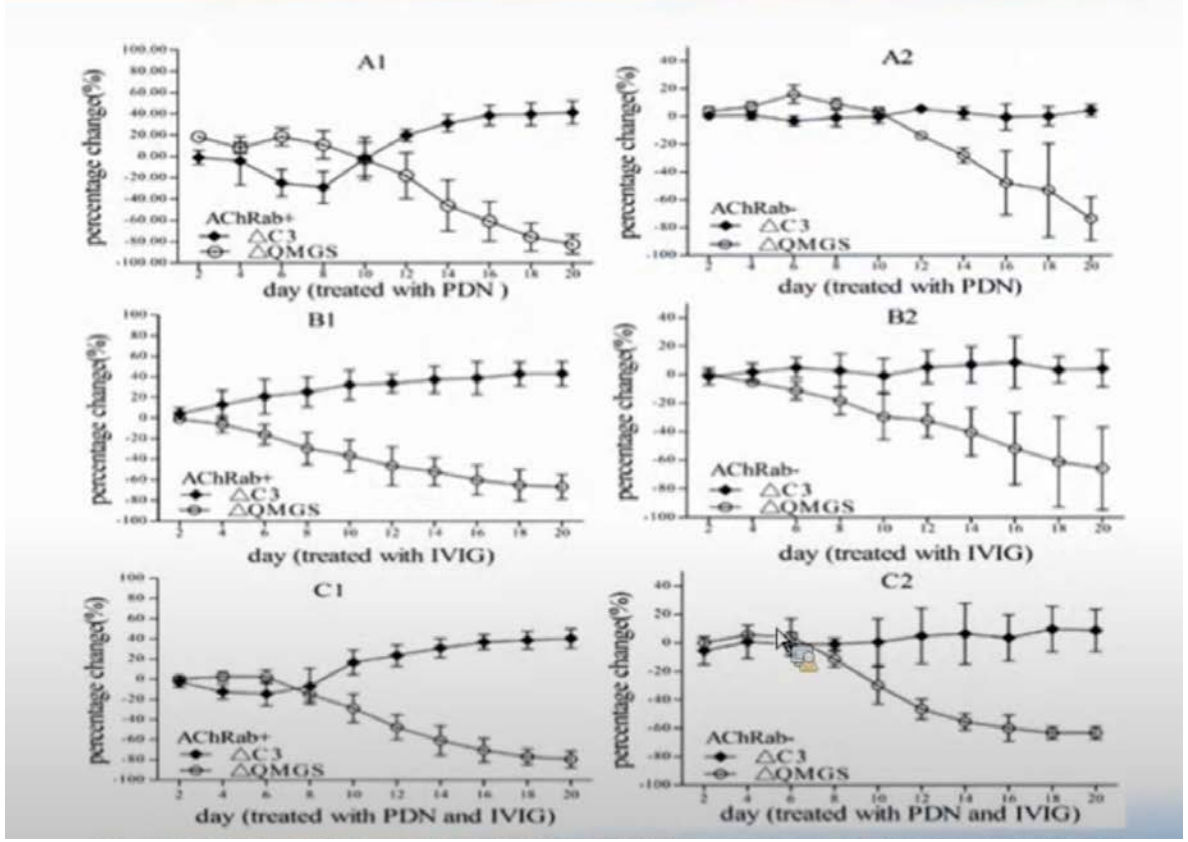
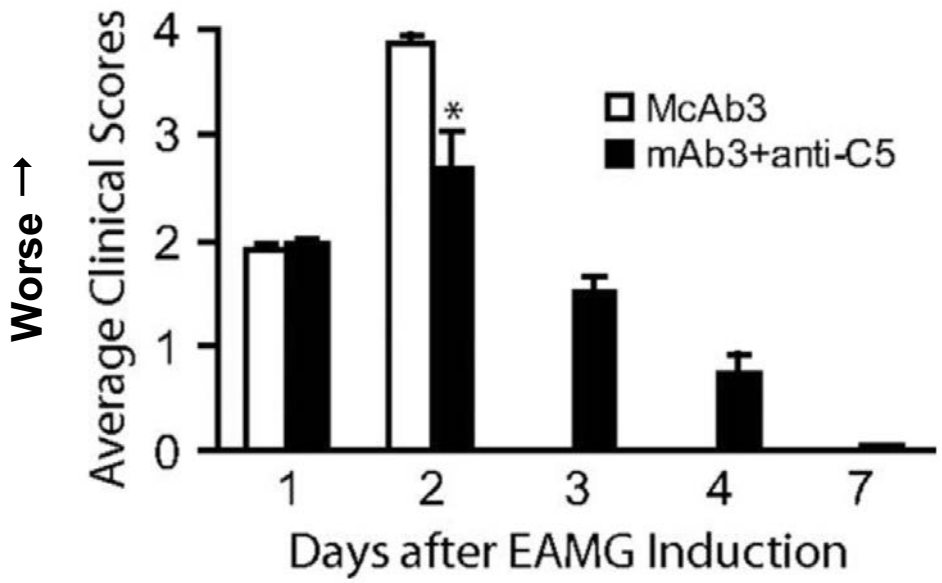
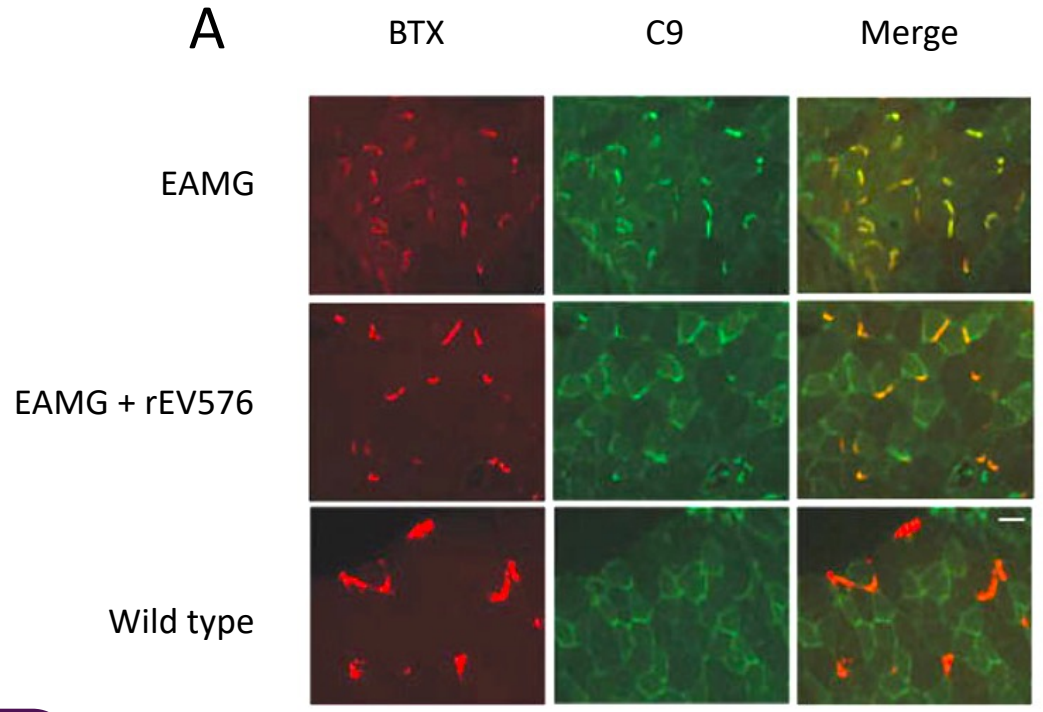


Figure recreated from Lui A et al. Muscle Nerve, 2009; 40: 801-8.

