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Myasthenia Gravis: The Evolving Landscape of Immunotherapy

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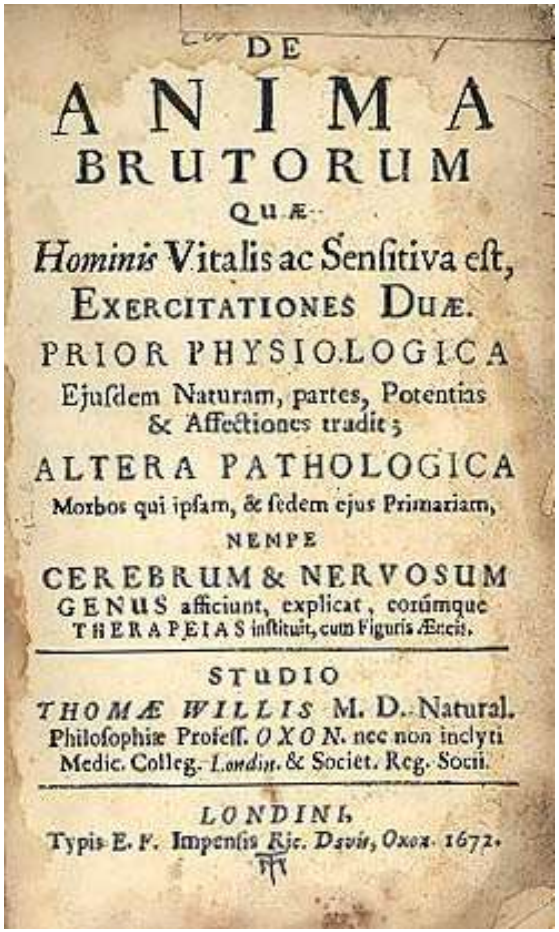
Disclosures

- UCB pharma - advisory board & consultant
- Immunovant - advisory board
- Argenx - advisory board
- Fichtenbaum Charitable Trust – research grant support

- Some medications discussed are off-label



DE
ANIMA
BRUTORUM
QUÆ
Hominis Vitalis ac Senſitiva eſt,
EXERCITATIONES DUÆ.
PRIOR PHYSIOLOGICA
Ejuſdem Naturam, partes, Potentias & Affectiones tradit;
ALTERA PATHOLOGICA
Morbos qui ipſam, & ſedem ejus Primariam,
NEMPE
CEREBRUM & NERVOSUM
GENUS afficiunt, explicat, eorúmque
THERAPEIAS inſtituit, cum Figuris Æneis.
STUDIO
THOMÆ WILLIS M. D. Natural.
Philoſophiæ Profeſſ. *OXON.* nec non inclyti
Medic. Colleg. *Londin.* & Societ. Reg. Socii.
LONDINI,
Typis E. F. Impenſis *Ric. Davis*, *Oxon.* 1672.

"Depend upon the fault of the explosive copula suffused everywhere from the blood into the moving fibres."

https://www.sciencedirect.com/science/article/pii/S0022510X19303600

Simpson hypothesized MG may be **caused by autoantibody** against motor end plate protein

Smithers launched **concept of MG as autoimmune disease**

Nastuk et al linked **serum complement levels** to MG disease status

Fambrough et al showed **post synaptic AchRs were reduced** in MG

Patrick & Lindstrom showed immunizing rabbits with purified **AchR led to muscle weakness** reversible by AchE inhibitors

Llyanage et al discussed **targeting agrin/MuSK** pathway

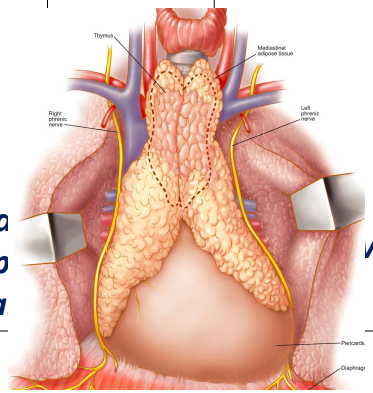
Hoch et al reported **Ab's to MuSK in MG** w/o AchR Ab

1958 1960 1973 2001

1954 1967 1976 1984 1987 1990 1998 2000 2002 **14 years** 2016

Pyridostigmine bromide

Aza
Cyclop
Cervica



VIG

Thymectomy: 1950's

Cyclosporine

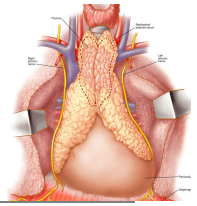
Combined cervicothoracic thymectomy

Mycophenolate Mofetil

Rituximab

Tacrolimus

Thymectomy



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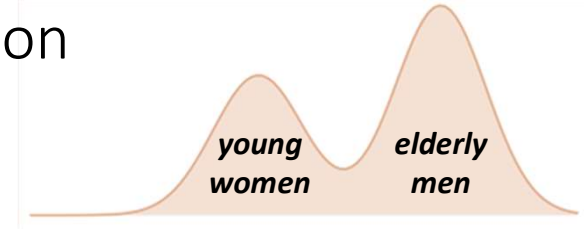
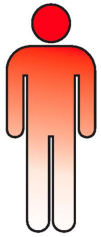
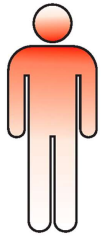
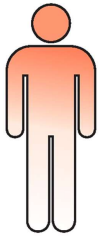
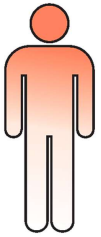
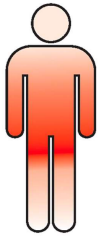
2017 – 2023: "Golden Era"

Complement inhibitors		
	Antibody status	*FDA approval*
Eculizumab	AchR Ab (+)	2017
Ravalizumab	AchR Ab (+)	2022
Zilucoplan	AchR Ab (+)	**2023**
Neonatal Fc Receptor Antagonists		
Efgartigimod	AchR Ab (+), seronegative	2021
Efgartigimod alpha	AchR Ab (+), seronegative	**2023**
Rozanolixizumab	AchR Ab (+), **MuSK Ab (+)**, seronegative	**2023**

Clinical presentation



Incidence: 14-40/100,000 in US

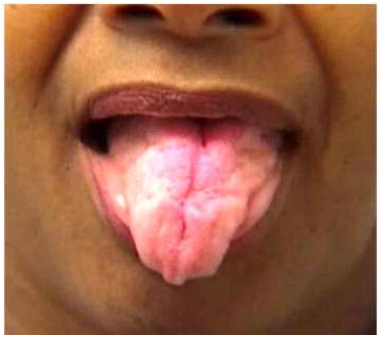
Subtype	AchR+	MuSK+	LRP4+	Seronegative	LEMS
					
Relative prevalence	80%	4%	2%	5%	4%

Gilhus, *Lancet Neurol*, Oct 2015

15% OMG, 85% generalized MG (gMG)

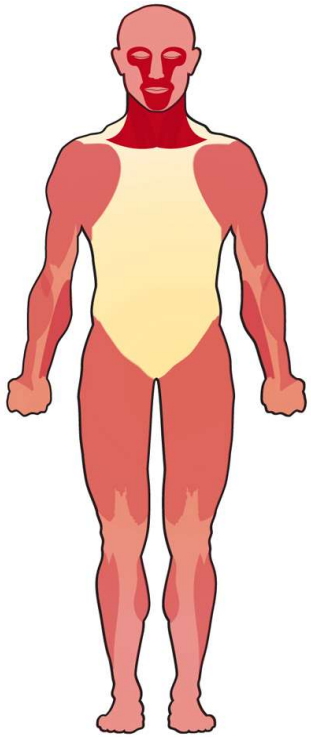
1st sx onset usually **ocular** (2/3 of pts)

- Pattern of ext weakness: proximal, extensors
- *Fluctuating, fatigable*
- Rarely distal weakness 1st sx – *foot drop, wrist drop*



