MYASTHENIA GRAVIS: SUBGROUP CLASSIFICATION & THERAPEUTIC STRATEGIES

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TEACHING COURSE: TC 12 - October 29, 2019

14:30 - 16:00 SHEIKH MAKTOUM B

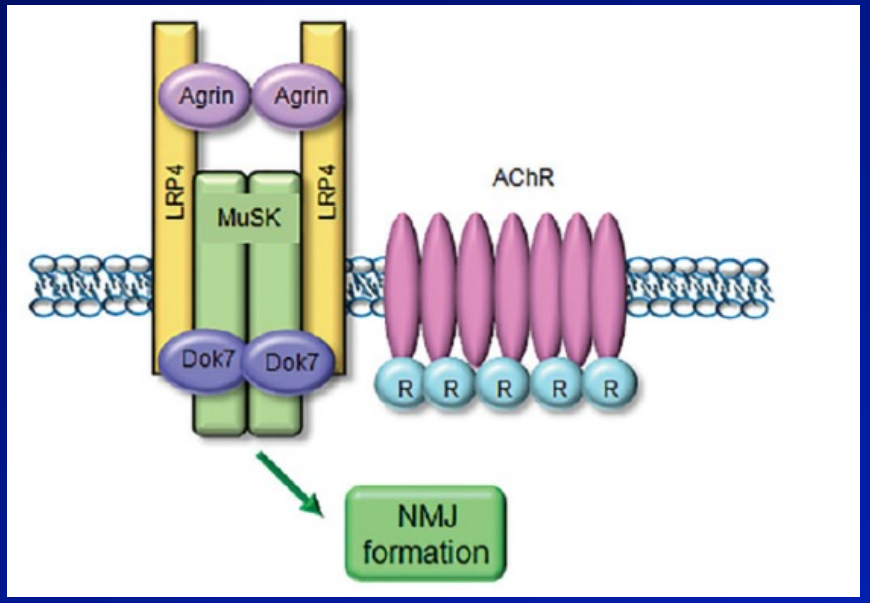
Dr. Dimachkie recently served as a consultant or on the speaker's bureau for Alnylam, Audentes, CSL-Behring, Sanofi Genzyme, Momenta, NuFactor, RMS Medical, Shire Takeda and Terumo. Dr. Dimachkie received grants from Alexion, Alnylam Pharmaceuticals, Amicus, Biomarin, Bristol-Myers Squibb, Catalyst, CSL-Behring, FDA/OPD, GlaxoSmithKline, Genentech, Grifols, MDA, NIH, Novartis, Genzyme, Octapharma, Orphazyme, UCB Biopharma, Viromed and TMA.

Objectives

- Identify specific and non–specific antibodies in MG
- Describe the presentation and treatment of MG based on Ab status
- Review current evidence of therapy in MG
- Explore ongoing clinical research trials in MG
- Summarize a treatment approach to MG

Clinically Useful Antibodies in Autoimmune Myasthenia Gravis

- Appel lab (1974)
  - AChR Ab Found in MG Pts
- Rødgaard et al (1987)
  - AChR Ab are IgG1 > IgG3
- Vincent lab (2001)
  - MuSK Ab to muscle specific tyrosine kinase – IgG4 Ab
  - 40% of AchR Ab-
  - interferes with binding of LRP4 to MuSK
- Vincent (2008): IgG1 Ab to rapsyn-clustered AChR in 66% of AChR Ab-
- Higuchi et al. (2011); Pevzner et al. (2012); Zhang et al. (2012)
  - LRP4 Antibodies – 10 to 13% of double negative MG (10% of ALS)
  - IgG1 > IgG2 & IgG3