Animal Studies





Anti-C5 treatment in rat model for myasthenia gravis improves clinical scores and C9 deposits at neuromuscular junctions.

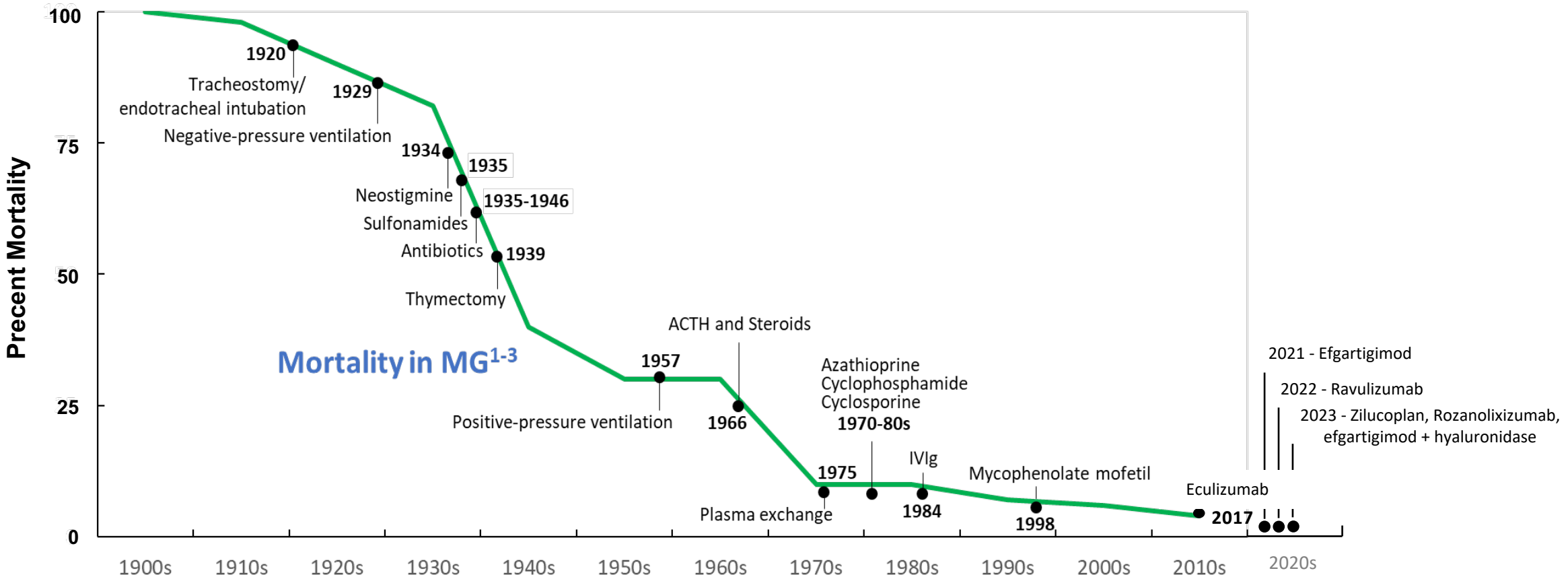
Figures from Zhou Y et al. *J Immunol* 2007; 179: 8562 and Soltys J et al. *Ann Neurol.* 2009; 65: 67-75. [creative commons]

Correlations

MG Treatments Acute and Chronic Limitations				
AChEI[2]	Steroids[2]	ISTs[1,3]	IVIg/PLEX[1,2,4]	Rituximab[1,2]
Nausea, diarrhea, abdominal cramping, increased salivation	Skin atrophy, glaucoma, mood disorders, risk of infection	Bone marrow suppression, leukopenia, hypertension, GI intolerance, infection	Allergic reactions, risk of infection, hypotension, high cost, requires long infusion times and special treatment	Infusion-related headache, nausea, chills, hypotension, anemia, leukopenia, thrombocytopenia
Added risk(s) with chronic use[1,2]				
N/A	Weight gain, osteoporosis, diabetes	Long-term hepato- and nephrotoxicity, malignancy	Nephrotoxicity, thrombosis	Progressive multifocal encephalopathy
Long Latency				

1. Farmakidis C, et al. *Neurol Clin.* 2018;36:311-37. 2. Gilhus NE. *N Engl J Med.* 2016;375:2570-2581. 3. Gilhus NE, et al. *Nat Rev Dis Primers*. 2019; 5:30. 4. Heatwole C, et al. *J Clin Neuromuscul Dis*. 2011;13:85-94.

History of Treatment Options



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Treating Myasthenia Gravis

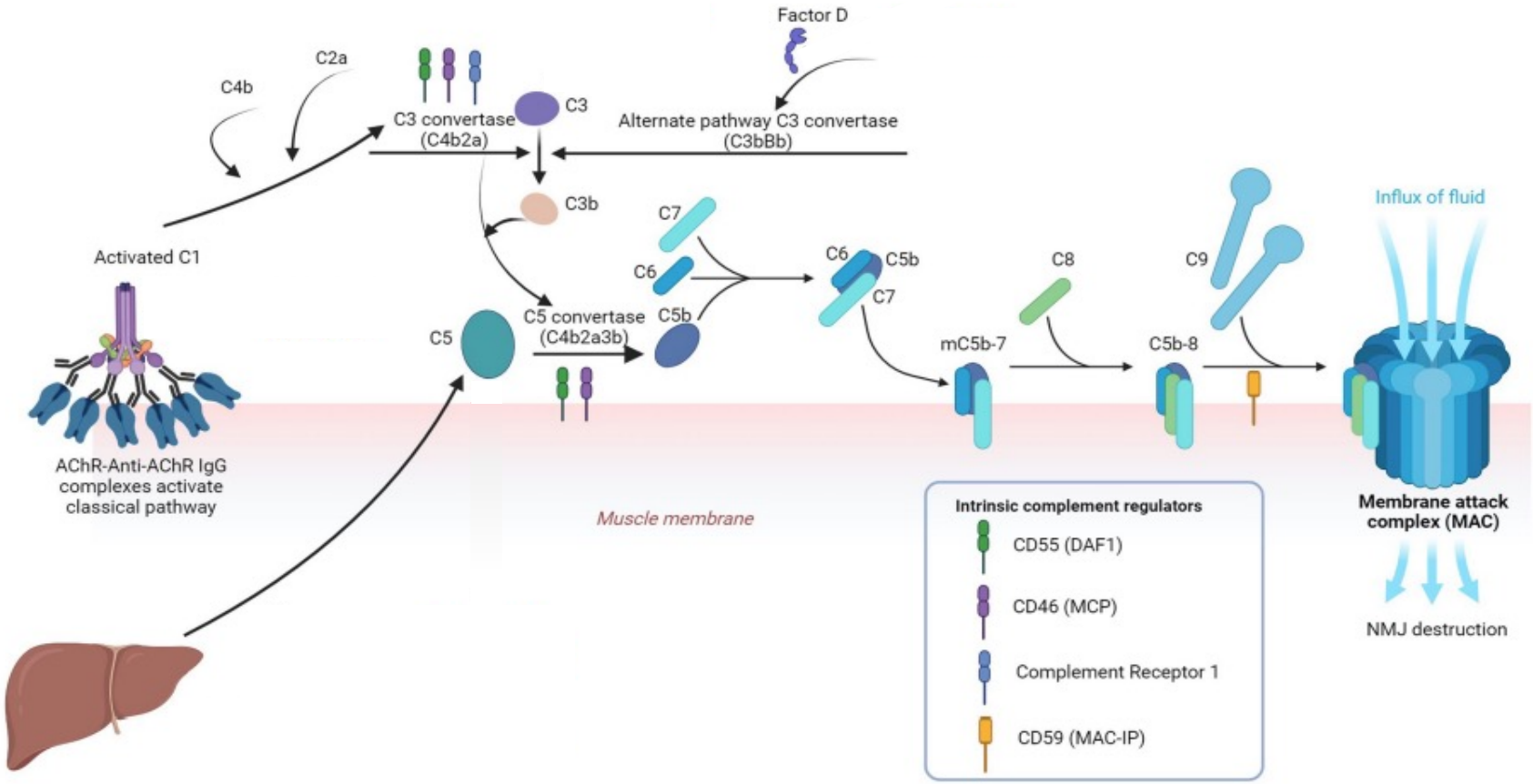


Figure from San PP, Jacob S. *Front Neurol.* 2023; 14: 1277596. [creative commons]