Sanders D, Juel. V, *J of Neuroimm*, Sept 2008

Pt with **MuSK+** MG



https://www.mda.org/disease/myasthenia-gravis

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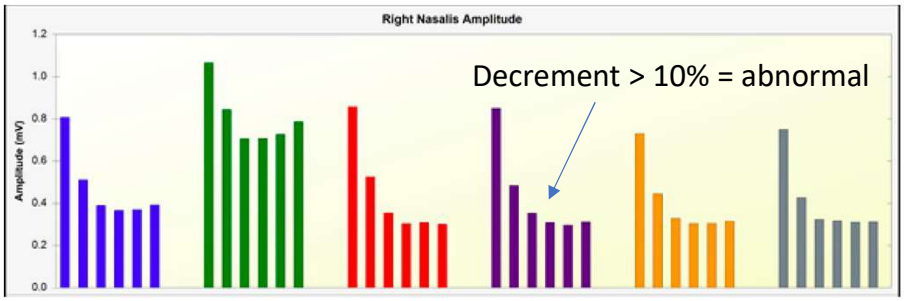
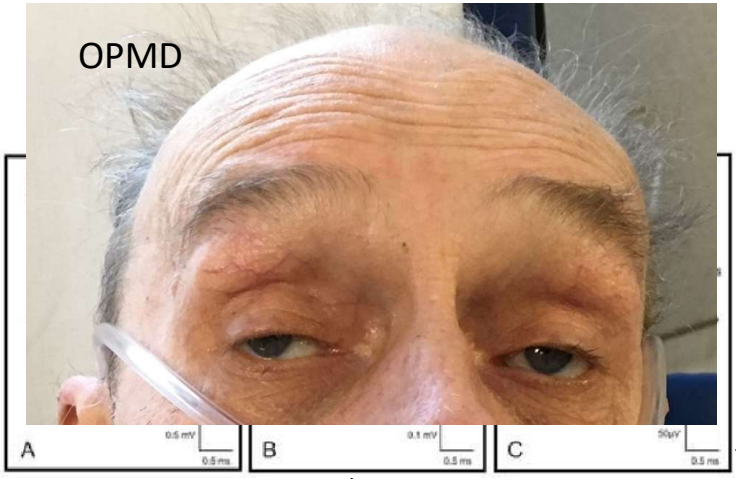
Additional workup (seronegative)

- EMG/NCS – *usually* normal
  - Abnl EMG activity can be seen with severe NMJ pathology (esp MuSK Ab+)
- 3 Hz RNS (nasalis, trapezius muscles), single fiber EMG ***(normal study does not exclude MG)***
- Repeat Ab testing
  - Cell based assay (CBA): increases sensitivity (binding to Ag more effective when expressed on cell surface), more native way to test for Ab vs RIPA or ELISA



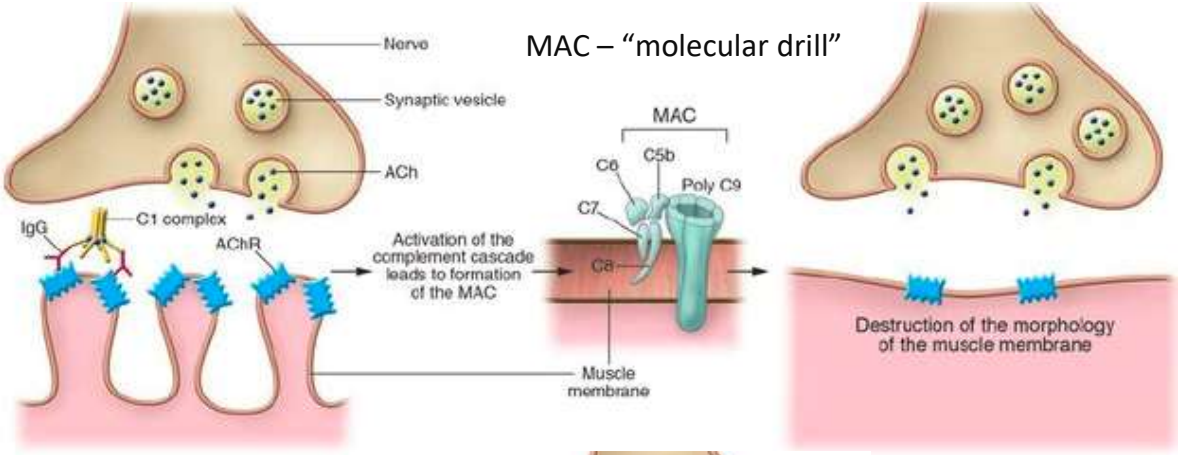
DDx

- Hereditary: congenital MG, mitochondrial disorders, oculopharyngeal muscular dystrophy
- Botulism
- Grave's disease
- Motor neuron disease (ie ALS)



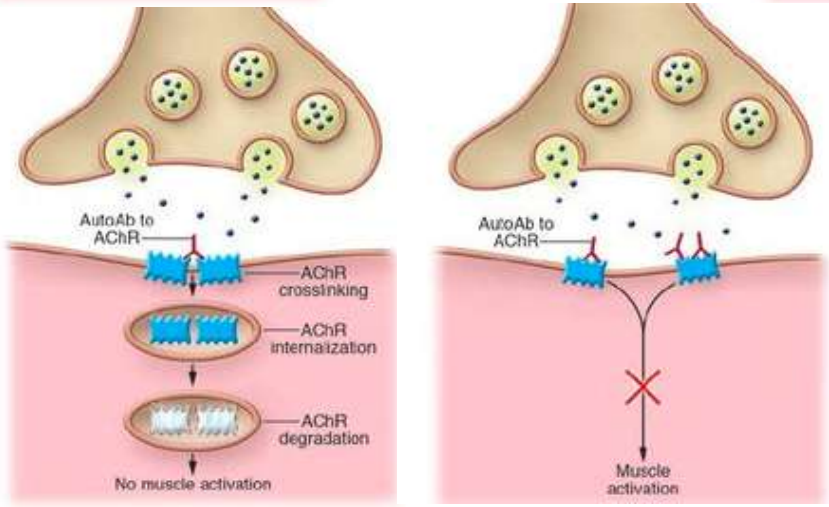
MAC – “molecular drill”

IgG1/IgG3



Complement binding & activation

Antigenic modulation



Functional AchR block

Conti Fine et al, *Journ of Clin Inves 2009*

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MG goals of treatment

MGFA-Post Intervention Status (PIS)

- **Minimal manifestation status (MMS)** = no sx or functional limitation
  - Allows *mild* weakness on exam, can be on meds
- **Remission**: same, only allows eyelid closure weakness but *no use of pyridostigmine*

Complete stable remission (CSR)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacological remission (PR)	The same criteria as for CSR, except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal manifestations (MM)	The patient has no symptoms of functional limitations from MG, but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least 1 year.
MM-1	The patient continues to receive some form of immunosuppression, but no cholinesterase inhibitors or other symptomatic therapy.
MM-2	The patient has received only low-dose cholinesterase inhibitors (<120 mg pyridostigmine/day) for at least 1 year.
MM-3	The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.

Initial presentation

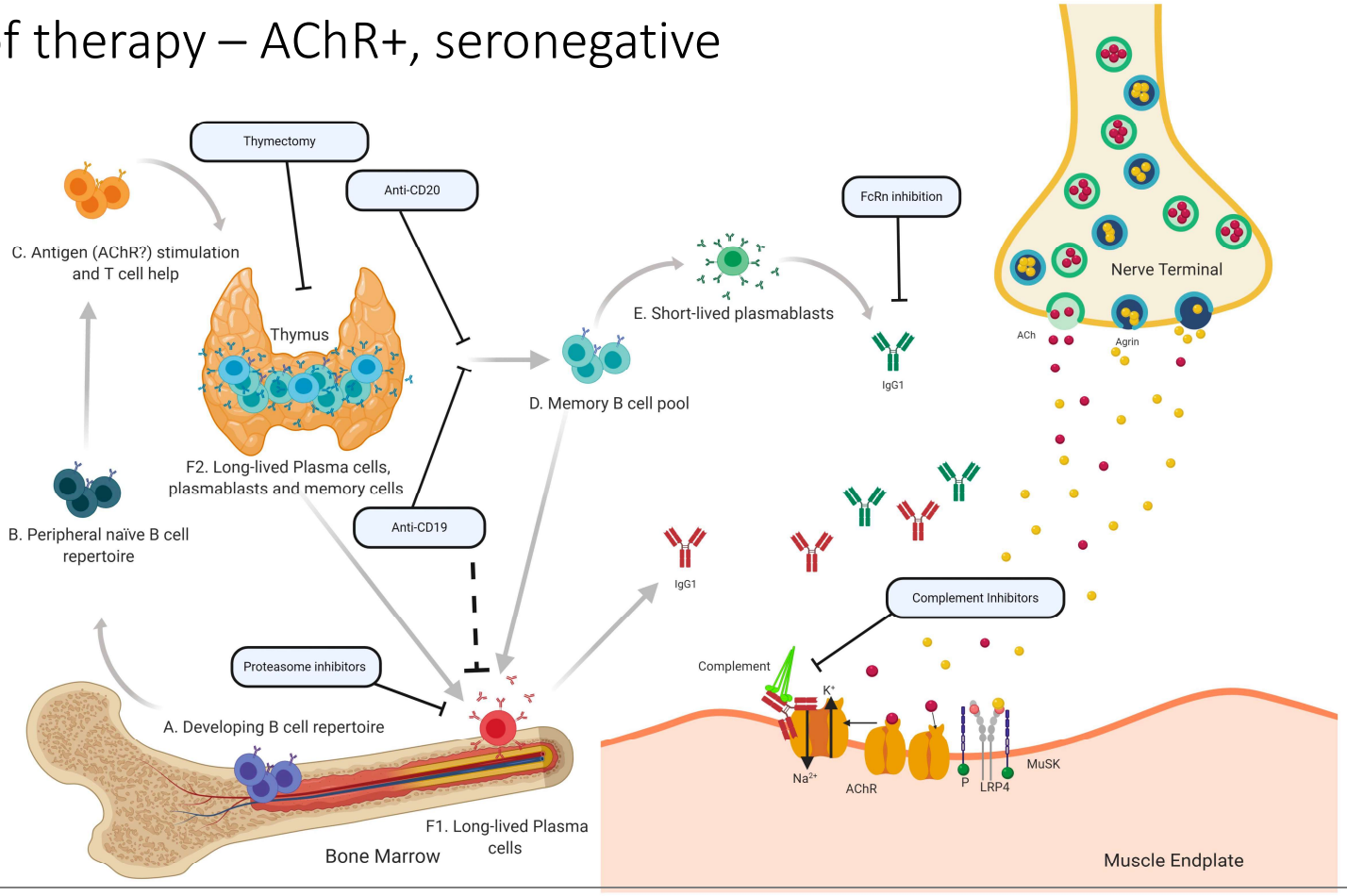
Tx with Pyrido + steroids +/- IST → Improved → MMS, remission