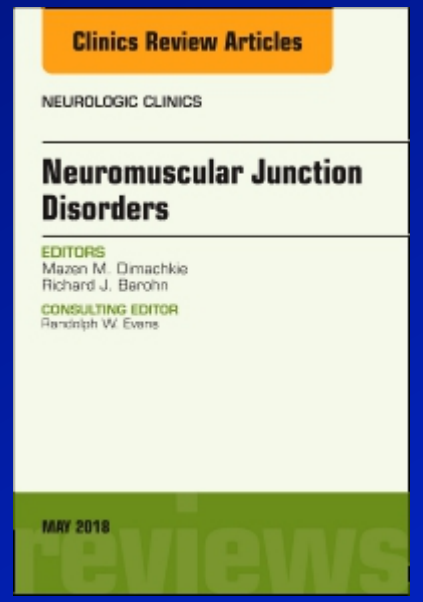


Ann N Y Acad Sci. 2018 Feb;1413(1):126-135

Neurol Clin. 2018 May;36(2):261-274
Neurol Clin. 2018 May;36(2):293-310

Limited Usefulness Antibodies in Autoimmune Myasthenia Gravis

- Antistriational Ab - does not replace the need for chest CT for thymoma detection
- Titin in seronegative - milder disease and are responsive to therapy
- Kv1.4 in Japan – Myocarditis & QT prolongation
- Agrin - mostly with other MG Ab (14 isolated cases)
- Rapsyn Ab – significance unclear in MG – non-specific
- Cortactin Ab – significance is unclear in MG:
  - 28/250 MG cases (201 AChR, 11 MuSK) – milder MG
  - 9 DNMG had cortactin Ab
  - 19 AChR+ had cortactin Ab - 9.5% of MG AChR+



Neurol Clin. 2018 May;36(2):293-310

Acetylcholine Receptor Antibody (AChR Ab)

- Most specific test for MG
- If positive, no other dx tests needed (usually)
- % positive: 85% Gen MG vs 50% Ocular MG
- "Binding" RIA most useful dx test
  - NL < 0.03 to 0.5 nmol/l
- "Blocking"/ "Modulating" Assays – add little to dx sensitivity:
  - very rarely present in the absence of AChR-binding Ab
  - 3–4% of AChR-binding Ab-
- Ab correlates poorly with disease severity

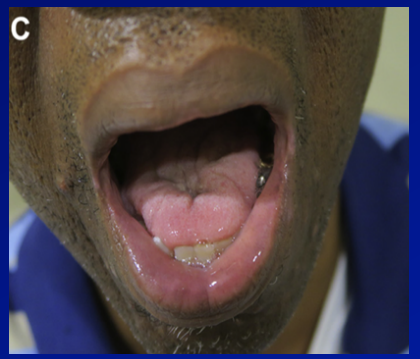
Neurol Clin. 2018 May;36(2):261-274

AChR Ab+ MG
Pattern of Onset

- Fluctuating symptoms; younger women; older men
- Ocular only MG 40%, 1/8 - 1/3 remain ocular:
  - Almost all MG pts develop ocular sxs within 1st year
  - If still ocular only at 1 yr, 84% chance to remain ocular
- Generalized MG (with ocular) 35%
- Bulbar MG (dysphagia, dysarthria) 15%
- MG confined to limbs 10%
- Respiratory failure < 1 %:
  - 15-20% MG crisis later on

Neurol Clin. 2018 May;36(2):253-260

Muscle Specific Tyrosine Kinase (MuSK) MG Presentations



- More women; more in Blacks; ocular symptoms are less prominent
- Three forms of MuSK (muscle specific tyrosine kinase) MG:
  - indistinguishable from AChR+ MG but more generalized muscle weakness
  - more focal with neck (head drop), shoulder & respiratory muscle weakness
  - severe with prevalent bulbar weakness, tongue fascis & respiratory crises
- Responds to prednisone, immunosuppressants and less likely to respond to anticholinesterase drugs
- Responds to PLEX or rituximab, lesser to IVIg
- Thymectomy may not be associated with clinical improvement

Illa et al. 2005; Lee et al. 2006; Ohta et al. 2007; Evoli et al. 2008; Chang et al. 2009; Guptill & Sanders, 2010; Clifford 2019; Neurol Clin. 2018 May;36(2):293-310