FDA Approved Treatments

Neonatal Fc receptor (FcRn)

Efgartigimod
FcRn antagonist

Efgartigimod + hyaluronidase
FcRn antagonist + endoglycosidase

Rozanolixizumab
Monoclonal antibody targeting FcRn

Complement system

Eculizumab
Monoclonal antibody targeting C5

Ravulizumab
Long-acting monoclonal antibody targeting C5

Zilucoplan
Peptide inhibitor of C5

Efgartigimod

FDA approval: 2021

Indication: To treat adults with generalized myasthenia gravis who are AChR antibody positive.

MOA: FcRn blocker.

Dosage: 10 mg/kg administered weekly for the first 4 weeks. Subsequent treatment cycles based on clinical evaluation. In persons weighing 120 Kg or more, recommended dose is 1200 mg.

Route of Administration: Intravenous infusion (60 minutes)

Boxed Warning: None

Efgartigimod + hyaluronidase

FDA approval: 2023

Indication: To treat adults with generalized myasthenia gravis who are AChR antibody positive.

MOA: FcRn blocker plus an endoglycosidase.

Dosage: 1,008 mg / 11,200 units (1,008 mg efgartigimod alfa and 11,200 units hyaluronidase) in cycles of once weekly injections for 4 weeks. Subsequent treatment cycles based on clinical evaluation.

Route of Administration: subcutaneous injections (30 to 90 sec by a healthcare professional).

Boxed Warning: None.

Rozanolixizumab

FDA approval: 2023

Indication: To treat adults with generalized myasthenia gravis who are AChR or MuSK antibody positive.

MOA: Monoclonal antibody targeting FcRn.

Dosage: 420 – 840 mg (based on body weight) infusions every week for six weeks. Subsequent treatment cycles based on clinical evaluation.

Route of Administration: subcutaneous infusions using an infusion pump.

Boxed Warning: None.

Eculizumab

FDA approval: 2017

Indication: To treat adults with generalized myasthenia gravis.

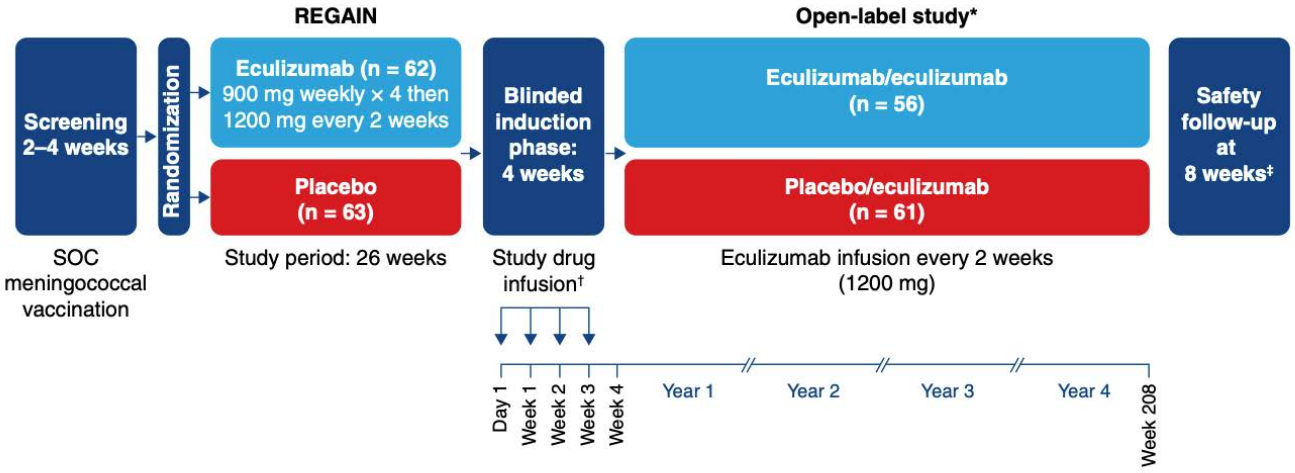
MOA: A terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity.

Dosage: 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter.

Route of Administration: Intravenous infusion (35 minutes).

Boxed Warning: Meningococcal infections.

Eculizumab: REGAIN Study



Variable	Eculizumab/ eculizumab, *n* = 56	Placebo/ eculizumab, *n* = 61	All patients, *N* = 117
Mean age (SD), y*	47.2 (15.5)	47.5 (17.9)	47.4 (16.7)
Sex, *n* (%)			
Men	18 (32.1)	20 (32.8)	38 (32.5)
Women	38 (67.9)	41 (67.2)	79 (67.5)
Race, *n* (%)			
Asian	3 (5.4)	16 (26.2)	19 (16.2)
Black	0 (0.0)	2 (3.3)	2 (1.7)
White	47 (83.9)	41 (67.2)	88 (75.2)
Multiple	1 (1.8)	0 (0.0)	1 (0.9)
Unknown	1 (1.8)	0 (0.0)	1 (0.9)
Other	4 (7.1)	2 (3.3)	6 (5.1)
MG duration, mean (SD), y†	10.7 (7.9)	9.8 (8.5)	10.2 (8.2)

MG, myasthenia gravis; SD, standard deviation.

*On day 1 of the open-label extension study.

†Time from MG diagnosis to first dose date in the open-label extension study.

Figures from Muppidi S et al. *Muscle Nerve.* 2019;60:14-24. [creative commons]

