Myasthenia Gravis and the Complement System: Pathophysiology

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Advisory Board/Consultant:

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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

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.

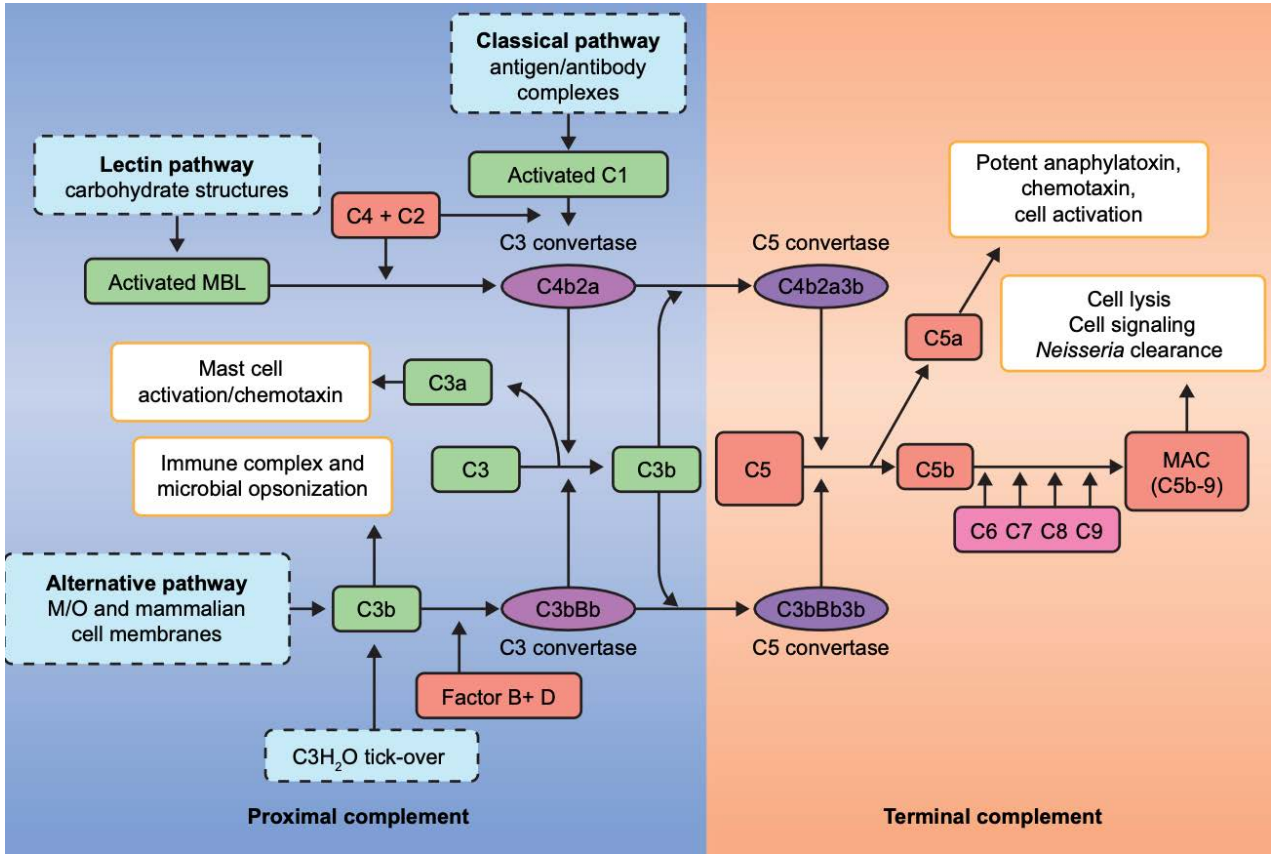

Figure from Howard JF Jr. *Ann NY Acad Sci.* 2018; 1412: 113-28. [creative commons]