6 – 24 mon

Sustain for >1 year

https://myasthenia.org/Portals/0/MGFA%20-%20PIS.pdf

Targets of therapy – AChR+, seronegative



Fichtner et al, *Front. Immunol*, May 2020

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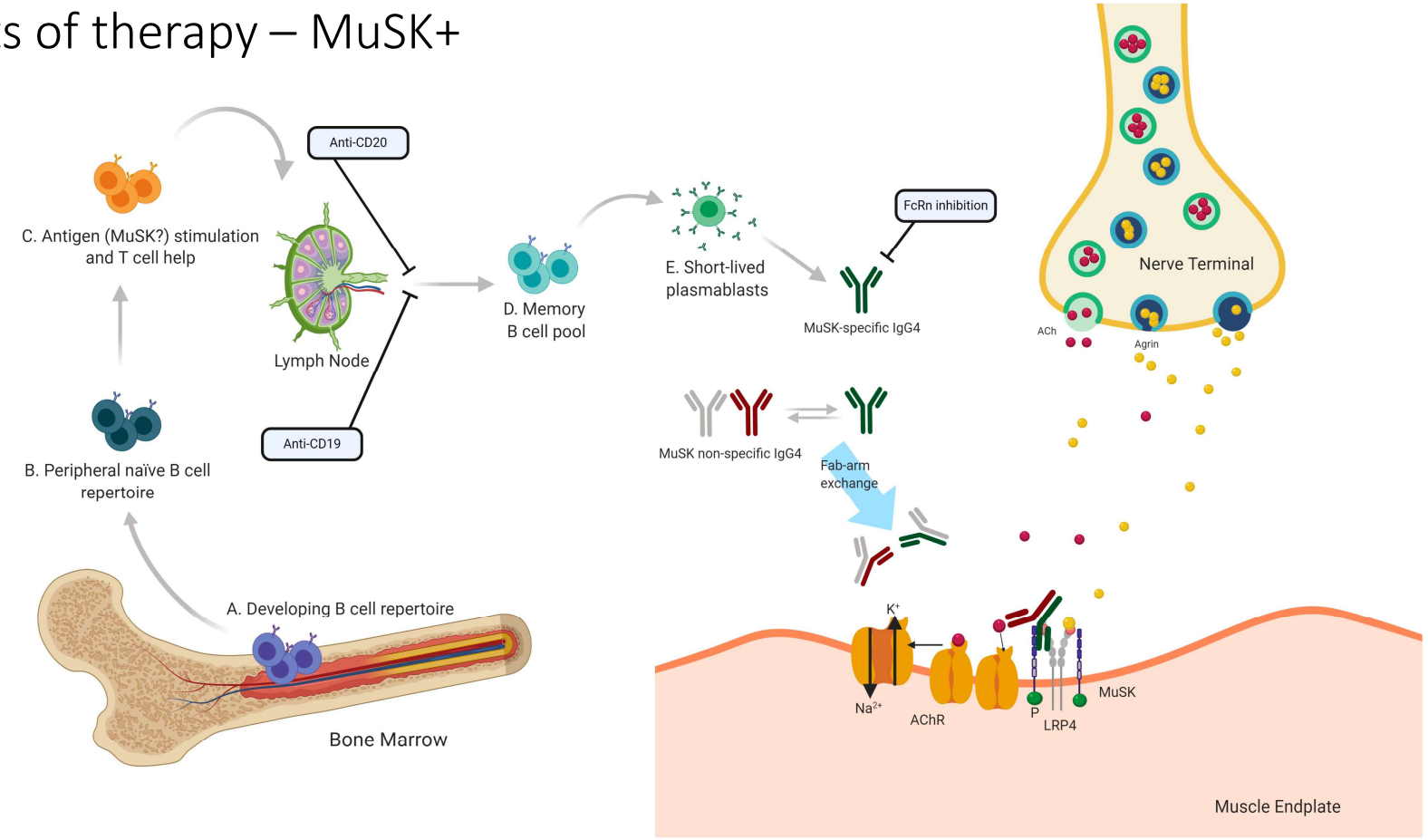
Targets of therapy – MuSK+



Neuromuscular Junction

Fichtner et al, *Front. Immunol*, May 2020

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> Arch Neurol. 2003 Feb;60(2):243-8. doi: 10.1001/archneur.60.2.243.

Development of generalized disease at 2 years in patients with ocular myasthenia gravis

Mark J Kupersmith [1], Robert Latkany, Peter Homel

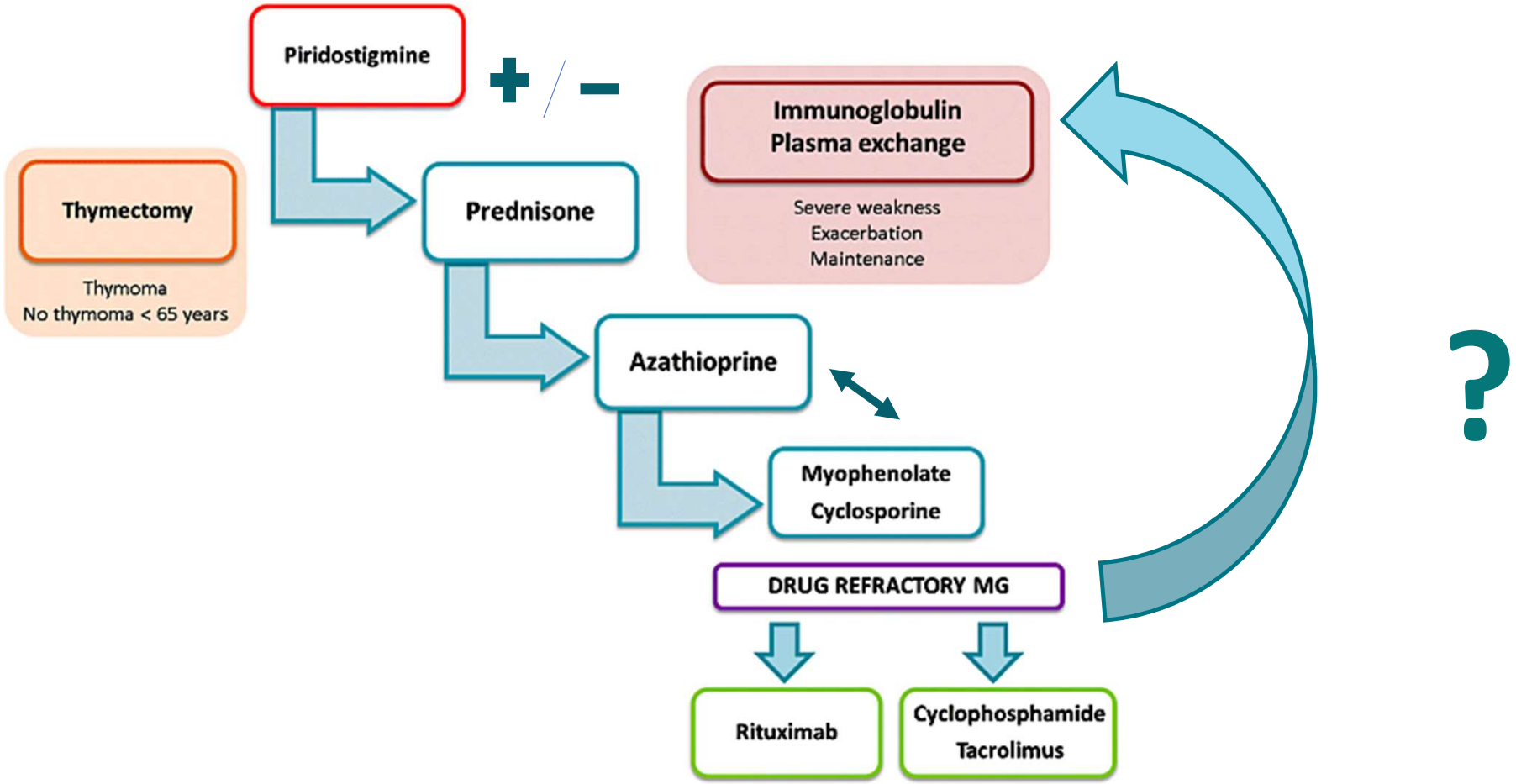
> J Clin Neuromuscul Dis. 2011 Sep;13(1):46-52. doi: 10.1097/CND.0b013e31821c5634.