Eculizumab: REGAIN Study

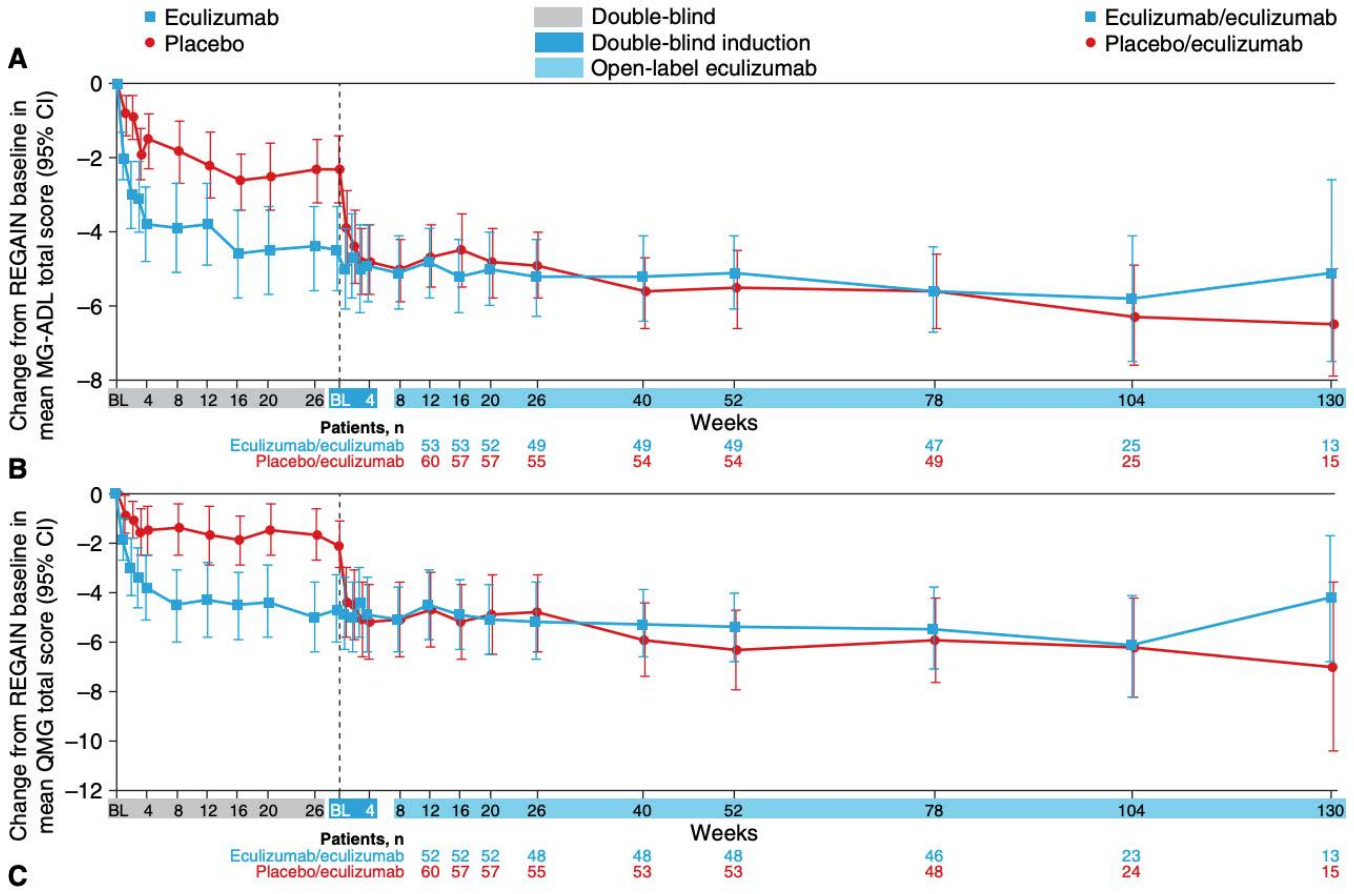


Figure from Muppidi S et al. *Muscle Nerve.* 2019;60:14-24. [creative commons]

Eculizumab: Additional Studies

Outcome	REGAIN placebo (n = 61, 30.9 PY[a])		REGAIN eculizumab (n = 56, 28.2 PY[a])		REGAIN and OLE eculizumab (N = 117, 305.1 PY[a])	
	Patients with event, n (%)	Event rate, events/100 PY[a]	Patients with event, n (%)	Event rate, events/100 PY[a]	Patients with event, n (%)	Event rate, events/100 PY[a]
Exacerbation	13 (21.3)	77.7	4 (7.1)	35.5	34 (29.1)	23.9
Rescue therapy use	10 (16.4)	68.0	4 (7.1)	35.5	30 (25.6)	22.0
Most common AEs[b,c] (> 15% of all patients)						
Headache	12 (19.7)	90.6	10 (17.9)	88.7	52 (44.4)	32.8
Nasopharyngitis	10 (16.4)	42.1	9 (16.1)	46.1	45 (38.5)	32.1
Diarrhea	8 (13.1)	29.1	8 (14.3)	35.5	33 (28.2)	17.4
Upper respiratory tract infection	12 (19.7)	45.3	9 (16.1)	46.1	31 (26.5)	25.2
Nausea	9 (14.8)	84.1	7 (12.5)	35.5	27 (23.1)	12.1
Myasthenia gravis[d]	9 (14.8)	58.3	4 (7.1)	14.2	30 (25.6)	17.4
Arthralgia	5 (8.2)	29.1	1 (1.8)	3.5	24 (20.5)	10.5
Pain in extremity	2 (3.3)	6.5	4 (7.1)	14.2	20 (17.1)	8.5
Urinary tract infection	5 (8.2)	22.7	3 (5.4)	14.2	20 (17.1)	12.5

Mantegazza R, et al. Neurology. 2021;96:e610-e618

Ravulizumab

FDA approval: 2022

Indication: To treat adults with AChR antibody-positive generalized myasthenia gravis.

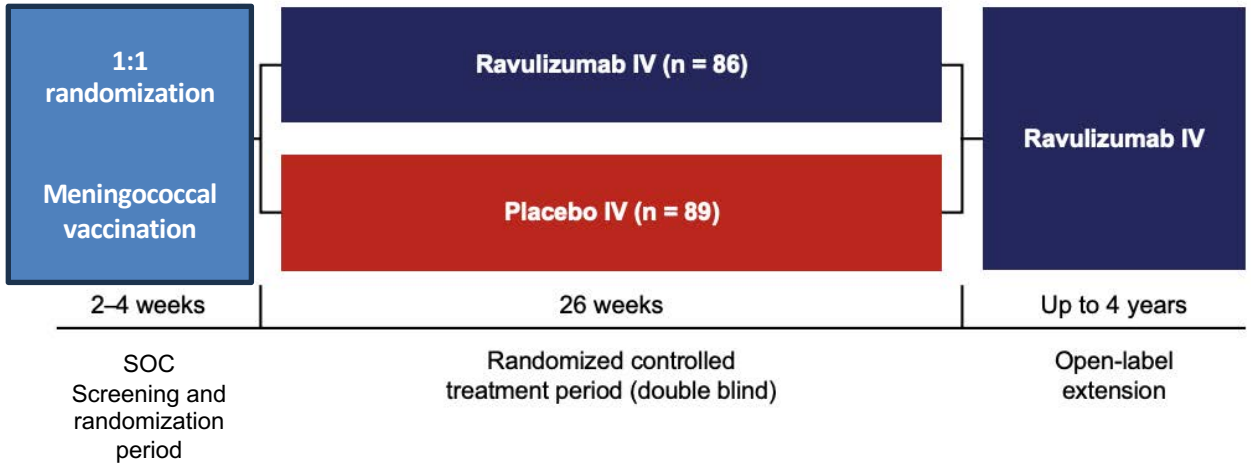
MOA: A recombinant humanized monoclonal IgG antibody that binds to the human C5 complement protein and inhibits the activation of terminal complement.

Dosage: Loading dose of 2,400 – 3,000 mg, and maintenance dose of 3,000 – 3,600 mg, depending on weight**.**

Route of Administration: Intravenous infusion once every 8 weeks.

Boxed Warning: Meningococcal infections.