Pathophysiology

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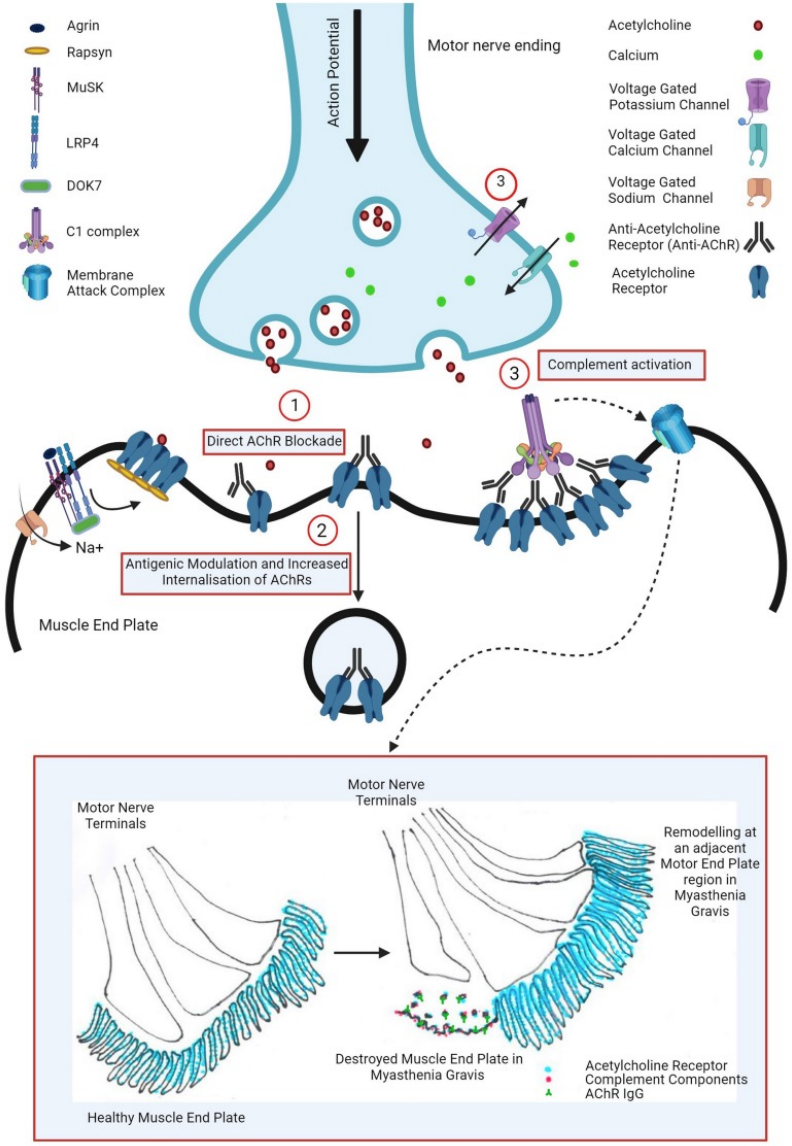
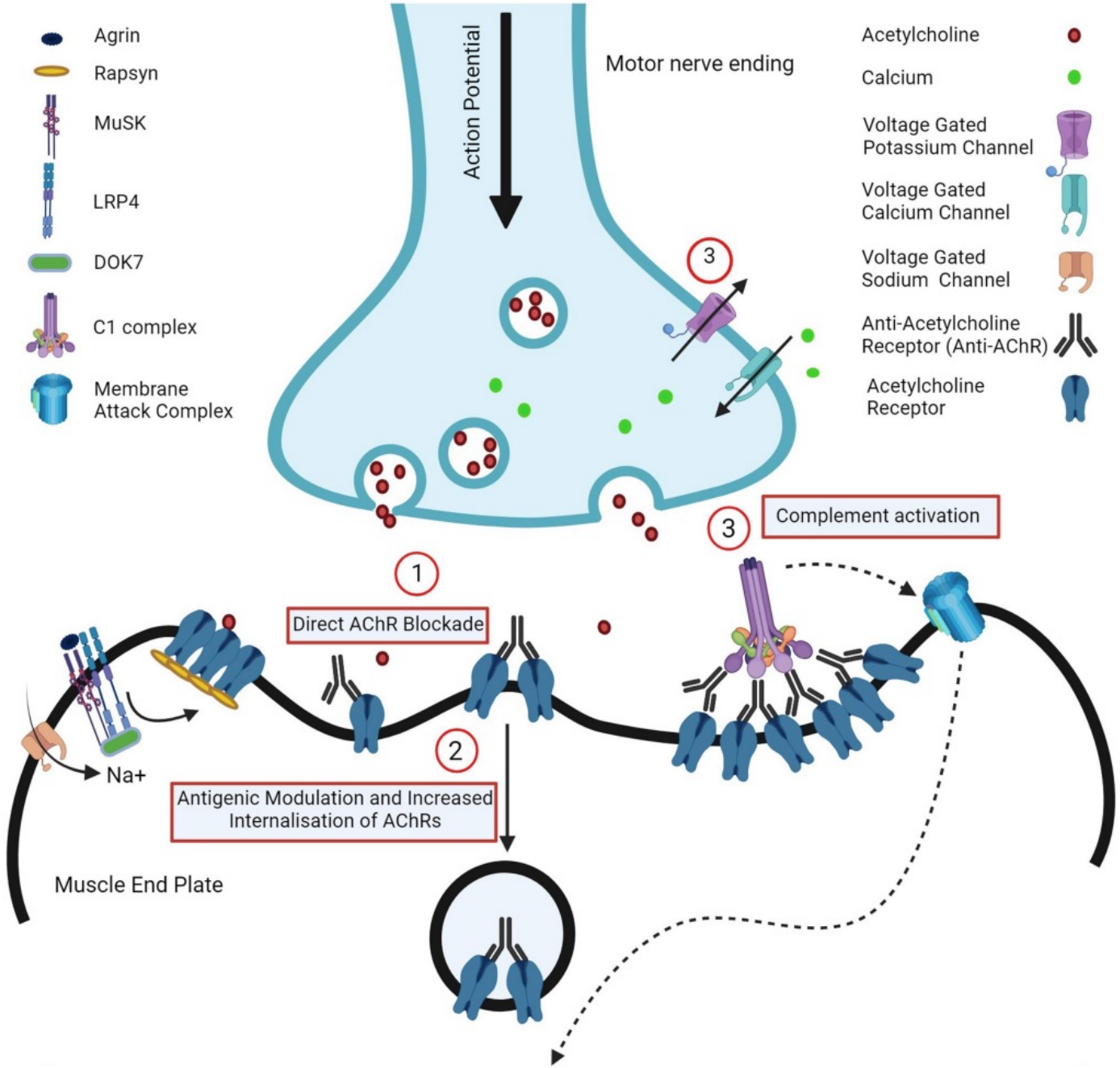