Ocular myasthenia gravis in an academic neuro-ophthalmology clinic: clinical features and therapeutic response

Manoj Kumar Mittal [1], Richard J Barohn, Mamatha Pasnoor, April McVey, Laura Herbelin, Thomas Whittaker, Mazen Dimachkie

- 147 OMG w diplopia (*Kupersmith et al*)
- **36%** progressed to gMG **not on pred** (13 of 36 pts) vs **7% on pred** (4 of 58 pts)
  - 2 yr FU
- Another retrospective study (*Mittal et al*): pyridostigmine alone in 59 of 97 OMG pts
  - 12 developed gMG, ***0 of 38 pred-treated cases developed gMG***

Traditional IST	General statement
Azathioprine	• Expert consensus & multiple RCT support *as **1st line***
Mycophenolate Mofetil	• Not supported by RCT, **widely used**
Cyclosporine/ Tacrolimus	• Not widely used • Works faster, more monitoring/side effects
Methotrexate	• Not widely used, not supported by RCT
Rituximab	• Refractory dz, BEAT-MG trial didn't show steroid-sparing effect for AchR+, helpful for MuSK+
PLEX/IVIG	• Used for exacerbation/crisis • Also used for bridge or maintenance therapy



Cortés-Vicente *et al.* Myasthenia Gravis Treatment Updates. *Curr Treat Options Neurol,* Jul 2020

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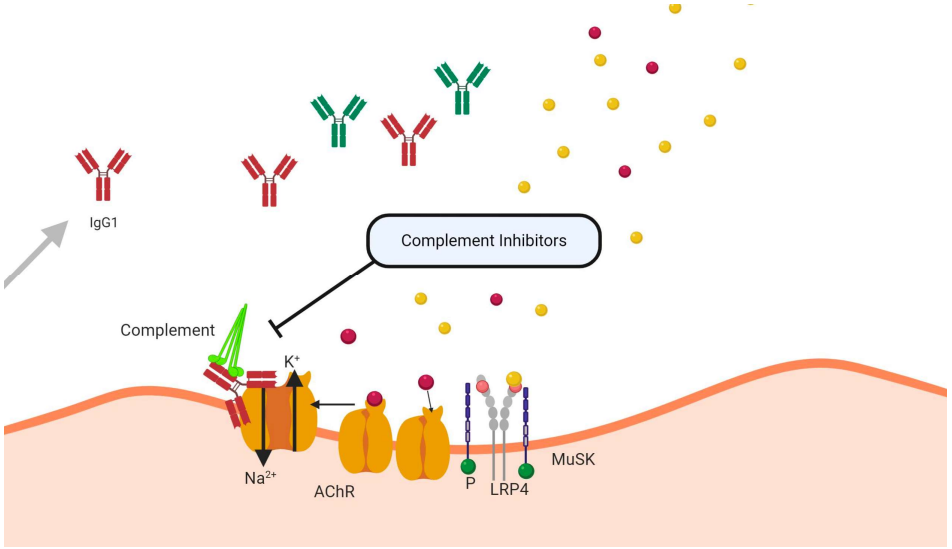
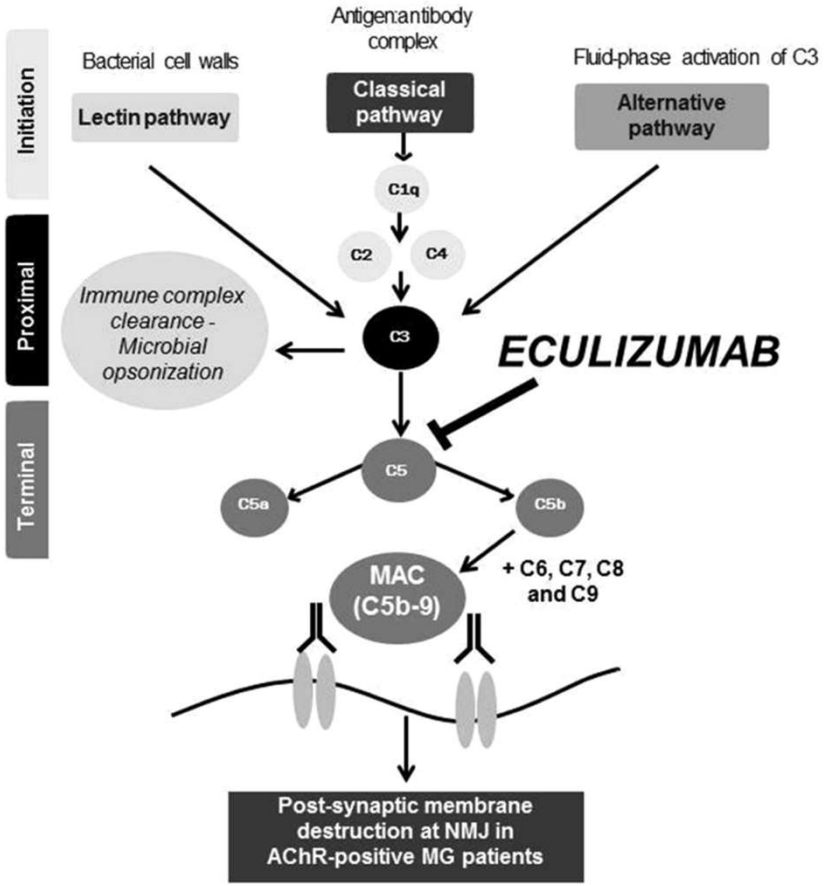
Complement inhibition

Eculizumab: 1st FDA approved treatment for AchR+ gMG (2017)





MG-ADL

- Validated outcome measure
- Simple 8 question survey of MG sx
- Easy to administer, correlates well with physician assessments
  - Most of the time…

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				Total Score:	

Physician Reported Outcome Measures

QMG Scale[1]

Test Item	None	Mild	Moderate	Severe
Grade	**0**	**1**	**2**	**3**
Double vision on lateral gaze Right or left (circle one), seconds	61	11-60	1-10	Spontaneous
Ptosis (upward gaze)	61	11-60	1-10	Spontaneous
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete
Swallowing 4 oz water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9
Right arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9
Left arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9
Forced vital capacity	≥80	65-79	50-64	≤50
Right-hand grip, kg Men Women	 ≥45 ≥30	 15-44 10-29	 5-14 5-9	 0-4 0-4
Left-hand grip, kg Men Women	 ≥35 ≥25	 15-34 10-24	 5-14 5-9	 0-4 0-4
Head lifted (45 degrees supine), seconds	120	30-119	1-29	0
Right leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0
Left leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0

MG composite scale

Ptosis, upward ease (physician examination)	>45 seconds = 0	11-45 seconds = 1	1-10 seconds = 2	Immediate = 3
Double vision on lateral Gaze, left or right (physician examination)	>45 seconds = 0	11-45 seconds = 1	1-10 seconds = 3	Immediate = 4
Eye closure (physician examination)	Normal = 0	Mild weakness (can be forced open with effort) = 0	Moderate weakness (can be forced open easily) = 1	Severe weakness (unable to keep eye closed) = 2
Talking (patient history)	Normal = 0	Intermittent slurring or nasal speech = 2	Constant slurring or nasal but can be understood = 4	Difficult to understand speech = 6
Chewing (patient history)	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6
Swallowing (patient history)	Normal = 0	Rare episode of choking or trouble swallowing = 2	Frequent trouble swallowing, for example necessitating change in diet = 5	Gastric tube = 6
Breathing (thought to be caused by MG)	Normal = 0	Shortness of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9
Neck flexion or extension (weakest) (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (i.e., ~50% weak, ±15%) = 3	Severe weakness = 4
Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4	Severe weakness = 5
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15%) = 4	Severe weakness = 5

Clinical Trial > Lancet Neurol. 2017 Dec;16(12):976-986.
doi: 10.1016/S1474-4422(17)30369-1. Epub 2017 Oct 20.

Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study

James F Howard Jr [1], Kimiaki Utsugisawa [2], Michael Benatar [3], Hiroyuki Murai [4], Richard J Barohn [5], Isabel Illa [6], Saiju Jacob [7], John Vissing [8], Ted M Burns [9], John T Kissel [10], Srikanth Muppidi [11], Richard J Nowak [12], Fanny O'Brien [13], Jing-Jing Wang [13], Renato Mantegazza [14]; REGAIN Study Group

Collaborators, Affiliations + expand

PMID: 29066163 DOI: 10.1016/S1474-4422(17)30369-1

Primary efficacy endpoint:
change from baseline to wk 26 in MG-ADL total score

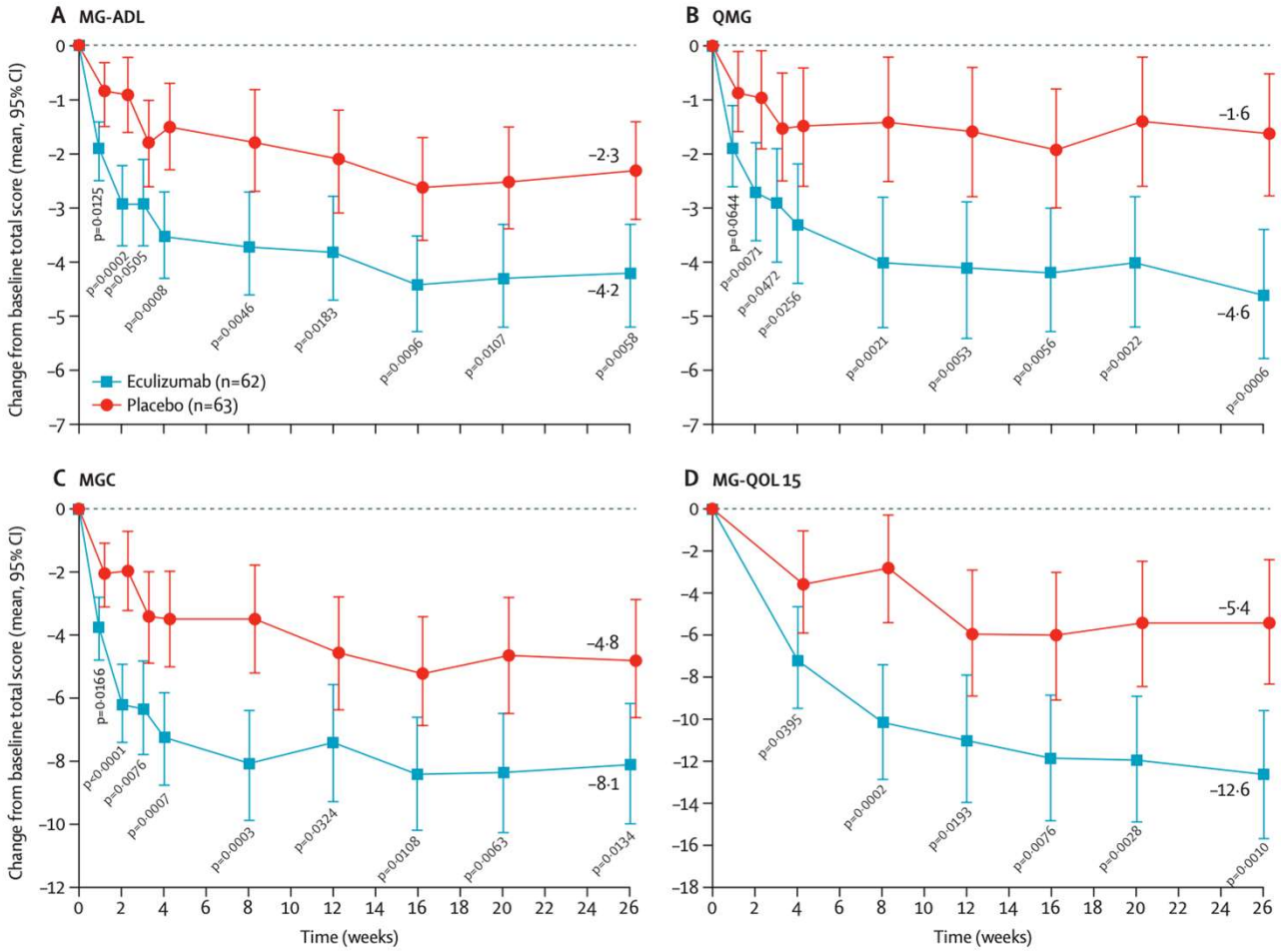
Inclusion Criteria

- 18 yrs
- **MG-ADL ≥ 6**
- MGFA class II-IV
- *N. meningitides* vaccine
- Previous tx with ≥2 IST or 1 IST + chronic IVIG or PLEX for 12 mon without sx control

Exclusion Criteria

- Hx of thymoma/thymic neoplasms
- Thymectomy within 12 mon before screening
- IVIG or PLEX within 4 wks before randomization
- Rituximab within 6 mon before screening

- 1:1 randomization - IV eculizumab vs IV matched placebo
- Maintenance q 2 wks (after weekly infusions x 5)



REGAIN: results

4.2-point improvement in mean MG-ADL score from baseline → wk 26 in Eculizumab group vs **2.3-pt** placebo (*p*=0.006)

4.6-point improvement in mean QMG score from baseline → wk 26 in Eculizumab group vs **1.6-pt** placebo (*p*=0.0006)

Criteria for response: improvement of ≥3 pts MG-ADL or ≥ 5 pts in QMG

↳ Both exceed the minimal clinically important difference accepted (≥2 pts MG-ADL, ≥3 pts QMG)

Howard et al. *The Lancet. Neurology.* 2017

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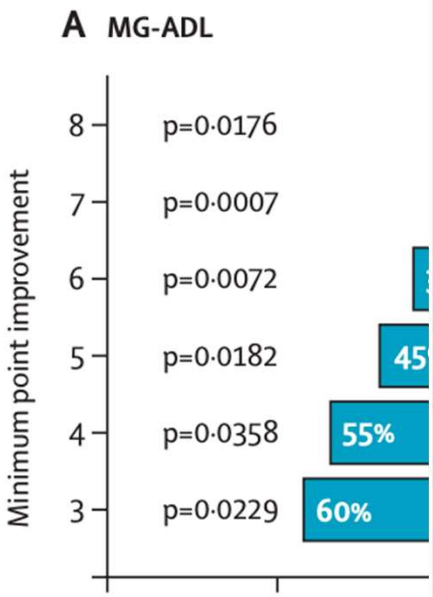
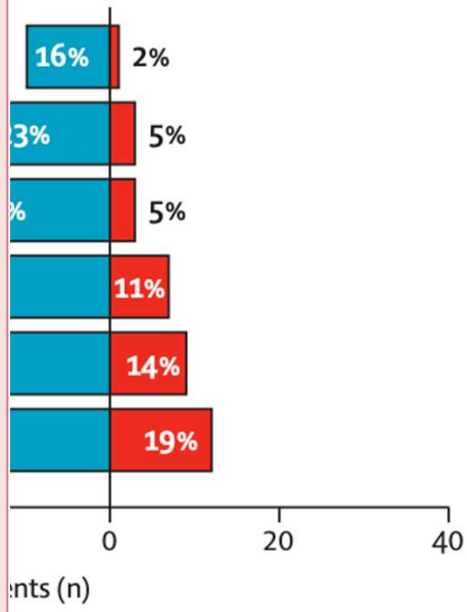
REGAIN – pre



	Eculizumab (n=62)	Placebo (n=63)	Total (n=125)
Admissions to hospital	9 (15%)	18 (29%)	27 (22%)
Discontinuations because of adverse events	4 (6%)	0	4 (3%)
Patient reports of myasthenia gravis exacerbations	6 (10%)	15 (24%)	21 (17%)
Rescue therapy used during the 26-week treatment period	6 (10%)	12 (19%)	18 (14%)
High-dose corticosteroids	0	5 (8%)	5 (4%)
Plasmapheresis or plasma exchange	3 (5%)	4 (6%)	7 (6%)
Intravenous immunoglobulin	4 (6%)	6 (10%)	10 (8%)
Other	1 (2%)	2 (3%)	3 (2%)
Most common adverse events* (≥10% in either group)			
Headache	10 (16%)	12 (19%)	22 (18%)
Upper respiratory tract infection	10 (16%)	12 (19%)	22 (18%)
Nasopharyngitis	9 (15%)	10 (16%)	19 (15%)
Nausea	8 (13%)	9 (14%)	17 (14%)
Diarrhoea	8 (13%)	8 (13%)	16 (13%)
Myasthenia gravis	6 (10%)	11 (17%)	17 (14%)

Data are n (%). Reports of myasthenia gravis exacerbations and crises were also reported separately from adverse events and serious adverse events. Common adverse events and serious adverse events were reported by the physician in accordance with their clinical discretion. Investigators were not required to report each myasthenia gravis exacerbation as an adverse event under the term myasthenia gravis unless it was a serious adverse event. *Preferred term in the Medical Dictionary for Regulatory Activities.