Ravulizumab: CHAMPION-MG Study



Characteristic	Ravulizumab–ravulizumab[a] (n = 78)	Placebo–ravulizumab[b] (n = 83)	All patients (N = 161)
Female, n (%)	40 (51.3)	42 (50.6)	82 (50.9)
Age, years, mean ± SD	58.2 ± 13.6	53.6 ± 16.4	55.9 ± 15.2
Race, n (%)			
White	61 (78.2)	57 (68.7)	118 (73.3)
Asian	13 (16.7)	14 (16.9)	27 (16.8)
Black or African American	2 (2.6)	4 (4.8)	6 (3.7)
Other/unknown/not reported	2 (2.6)	8 (9.6)	10 (6.2)
MGFA clinical classification, n (%)			
Class IIa/b	36 (46.2)	35 (42.2)	71 (44.1)
Class IIIa/b	37 (47.4)	43 (51.8)	80 (49.7)
Class IVa/b	5 (6.4)	5 (6.0)	10 (6.2)
MG-ADL total score, mean ± SD	9.2 ± 2.6	8.9 ± 2.2	9.0 ± 2.4
QMG total score, mean ± SD	14.8 ± 5.2	14.3 ± 5.2	14.5 ± 5.2

MG-ADL, Myasthenia Gravis–Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; OLE, open-label extension; QMG, Quantitative Myasthenia Gravis; RCP, randomized controlled period; SD, standard deviation

[a]Patients treated with ravulizumab during both the RCP and OLE. [b]Patients treated with placebo during the RCP and ravulizumab during the OLE

Figures from Meisel A et al. J Neurol. 2023;270:3862-75. [creative commons]

Ravulizumab: CHAMPION-MG Study

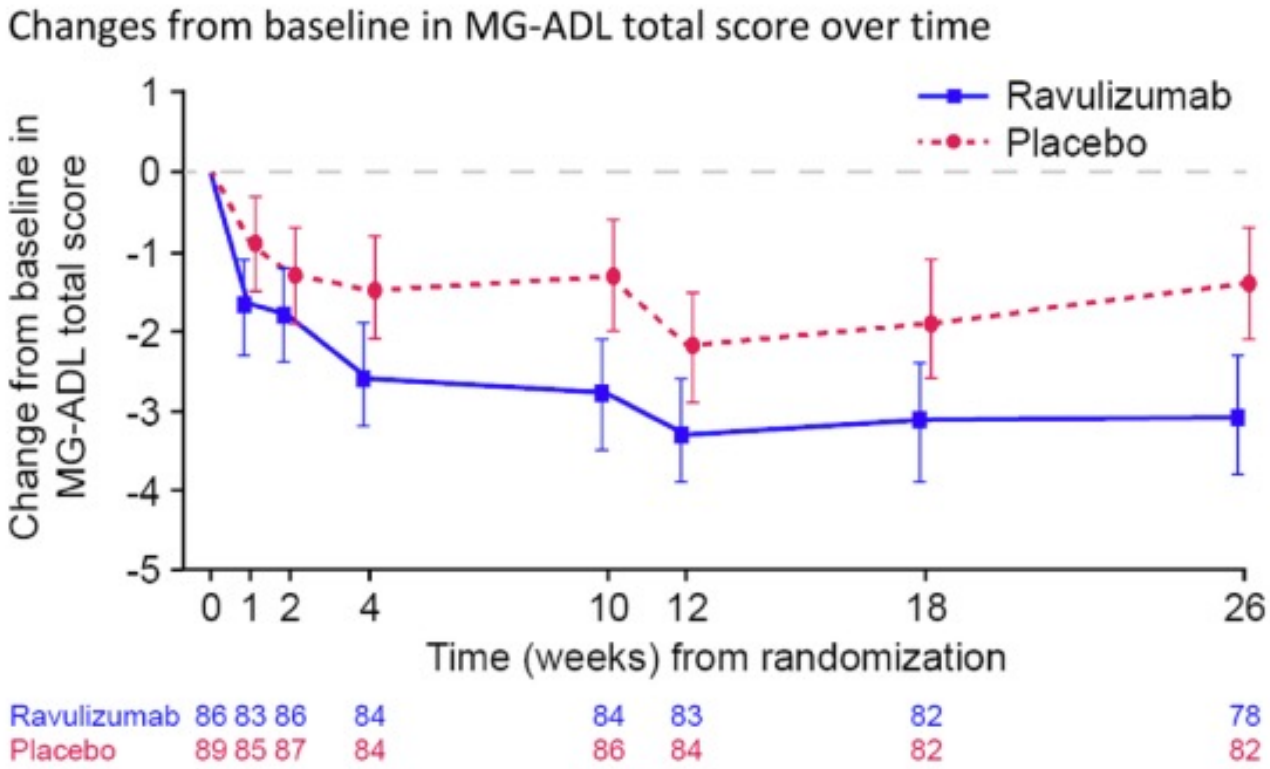


Figure from Vu T et al. *Neurol Ther.* 2023;12:1435-8. [creative commons]

Ravulizumab: CHAMPION-MG Study

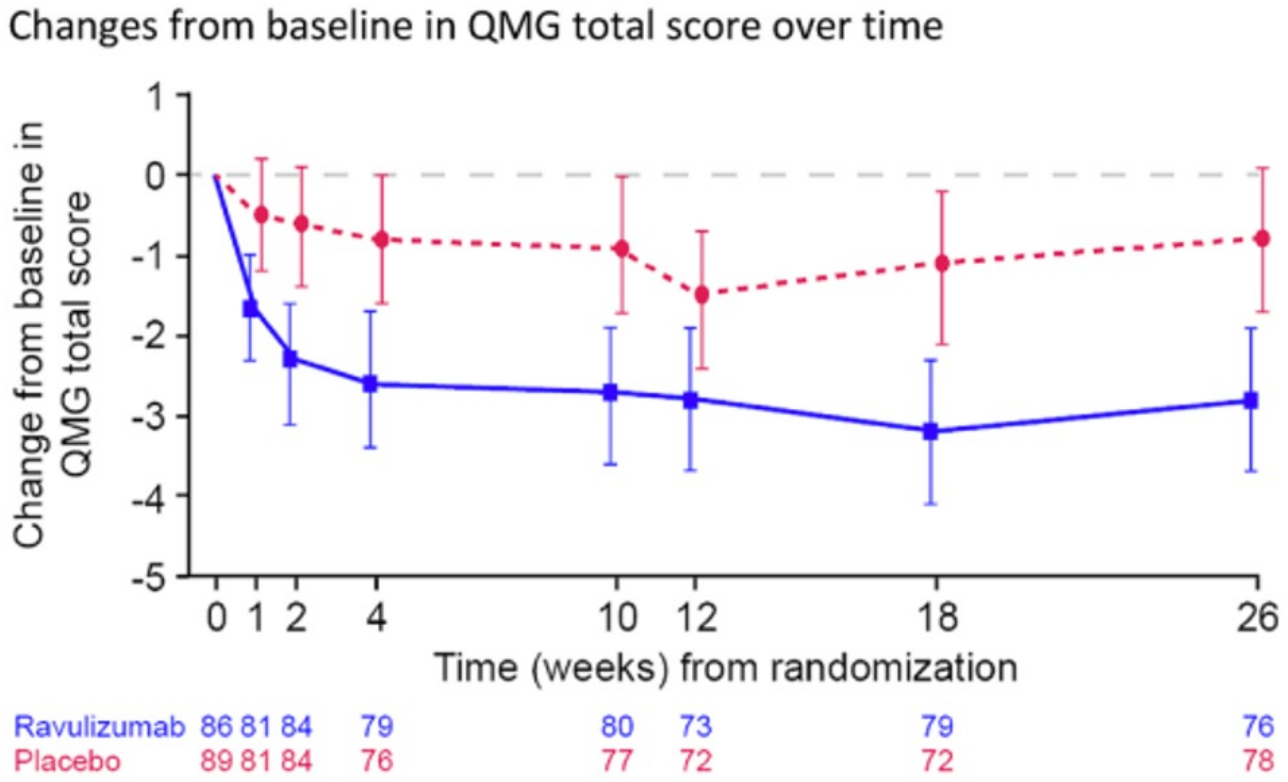


Figure from Vu T et al. *Neurol Ther.* 2023;12:1435-8. [creative commons]