Figure from San PP, Jacob S. *Front Neurol.* 2033; 14: 1277596. [creative commons]



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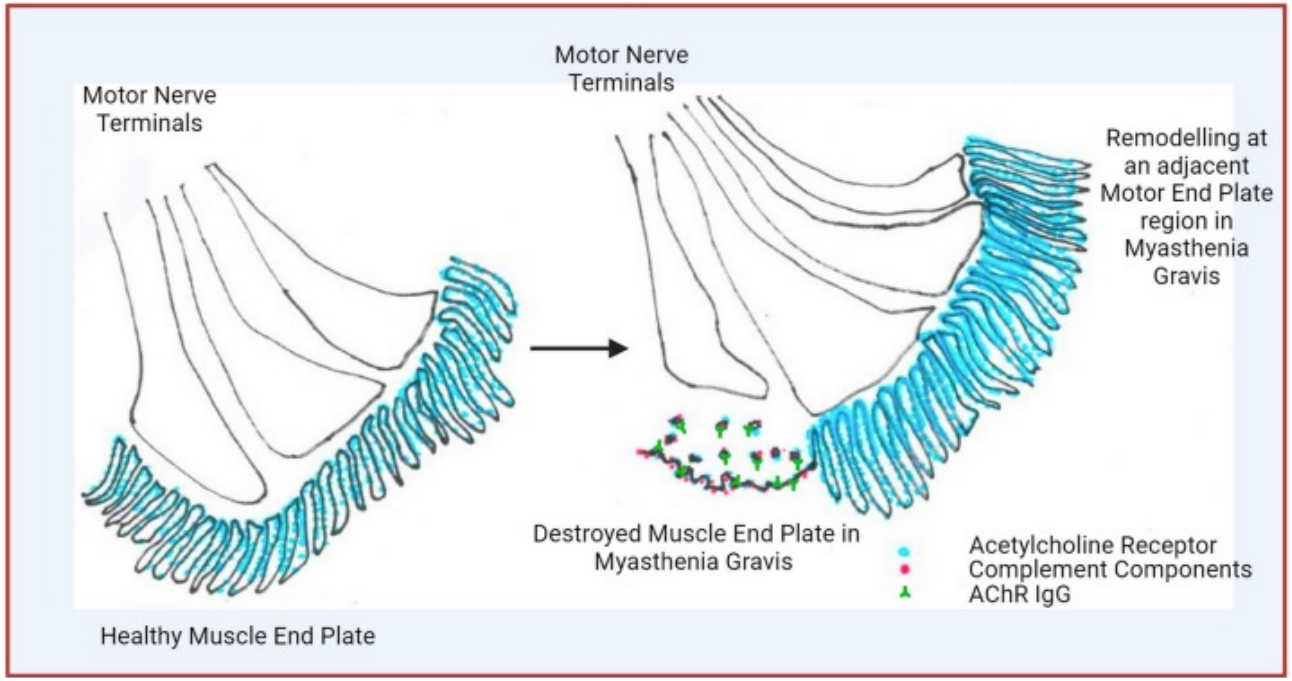