Lipoprotein receptor-related protein 4 (LRP4) Phenotype

- More in women than men; lower frequency in Asians
- Interacts with Agrin and activates MuSK to promote AChR clustering
- Often no decrement on RNS and jitter lesser frequently abnormal
- Thymus pathology usually not present but has been described including thymoma
- Generally presents similarly to AChR antibody+ MG but:
  - Milder or ocular MG (but this is being challenged)
  - Some are MGFA grade III or IV
- Respiratory dysfunction in most is mild - respiratory failure rare
- Most respond to pyridostigmine, steroids and immunosuppressants like other MG patients

Neurol Clin. 2018 May;36(2):293-310

MG Rx: Clinical Trials

50 years 1964 to 2008

1. Mount 1964 – ACTH vs. placebo
2. Howard 1976 – Alt day pred vs. placebo*
3. **Tindall 1987 – CSA vs. placebo/virgin pts***
4. **Tindall 1993 – CSA vs. placebo/IS pts***
5. **Gajdos 1997 – PE vs. IVIg**
6. **Lindberg 1998 – Pulse methylpred vs. placebo***
7. **Palace 1998 – Aza/pred vs. aza/placebo***
8. Wolfe 2002 – IVIg vs. placebo*
9. Meriggioli 2003 – MM vs. placebo*
10. **Gajdos 2005 – IVIg-2 doses***
11. **Nagane 2005 – Tacrolimus vs. placebo**
12. Sanders/MSG 2007 – MM vs. placebo*
13. Aspreva-unpublished – MM vs. placebo*
14. **Zinman 2007 – IVIg vs. placebo***
15. **Soliven 2008 – Terbutaline vs. placebo***

Last Decade

16. **Barth 2011: IVIg vs. PE***
17. **Heckmann 2011: MTX vs. Aza***
18. **Howard 2013: Eculizumab vs placebo***
19. Pasnoor 2016: MTX vs. placebo*
20. **Wolfe 2016 – Thymectomy (single blind)**
21. **Howard 2016 – Eculizumab vs placebo Phase 3***
22. Nowack 2018: Rituximab vs. placebo*
23. **Bonanno 2018: Amifampridine vs. placebo in MuSK***
24. Hewett 2019 - Belimumab vs PBO*
25. **Howard 2019: Efgartigimod vs. placebo***

*** Or * Blinded**

Yellow Bold Positive trials

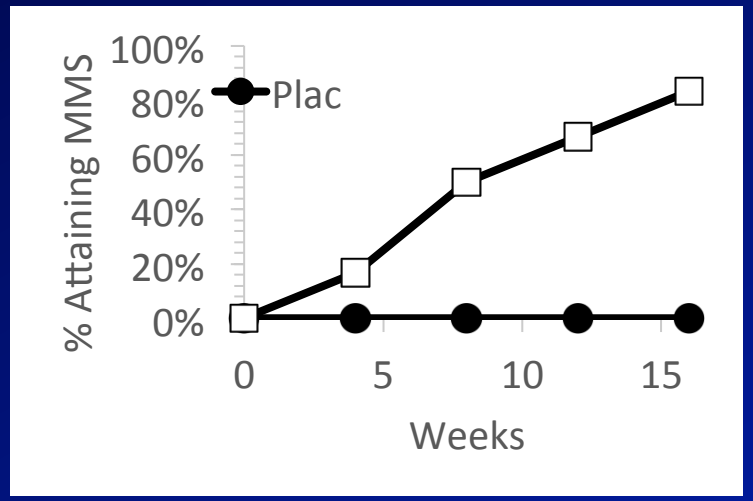
Prednisone Rx for MG

- High Dose
  - 60 to 100 mg/day x 2 weeks
  - Then 60 to 100 mg qod until much better
  - Then taper 5 mg q 2 wks
  - May require initial inpatient admission if severe MG or bulbar MG
- Low / Slow Approach
  - Seybold & Drachman 1974
  - Gradual increase to avoid initial worsening
  - 10 mg/day; increase by 10 mg q 5-7 days
  - Then switch to qod
- In-between Approach
  - Mycophenolate trial protocol
    - Pred 20 mg/day

- No randomized trial of prednisone in general MG, but it works!
- Probably most effective drug for MG
  - Even given potential side effects