***Table* 3: Treatment-emergent safety outcomes in all treated patients**



Howard et al. *The Lancet. Neurology.* 2017

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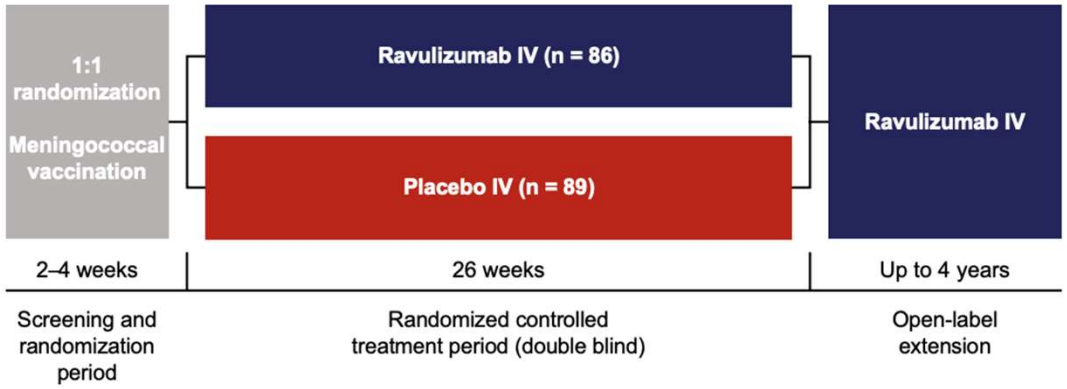
Ravulizumab

- Complement inhibitor
- *Engineered to maintain therapeutic serum concentrations over a longer dosing interval*
- Phase III CHAMPION-MG trial, OLE
- Single weight-based loading dose day 1 → weight-based maintenance dosing day 15 → **every 8 wks**
- Primary endpoint: change from baseline MG-ADL total score wk 26
- ***Did not have to be refractory to prior treatments***

CHAMPION trial

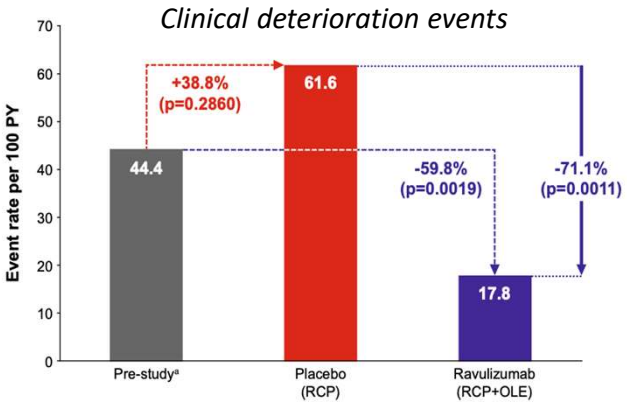
175 pts enrolled

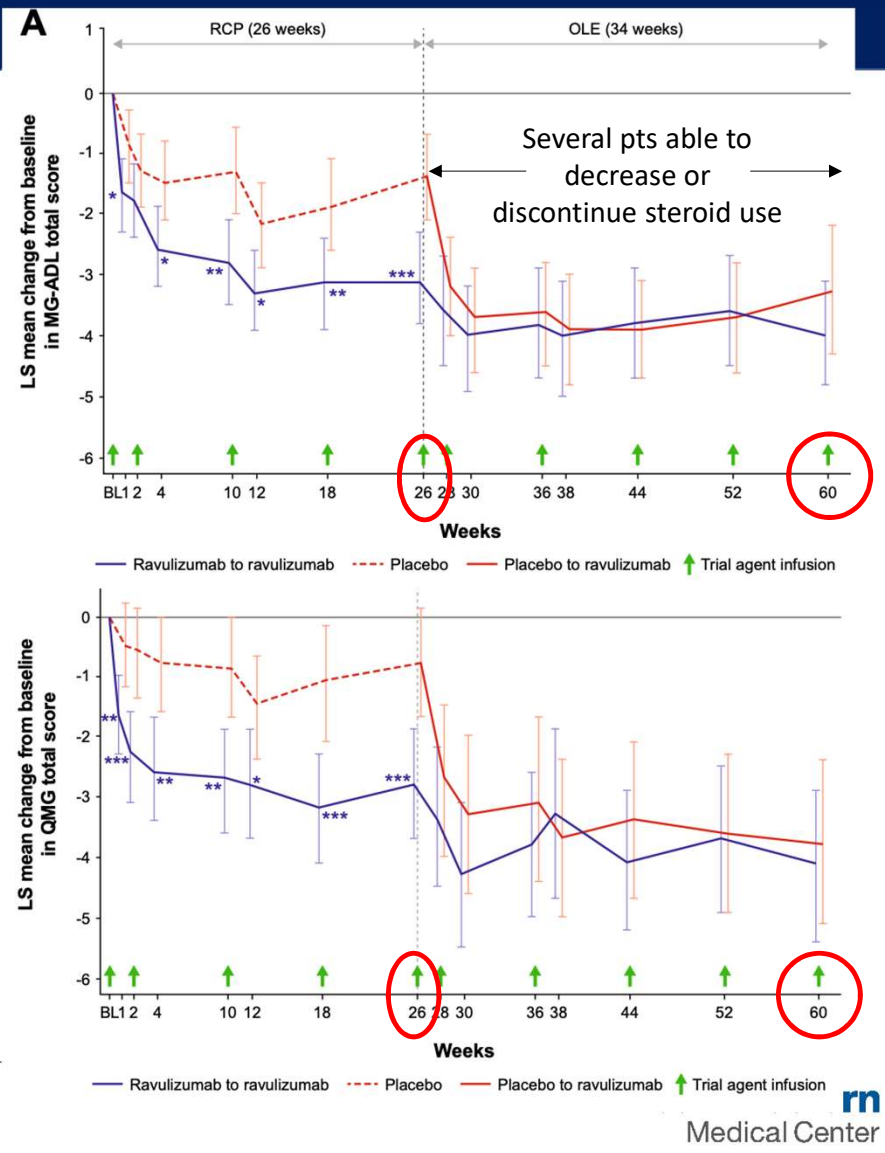


Criteria for response: improvement of ≥3 pts on MG-ADL or ≥ 5 pts in QMG score

Ravulizumab

- Significantly improved score from baseline to wk 26 in both MG-ADL + QMG scores in Rava group
  - MG-ADL [−3.1 vs. −1.4; *p<0.001*]
  - QMG [−2.8 vs. −0.8; *p<0.001*]
- Improvements in both measures occurred within **1 wk** of initiation, sustained through wk 26
- **QMG score improved by ≥5 pts** in a significantly greater proportion of Rav-treated pts vs placebo (**30.0**% vs. 11.3%; *p*
- Abd pain, dizziness, at a higher rate in R extension)





rn Medical Center

Clinical Trial > Lancet Neurol. 2023 May;22(5):395-406.
doi: 10.1016/S1474-4422(23)00080-7.

Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study

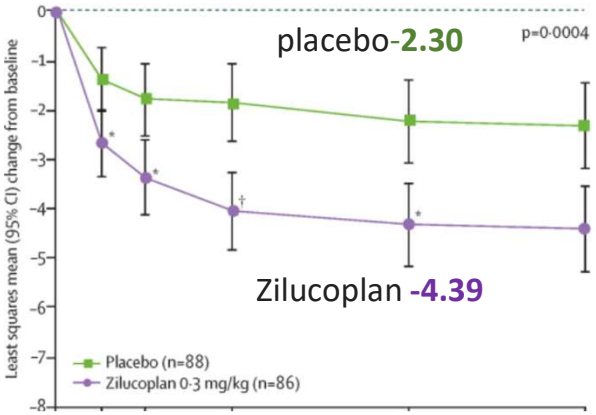
James F Howard Jr [1], Saskia Bresch [2], Angela Genge [3], Channa Hewamadduma [4], John Hinton [5], Yessar Hussain [6], Raul Juntas-Morales [7], Henry J Kaminski [8], Angelina Maniaol [9], Renato Mantegazza [10], Masayuki Masuda [11], Kumaraswamy Sivakumar [12], Marek Śmiłowski [13], Kimiaki Utsugisawa [14], Tuan Vu [15], Michael D Weiss [16], Małgorzata Zajda [17], Babak Boroojerdi [18], Melissa Brock [19], Guillemette de la Borderie [20], Petra W Duda [21], Romana Lowcock [22], Mark Vanderkelen [23], M Isabel Leite [24]; RAISE Study Team