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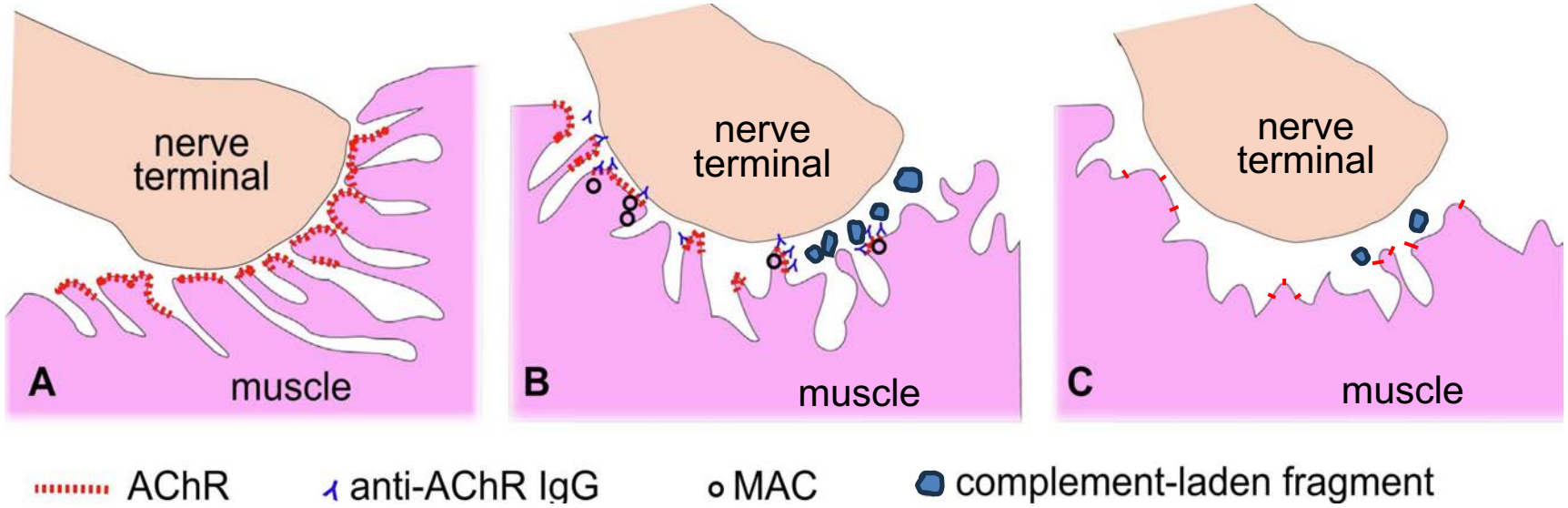
Pathophysiology



Normal neuromuscular junction.