Ravulizumab: Open Label Extension - Safety and Tolerability

Safety outcomes in all ravulizumab-treated patients during the RCP and OLE[a]		
	Patients (n=169)	
Adverse event	No. of events	No. of patients (%)
Any adverse event	881	150 (88.8)
Related to trial agent[b]	146	58 (34.3)
Any adverse event, by severity[c]		
Grade 1	577	127 (75.1)
Grade 2	210	82 (48.5)
Grade 3	81	39 (23.1)
Grade 4	9	9 (5.3)
Grade 5	4	4 (2.4)
Any SAE	75	41 (24.3)
Related to trial agent[b]	6	5 (3.0)
Death[d]	4	4 (2.4)
Adverse event reported in ≥10% of pts		
Headache	43	28 (16.6)
Diarrhea	26	23 (13.6)

[a]Includes data available for all patients up to Week 60 at data cut-off (November 9, 2021).
[b]As determined by the investigator.
[c]Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
[d]Two deaths occurred during the RCP and two during the OLE

MG, myasthenia gravis; OLE, open-label extension; RCP, randomized-controlled period; SAE, serious adverse event.

Howard JF, et al. 2022 AAN Annual Meeting, 2–7 April, 2022; Seattle, USA

Ravulizumab: Open-label Extension - Safety and Tolerability

Ravulizumab was well tolerated in both the RCP and OLE

The safety analysis set comprised 169 patients

- Ravulizumab in RCP: 86
- Placebo → ravulizumab: 83

Mean ravulizumab exposure

- Ravulizumab → ravulizumab: 384 days
- Placebo → ravulizumab: 226 days

Six SAEs in five patients were categorized by the investigators as being related to study treatment:

- One patient each with dysphagia, tendonitis, worsening MG, and erysipelas
- One patient with pneumonia and mitral valve stenosis

No cases of meningococcal infection

One case of meningitis was reported; the causative organism was not identified as *Neisseria meningitidis*

Four deaths: three due to COVID-19, one due to cerebral hemorrhage; all assessed by investigators as unrelated to study treatment

Howard JF, et al. 2022 AAN Annual Meeting, 2–7 April, 2022; Seattle, USA

Zilucoplan

FDA approval: 2023

Indication: To treat adults with AChR antibody-positive generalized myasthenia gravis.

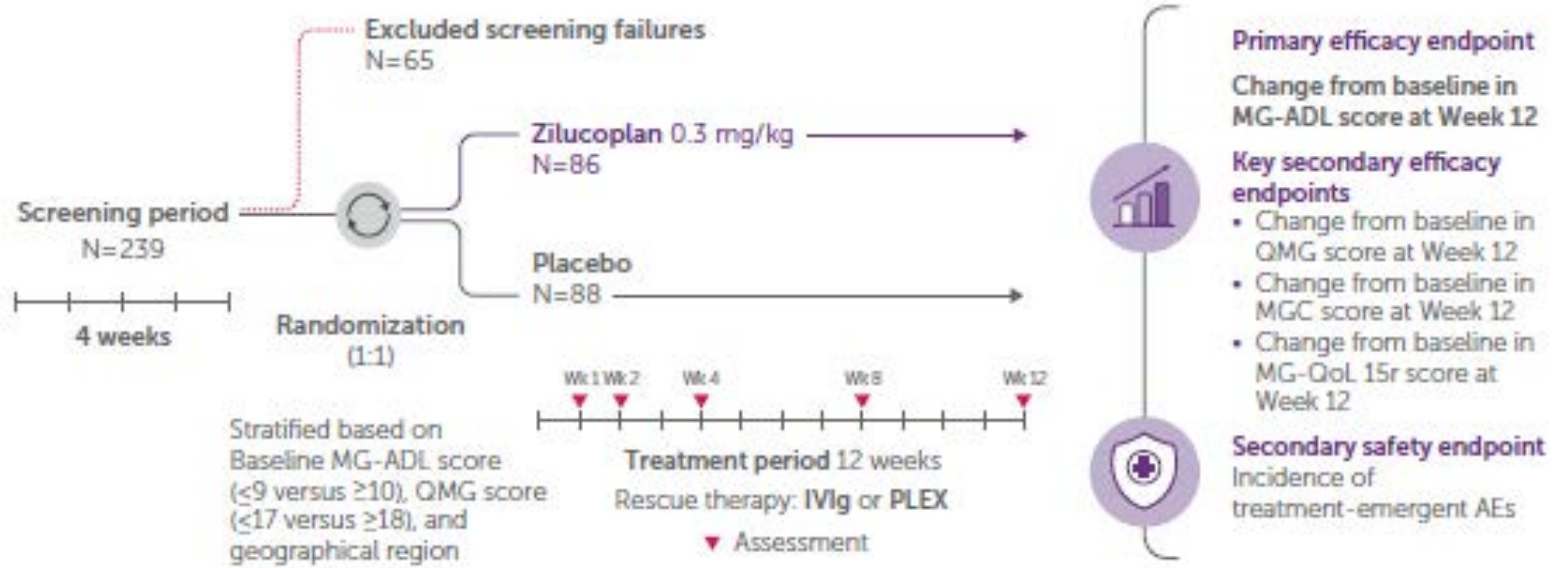
MOA: Peptide inhibitor of complement C5.

Dosage: 0.3 mg/kg once daily.

Route of Administration: Subcutaneous.

Boxed Warning: None.

Zilucoplan: RAISE Study



	Placebo (n=88)	Zilucoplan (n=86)
Age, years	53·3 (15·7)	52·6 (14·6)
Sex		
Female	47 (53%)	52 (60%)
Male	41 (47%)	34 (40%)
Bodyweight, kg	88·2 (26·6)	90·1 (22·9)
Geographic region		
Europe	33 (38%)	34 (40%)
Japan	9 (10%)	7 (8%)
North America	46 (52%)	45 (52%)
Race		
White	62 (70%)	66 (77%)
Asian	14 (16%)	7 (8%)
Black	7 (8%)	6 (7%)
American Indian or Alaskan native	1 (1%)	0
Missing	4 (5%)	7 (8%)
Ethnicity		
Hispanic or Latino	5 (6%)	7 (8%)
Not Hispanic or Latino	79 (90%)	72 (84%)
Missing	4 (5%)	7 (8%)
Age at onset, years	44·0 (18·7)	43·5 (17·4)
Duration of disease, years	9·0 (10·4)	9·3 (9·5)
MGFA disease class		
Class II	27 (31%)	22 (26%)
Class III	57 (65%)	60 (70%)
Class IV	4 (5%)	4 (5%)
MG-ADL score	10·9 (3·4)	10·3 (2·5)
QMG score	19·4 (4·5)	18·7 (3·6)

Figure from Howard JF Jr et al. *Lancet Neurol*. 2023;22:395-406. [creative commons]