RAISE (MG0010) study investigators
Jeffrey Allen, Thomas Arnold, Marta Banach, Krzysztof Banaszkiewicz, Gelasio Baras, Alexandru Barboi, Said Beydoun, Cynthia Bodkin, Saskia Bresch, Mark Bromberg, Urszula Chyrchel-Paszkiewicz, Elena Cortés-Vicente, Kazushi Deguchi, Sophie Demeret, Amelia Evoli, Constantine Farmakidis, Miriam Freimer, Solange Kapetanovic Garcia, Angela Genge, Anthony Geraci, Nils Erik Gilhus, Raghav Govindarajan, Jeff Guptill, Ali A Habib, Channa Hewamadduma, John Hinton, James F Howard Jr, Yessar Hussain, Jan Ilkowski, Sarah Jones, Raul Juntas-Morales, Henry J Kaminski, Jonathan Katz, Shaida Khan, Bhupendra Khatri, Agata Kłósek, Shingo Konno, Klaudiusz Kumor, Dale Lange, M Isabel Leite, Yuebing Li, Kore Liow, Robert Lisak, Angelina Maniaol, Renato Mantegazza, Masayuki Masuda, Jonathan McKinnon, Naoya Minami, Hiroyuki Murai, Aleksandra Nadaj-Pakleza, Michael Nicolle, Richard Nowak, Michael Rivner, Katherine Ruzhansky, Amit Sachdev, Jens Schmidt, Mark Sivak, Kumaraswamy Sivakumar, Marek Śmiłowski, Marco Spinazzi, Shigeaki Suzuki, Yasushi Suzuki, Mariola Świderek-Matysiak, Andrzej Szczudlik, Masanori Takahashi, Celine Tard, Akira Tsujino, Kimiaki Utsugisawa, Akiyuki Uzawa, Tuan Vu, Michael D Weiss, Sharon Yegiaian, Małgorzata Zajda, Tomasz Zielinski, and Ulf Ziemann.

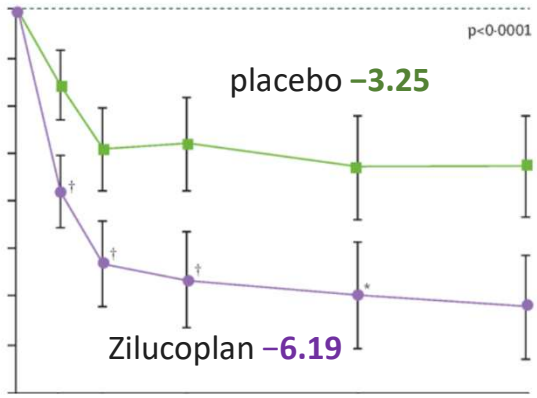
- Daily SQ injection - little peak to trough, steadier levels
- **Small molecule peptide (3.5 kDa**, 15–amino acid) **- 40 x smaller than IgG**
- Eculizumab/Ravalizumab: humanized monoclonal Ab - molecular weight of ~**148 kDa**
- Binds to C5 (*and C5b*) w high affinity & specificity

https://www.rarediseaseadvisor.com/therapies

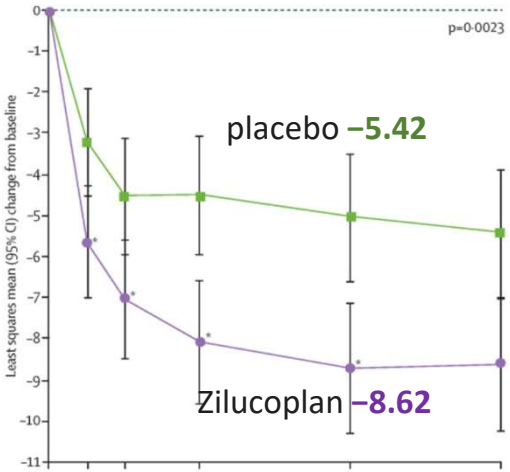
MG-ADL – *primary endpoint*



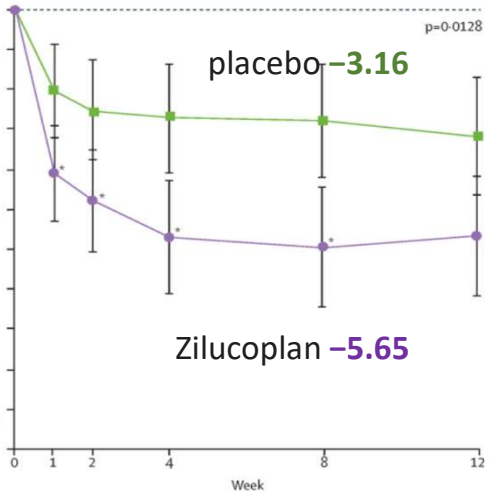
QMG score



MGC score



MG-QOL15 score



Zilucoplan - RAISE

- Achieves significant clinical improvements **within 1 wk** → *sustained 12 wks*
- TEAE's same
- Gives evidence for complement inhibition in a **broader population of pts**
  - Earlier in dz course, didn't have to fail prior therapies, inclusive of pts with Hx of thymoma
- **C5 inhibition given earlier in course could reduce need for more invasive treatments**
  - Shown by reduction of rescue therapy need in zilucoplan arm

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More than two decades of UTSW research paves way for first-in-kind drug

January 03, 2022

> Nat Biotechnol. 2005 Oct;23(10):1283-8. doi: 10.1038/nbt1143. Epub 2005 Sep 25.

Engineering the Fc region of immunoglobulin G to modulate in vivo antibody levels

Carlos Vaccaro [1], Jinchun Zhou, Raimund J Ober, E Sally Ward

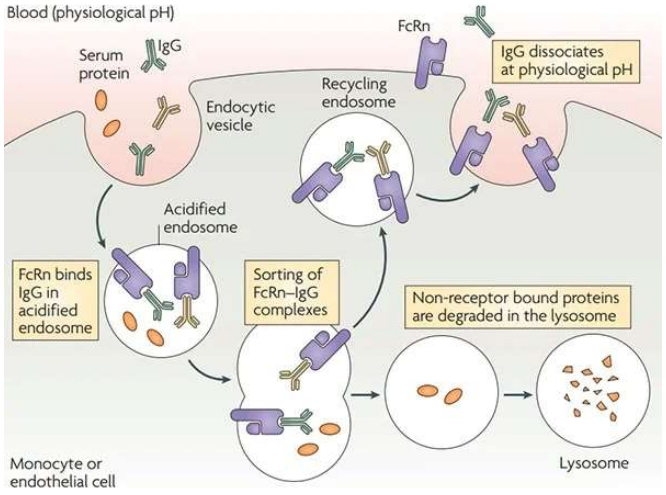
Affiliations + expand

PMID: 16186811 DOI: 10.1038/nbt1143

Review > Mol Immunol. 2015 Oct;67(2 Pt A):131-41. doi: 10.1016/j.molimm.2015.02.007. Epub 2015 Mar 9.

Targeting FcRn for the modulation of antibody dynamics

E Sally Ward [1], Siva Charan Devanaboyina [2], Raimund J Ober [3]



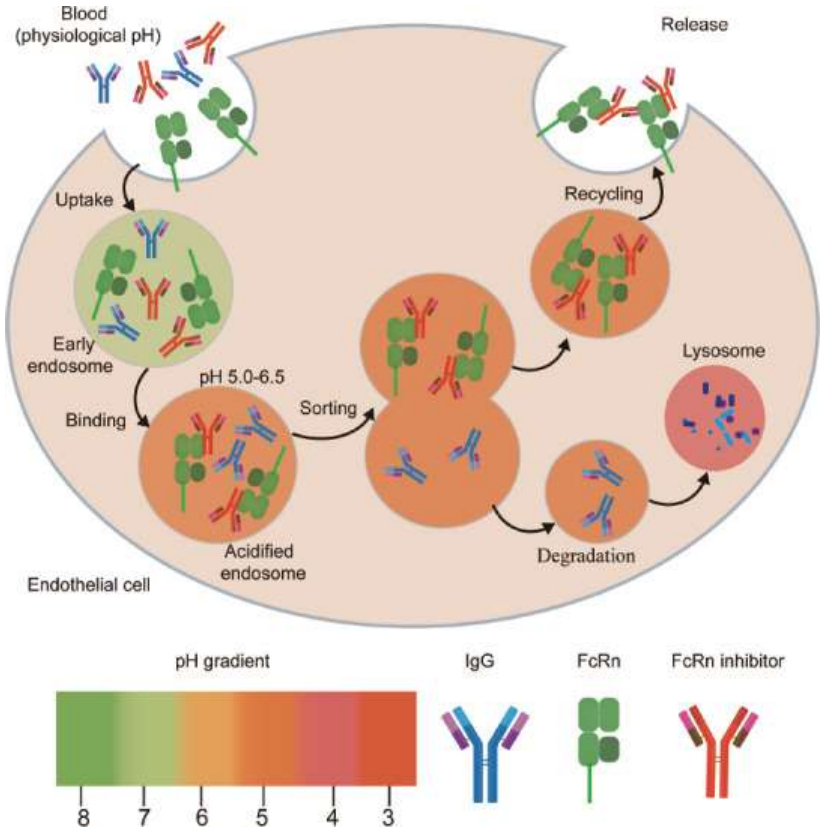
https://www.news-medical.net/whitepaper/20211110/FcRn-and-its-role-as-a-therapeutic-target.aspx