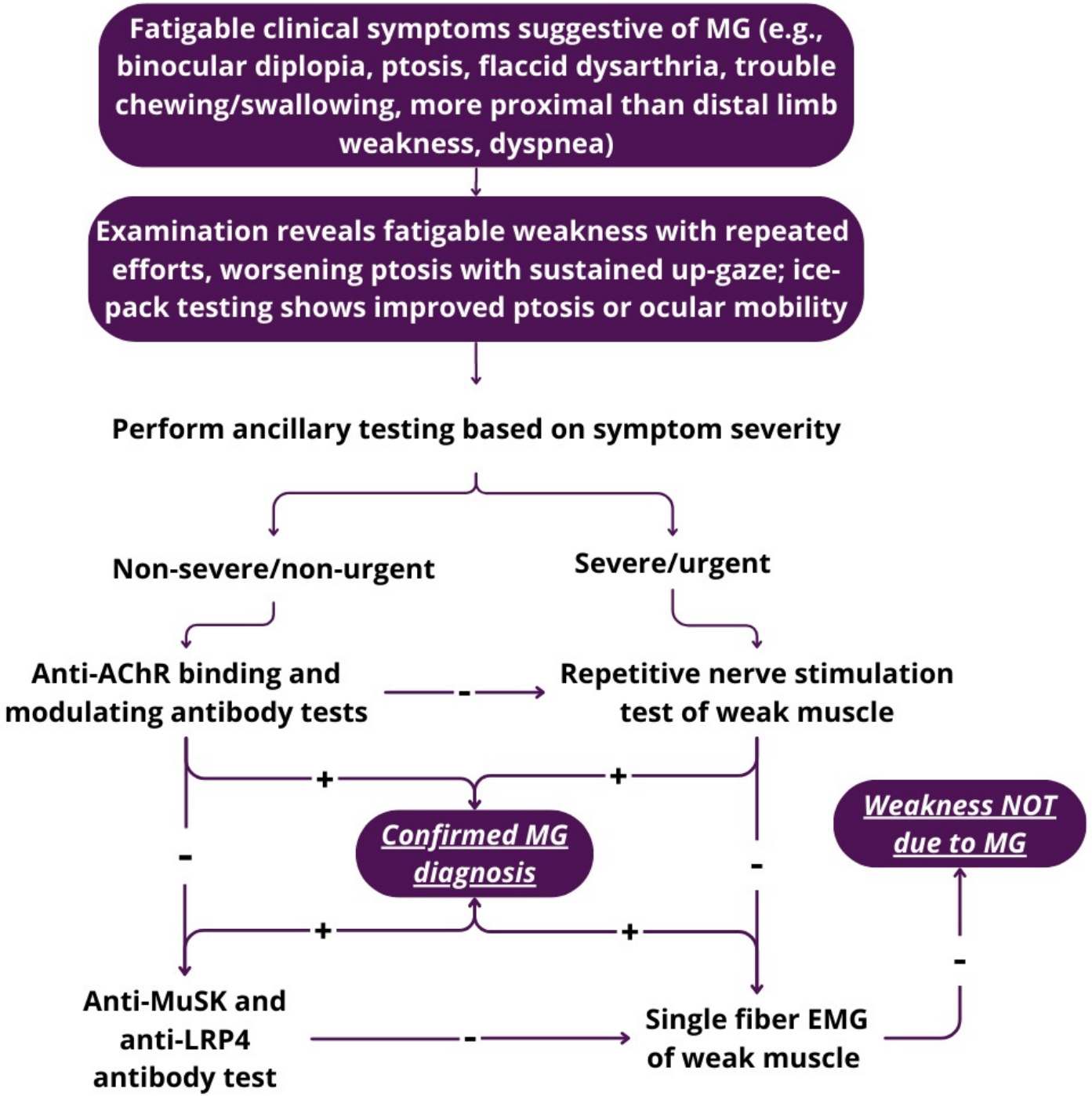
Autoantibodies bind to AChR that initiates activation of complement that forms terminal complement complex (TCC) or membrane attack complex (MAC).

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

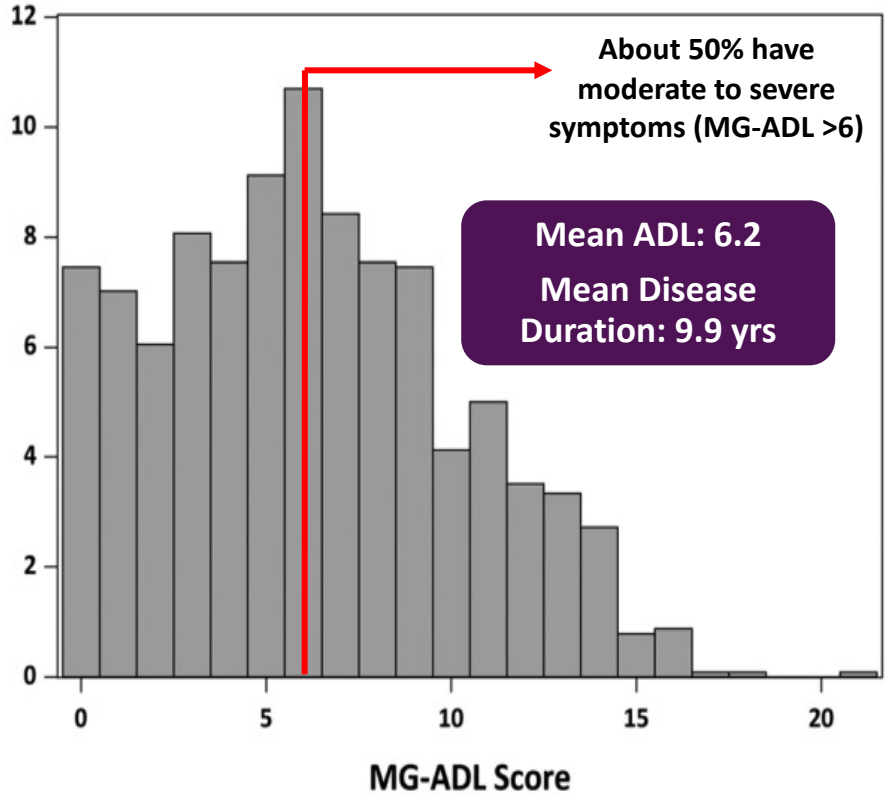
Figure from Sanderson NSR. *Mol Immunol* 2023; 151: 22-8. [creative commons]