Zilucoplan: RAISE Study

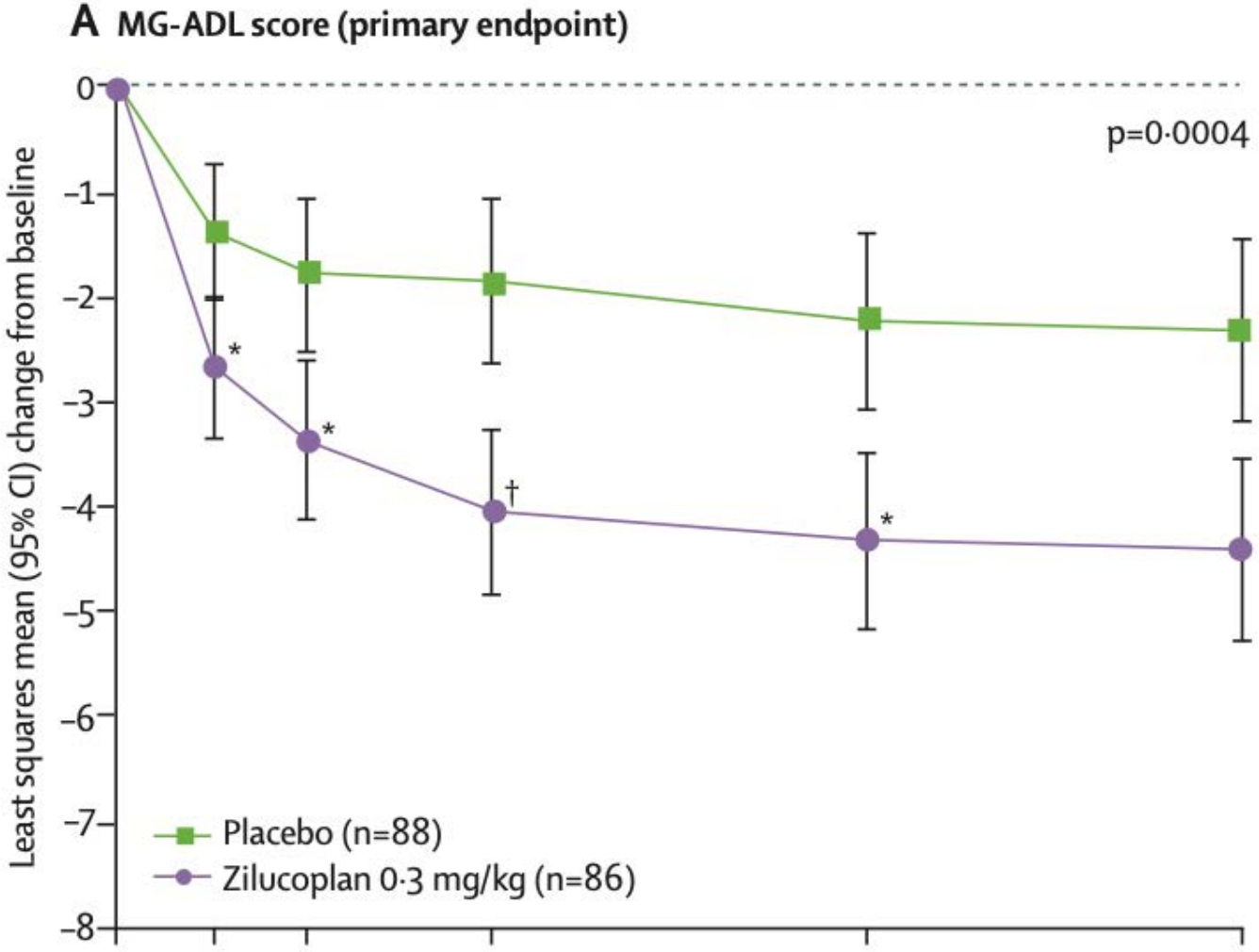
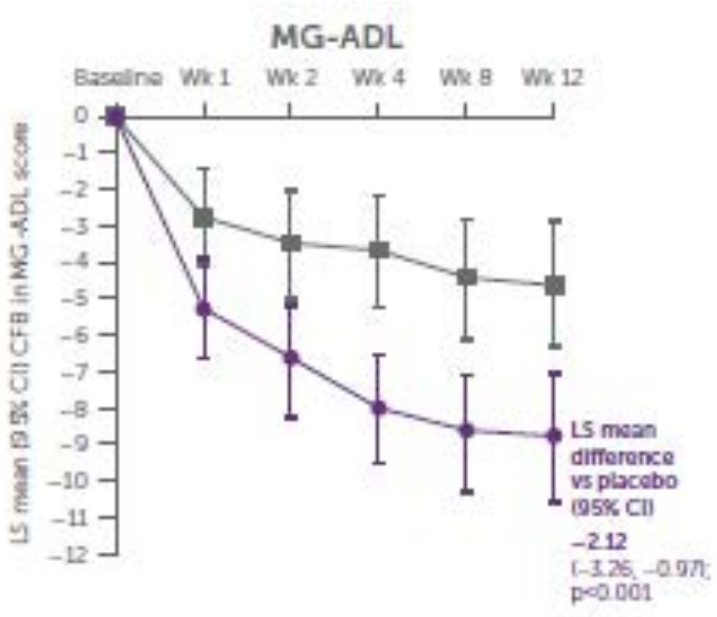
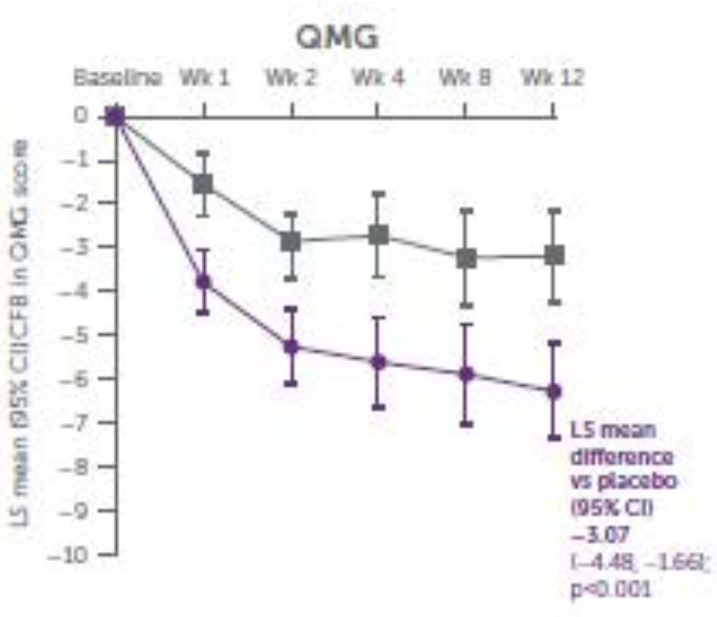