FcRN extends half life of IgG - allowing IgG to "escape" lysosomal degradation

E. Sally Ward, Ph.D., at UT Southwestern in 2004

Efgartigimod

- First-in-class - IgG Fc fragment
- Designed to binds to FcRn, *reducing circulating IgG Ab levels*
  - **Blocks the IgG recycling process**
- Does <u>not</u> affect adaptive or innate immune systems
  - Given specificity of MOA, *many side effects associated with immunosuppression could be avoided*
- FcRN: *one* of the targets of IVIG



Zhu et al. Neural Regen Res, 2023

2 weeks

Screening period
1:1 randomization

N=167

Weeks 0-3

Treatment cycle
1 dose per wk x 4 wks

Dose 1 | Dose 2 | Dose 3 | Dose 4

Efgartigimod + current Tx
10mg/kg IV (n=84)

Treatment cycle
1 dose per wk x 4 wks

Dose 1 | Dose 2 | Dose 3 | Dose 4

Placebo + current Tx
10mg/kg IV (n=83)

Weeks 4-8

Weekly evaluations

Primary endpoint:
# of AChR-Ab+ who achieved MG-ADL ≥2 pt improvement for ≥4 consecutive wks

Assessed by **wk 8**

Weeks 9-26

Subsequent treatment cycles if needed

Up to 2 subsequent treatment cycles, based on clinical evaluation

ADAPT

Mean age: **46**
Female: **75%**
AchR Ab (+): **n=65/84**
Mean baseline MG-ADL: **9** (both arms)
Mean QMG: **16** (both arms)
MGFA II (mild): 40%
MGFA III (mod): 56%
MGFA IV (severe): 4%

Highlights of ADAPT

68%

of AChR-Ab+ pts treated with efgart ***achieved primary endpoint*** compared with **29.7% on placebo** *(p<0.0001)*

63%

of AChR-Ab+ pts pts **responded to efgart on QMG score** compared with **14.1% on placebo** *(p<0.0001)*

40%

of AChR-Ab+ pts treated with efgart **achieved minimal symptom expression (MG-ADL 0 or 1)**, vs **11% placebo**

Remember mean MG-ADL = 9

- *Clinical responses were also observed in seronegative pts*
- Well-tolerated, safety profile comparable to placebo

SC FcRN - Efgartigimod alfa

2 weeks

Screening period
1:1 randomization

N=110

Weeks 0-3

Treatment cycle
1 dose per wk x 4 wks

Dose 1 | Dose 2 | Dose 3 | Dose 4

Efgartigimod alfa + current Tx
1,008mg Efgartigimod alfa/11,200 hyaluronidase SC injection (n=55)

Weeks 4-10

Subsequent evaluations

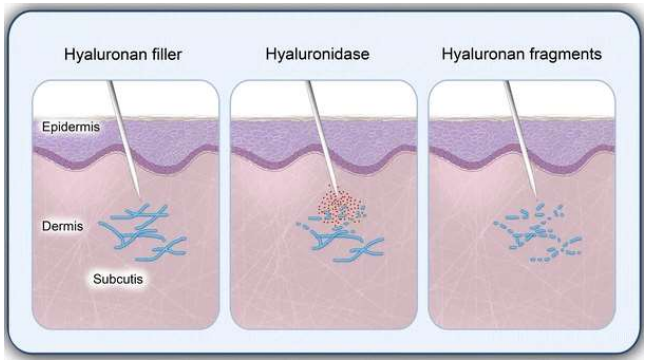
PD endpoint assessed at **week 4** (day 29)

Treatment cycle
1 dose per wk x 4 wks

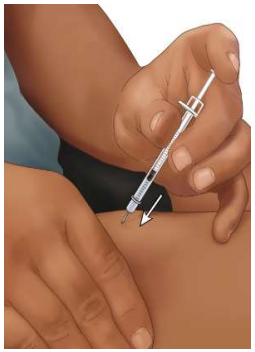
Dose 1 | Dose 2 | Dose 3 | Dose 4

Efgartigimod + current Tx
10mg/kg IV (n=55)

- Clinical trial bridging study: Efgartigimod IV & Efgartigimod alfa SC (non-inferiority study)
- Essentially, outcomes same btwn both studies (MG-ADL, QMG, MSE) as well as SE except injection site reaction (38% in SC group vs 1.8% in IV group)
- 6 mL injection, administered over **30 - 90 sec**



Buhren *et al. Eur J Med Res,* 2016



Uptodate.com

UT Southwestern Medical Center

Clinical Trial > Lancet Neurol. 2023 May;22(5):383-394.
doi: 10.1016/S1474-4422(23)00077-7.

Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study

Vera Bril [1], Artur Drużdż [2], Julian Grosskreutz [3], Ali A Habib [4], Renato Mantegazza [5], Sabrina Sacconi [6], Kimiaki Utsugisawa [7], John Vissing [8], Tuan Vu [9], Marion Boehnlein [10], Ali Bozorg [11], Maryam Gayfieva [12], Bernhard Greve [10], Franz Woltering [10], Henry J Kaminski [13]; MG0003 study team

*9 wks (63 days)

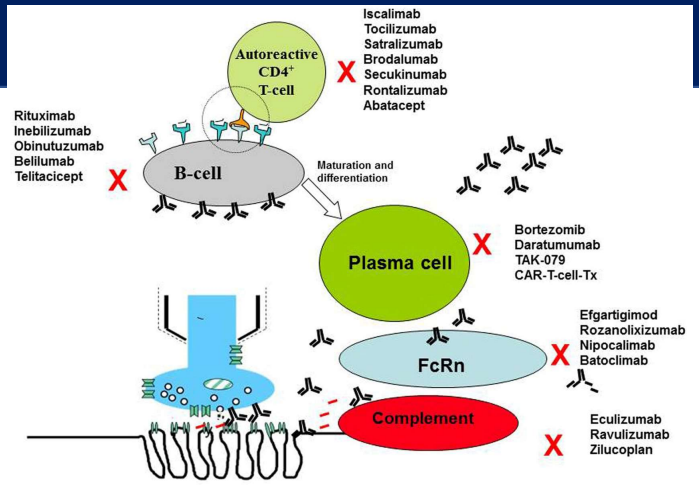
*Minimum length of time btwn start of treatment cycles

Rozanolixizumab

- SC IgG 4 mAB (not fragment), ~15 min infusion
- Approved for AchR **and MuSK+ pts**
- 200 pts enrolled; 1:1:1 (90% AchR, 10% MuSK)
- Reductions in MG-ADL score from baseline → day 43 were greater in the Roz 7 mg/kg group (mean change **–3.37**) & Roz 10 mg/kg group **(–3.40)** than with placebo **(–0.78)**
- Most frequent TEAEs: HA & pyrexia (diarrhea, equivalent to placebo)
- Equivalent serious TEAE – 8 % Roz 7 mg/kg group, 10% in Roz 10 mg/kg group, 9% placebo
- No deaths occurred

DISCUSSION

- Complement vs FcRN – which one, when?
- *What approach can induce **remission**?*
- Combo treatments?
- When should immunosuppression be weaned?
- Predictive biomarkers for disease activity and/or treatment response? Ocular → gMG – conversion prediction?
  - Currently, treatment based only on clinical status + responses to treatment
- COST

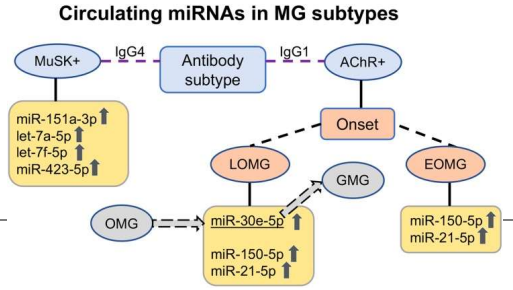


Schneider-Gold et al, *Therapeutic Advances in Neurological Disorders*, 2021

Front Immunol. 2020; 11: 213. PMCID: PMC7065262
Published online 2020 Mar 4. doi: 10.3389/fimmu.2020.00213 PMID: 32194544

Circulating miRNAs as Potential Biomarkers in Myasthenia Gravis: Tools for Personalized Medicine

Liis Sabre,[1,2,†] Tanel Punga,[3,†] and Anna Rostedt Punga[2,*]



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