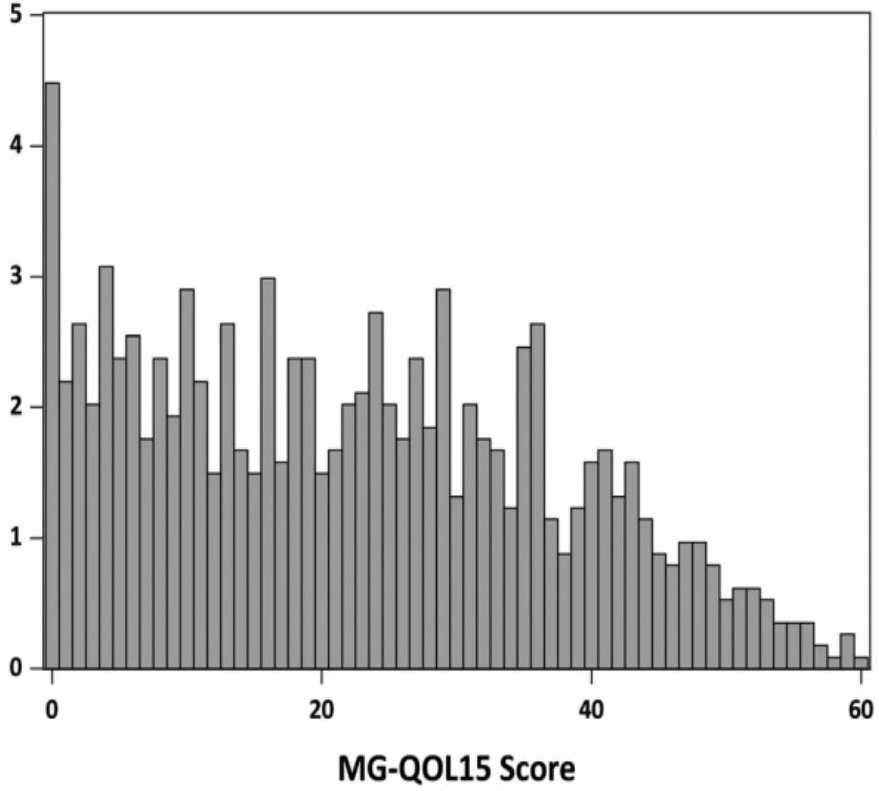
Symptoms and Diagnosis

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



Disease Burden

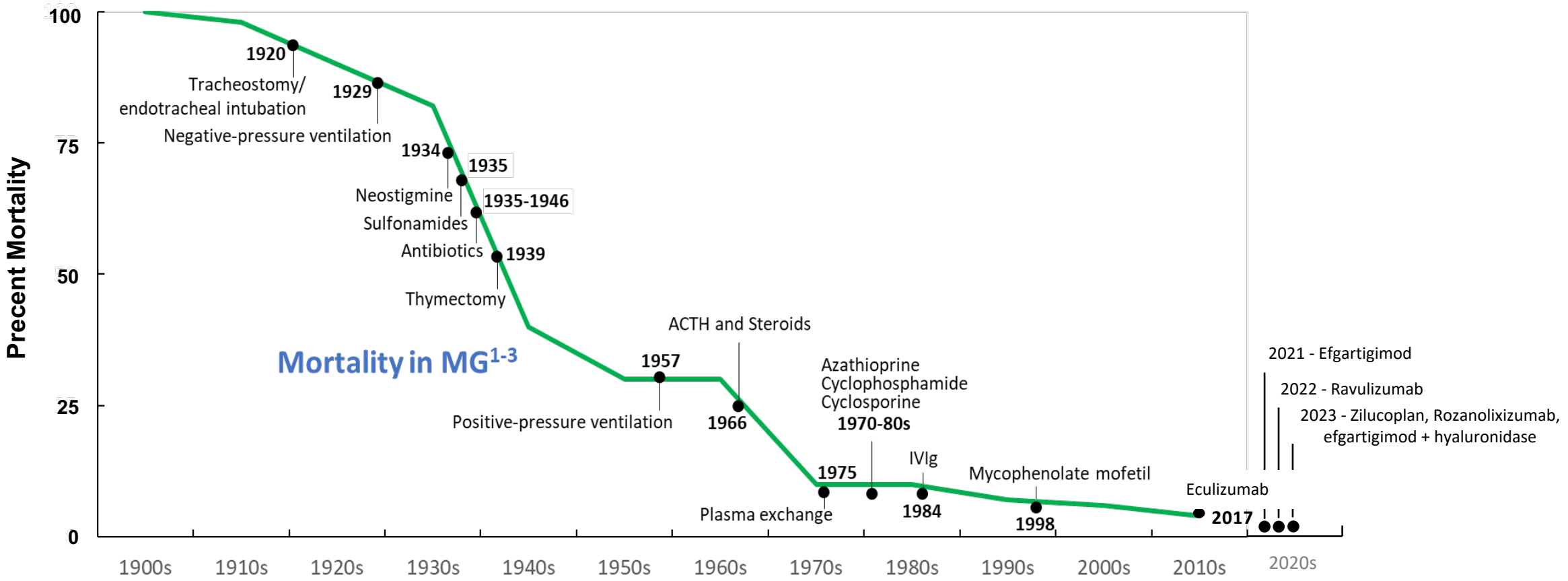




Distribution of MG-ADL (N=1138) and MG-QOL15 (N=1140) scores in patients in myasthenia gravis. The majority of patients reported moderate to severe impairment in activities of daily living.

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.