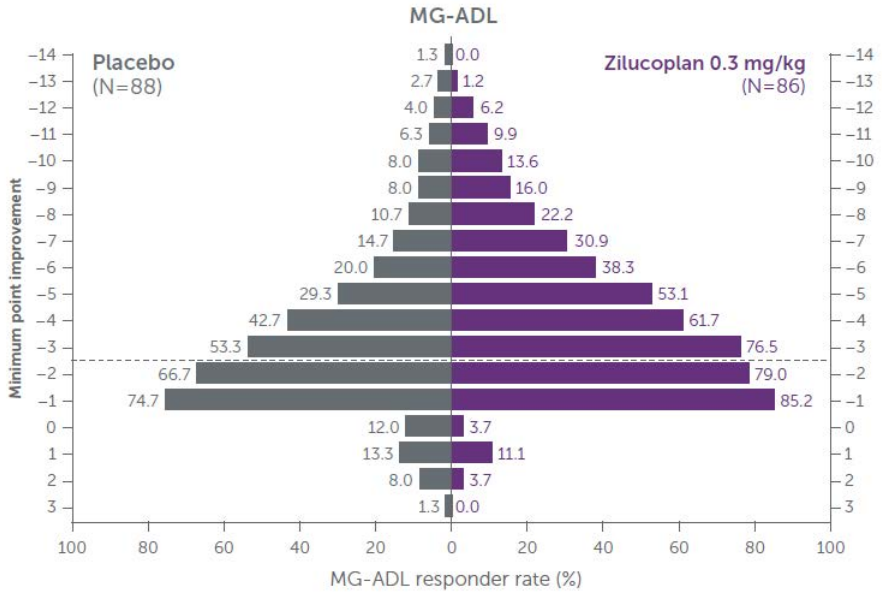
Figure from Howard JF Jr et al. *Lancet Neurol*. 2023;22:395-406. [creative commons]

Zilucoplan: RAISE Study – Secondary Endpoints





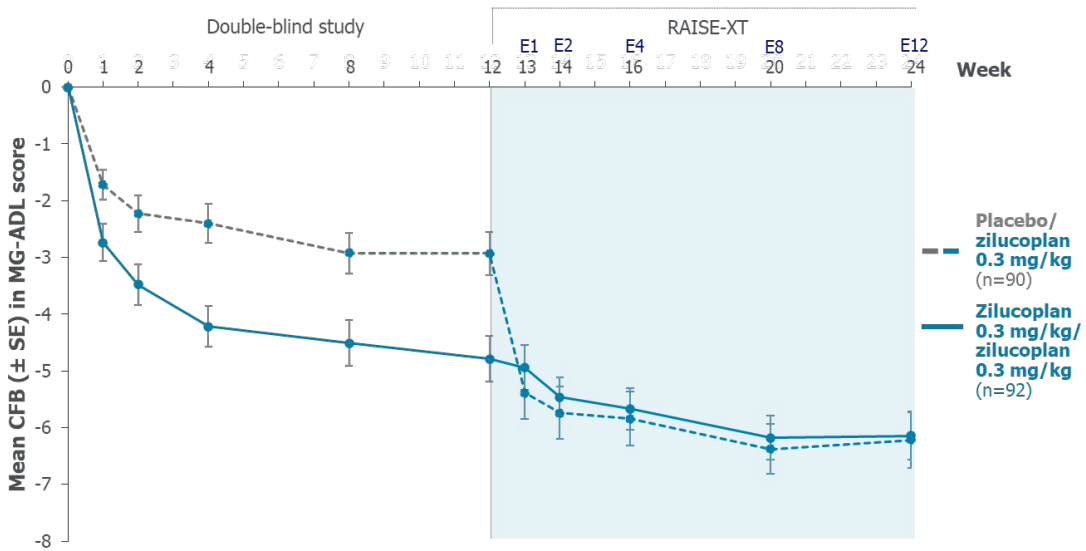
Responder Analysis



Howard JF Jr, et al. 14th MGFA International Conference on Myasthenia and Related Disorders, Miami FL, May 10-12, 2022

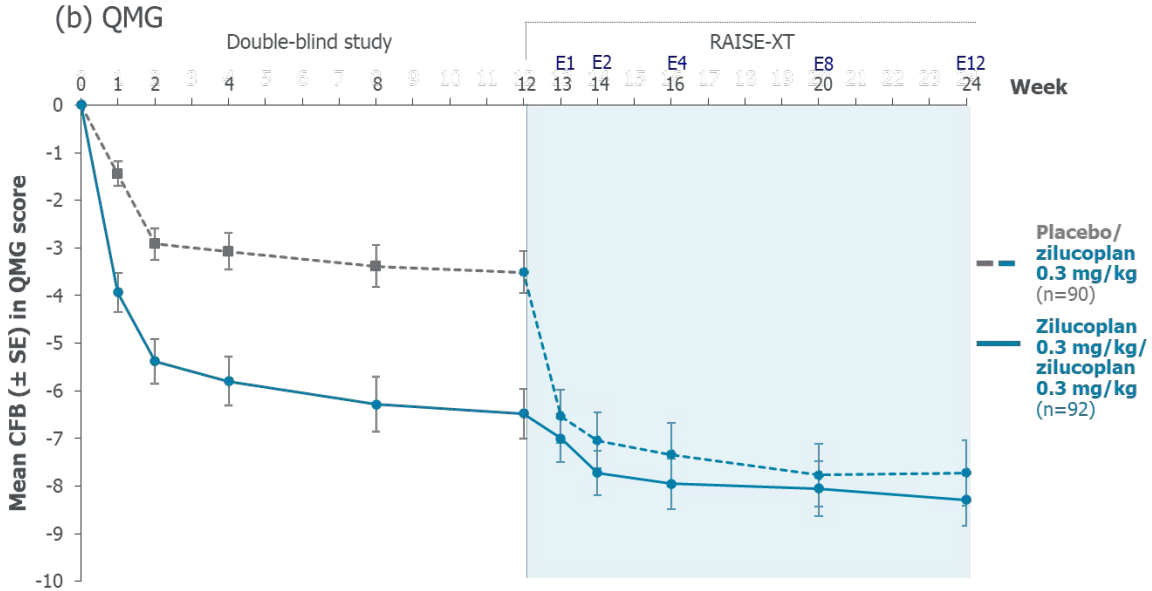
Zilucoplan: Phase 3 - Additional Improvement at Week 24

(a) MG-ADL



	LS mean change between Week 12 vs Week 24 (95% CI)	LS mean change between DB baseline vs Week 24 (95% CI)
Placebo/ zilucoplan 0.3 mg/kg	**−3.39** (−5.85, −0.93) p=0.0075	**−6.32** (−8.00, −4.65)
Zilucoplan 0.3 mg/kg/ zilucoplan 0.3 mg/kg	**−2.25** (−3.41, −1.10) p=0.0002	**−6.30** (−7.44, −5.15)

(b) QMG



	LS mean change between Week 12 vs Week 24 (95% CI)	LS mean change between DB baseline vs Week 24 (95% CI)
Placebo/ zilucoplan 0.3 mg/kg	**−5.33** (−8.54, −2.12) p=0.0014	**−8.52** (−10.89, −6.16)
Zilucoplan 0.3 mg/kg/ zilucoplan 0.3 mg/kg	**−1.82** (−3.60, −0.04) p=0.0450	**−8.87** (−10.31, −7.42)

Friemer M, et al. 2022 AAN Annual Meeting, 2–7 April, 2022; Seattle, USA

Clinical Pearls

- The diagnosis of myasthenia gravis is a clinical one, based on a detailed neuromuscular history and examination, confirmed by serology and electrodiagnostic testing
- The overarching goal of current management is that of no symptoms with Grade 1 or less adverse events
- Targeted therapies offer a faster onset of action with less (better tolerated) adverse events
- Complement inhibition currently targets the terminal complement pathway to reduce the formation of the terminal complement complex; whose function is to architecturally destroy the neuromuscular junction
- Complement activation is mediated by antibodies to the acetylcholine receptor (AChR) binding to the neuromuscular junction
- Complement inhibition is not efficacious in MuSK myasthenia gravis as MuSK antibody (IGG4) does not activate complement
- All patients receiving complement inhibitors must be vaccinated against Neisseria meningitidis according to local guidelines. In the US, both ACWY and B-serotype vaccines are used.