Weak Correlation Between C3 and QMG

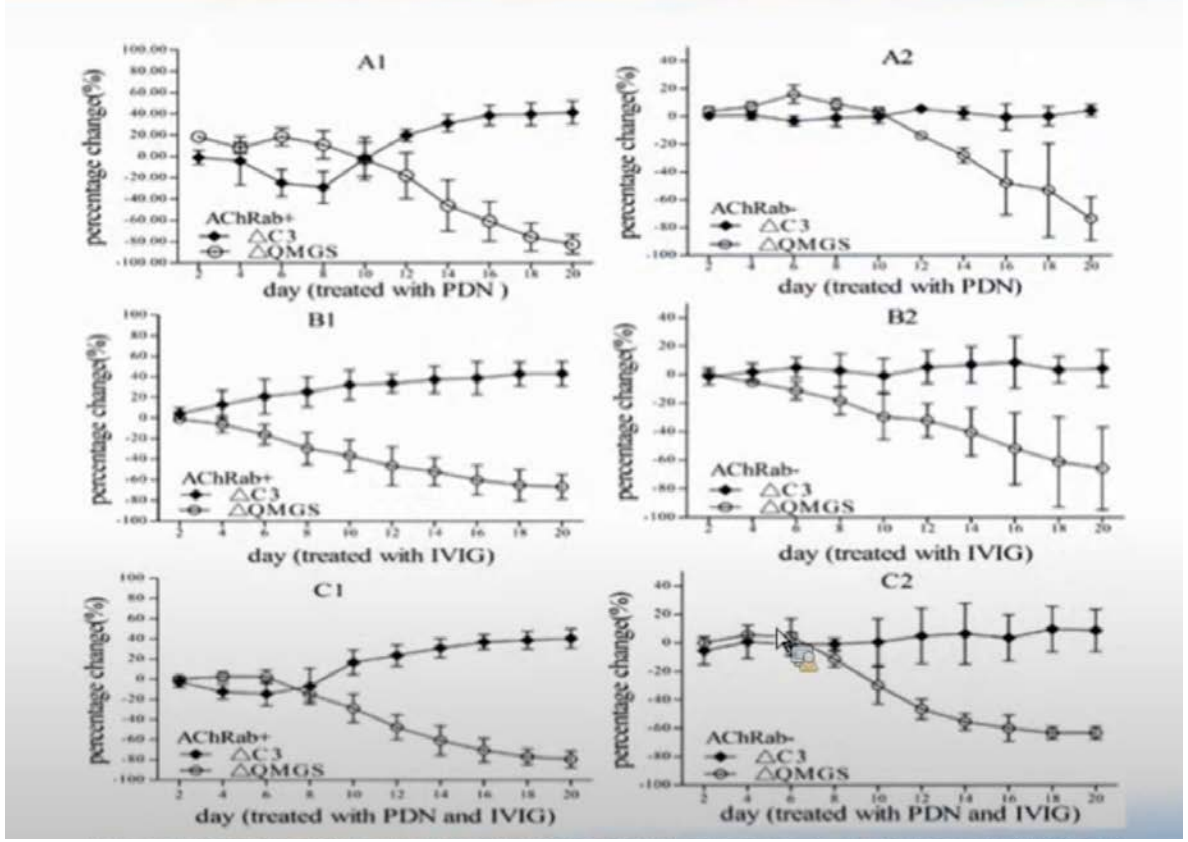
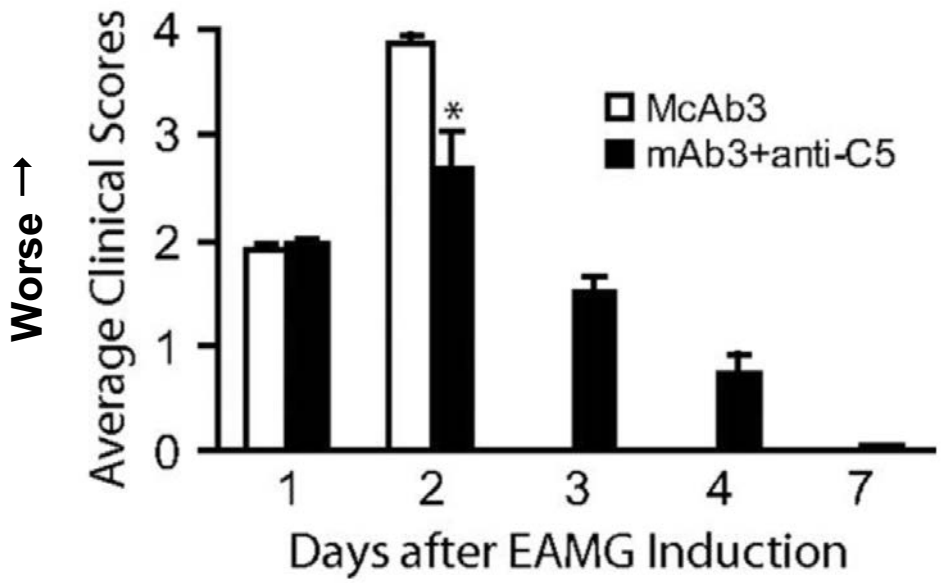
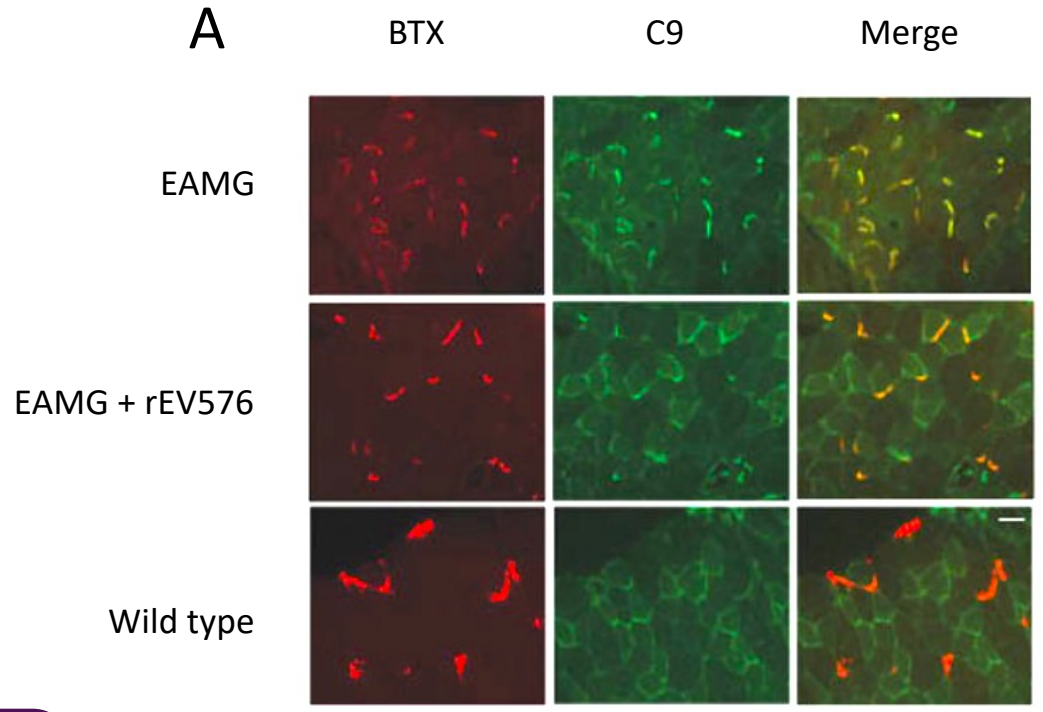


Figure recreated from Lui A et al. Muscle Nerve, 2009; 40: 801-8.

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.