Neurol Clin. 2018 May;36(2):311-337

Remission in Ocular MG



- Planned 88 patients
- 11 randomized (6 pred/5 plac)
- Up to 60 mg/day
- Failure to reach remission
  - 100% PLAC
  - 17% PRED
- NNT 1.2

EFFICACY OF PREDNISONE FOR THE TREATMENT OF OCULAR MYASTHENIA (EPITOME): A RANDOMIZED, CONTROLLED TRIAL

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ABSTRACT: *Introduction:* In this study we evaluated the safety, tolerability, and efficacy of prednisone in patients with ocular myasthenia gravis (OMG) concurrently treated with pyridostigmine. *Methods:* This investigation was a randomized, double-blind, placebo-controlled trial. Participants whose symptoms failed to remit on pyridostigmine were randomized to receive placebo or prednisone, initiated at 10 mg every other day, and titrated to a maximum of 40 mg/day over 16 weeks. The primary outcome measure was treatment failure. *Results:* Fewer subjects were randomized than the 88 planned. Of the 11 randomized, 9 completed 16 weeks of double-blind therapy. Treatment failure incidence was 100% (95% CI 48%–100%) in the placebo group ($n = 5$) vs. 17% (95% CI 0%–64%) in the prednisone group, $P = 0.02$ ($n = 6$). Median time to sustained minimal manifestation status (MMS) was 14 weeks, requiring an average prednisone dose of 15 mg/day. Adverse events were infrequent and generally mild in both groups. *Conclusions:* A strategy of low-dose prednisone with gradual escalation appears to be safe, well-tolerated, and effective in treating OMG.

Muscle Nerve **53**: 363–369, 2016

Myasthenia gravis (MG) is a generalized disorder that often manifests initially as focal weakness. The most common focal presentation involves weakness of the extraocular muscles, eyelid elevators, and orbicularis oculi, with symptoms of ptosis and diplopia. The estimated prevalence of MG is approximately 10 per 100,000 individuals, and approximately 60% of patients initially present with isolated ocular symptoms.[1–3] Estimates of the frequency with which these patients progress to develop generalized MG vary widely from 50% to 80%.[2,4–12]

The goals of treatment for ocular myasthenia gravis (OMG) include returning the individual to a state of clear vision and preventing the development or limiting the severity of generalized myasthenia gravis (GMG). Treatments proposed for OMG include drugs with a purely symptomatic effect, such as cholinesterase inhibitors, and drugs that suppress the immune system, such as corticosteroids. Proponents of steroids point to the limited efficacy of pyridostigmine, the possibility that chronic cholinesterase-inhibitor therapy may exacerbate the cholinergic deficit in myasthenia,[13] the potentially greater beneficial effects of prednisone, and the potential for steroids to reduce the risk of progression from ocular to generalized disease. Opponents of steroids emphasize the potential risk of serious side effects and question whether these risks are justified in the setting of purely ocular symptoms.

There has been 1 prior randomized, controlled trial (RCT) relevant to the use of steroids in OMG.[5,9,14] This trial, however, did not permit any conclusion regarding the efficacy of steroid therapy, as patients were only treated for 8 days and outcomes were reported solely in terms of the degree of ophthalmoplegia. There have also been 7 non-randomized observational studies,[15–21] 5 of which suggested a possible benefit of steroids in reducing the risk of progression to GMG[15–17,19,21] and 2 suggesting a favorable symptomatic effect.[20,21] However, in view of the paucity and limited methodological quality of the available data, controversy persists regarding the optimal approach to treatment of patients with OMG.[22–24] The importance of the clinical question and the absence of convincing evidence of efficacy and safety, combined with the equipoise among neuromuscular specialists, provide justification for an RCT to evaluate the safety and efficacy of prednisone in the treatment of OMG.[14]

METHODS

Study Design. The Efficacy of Prednisone in the Treatment of Ocular Myasthenia (EPITOME)[25] trial was a randomized, double-blind, parallel-group,

Additional Supporting Information may be found in the online version of this article.

Abbreviations: AE, adverse event; CMSU, Clinical Material Services Unit; DEXA, dual-energy X-ray absorptiometry; DSMB, Data Safety Monitoring Board; EPITOME, Efficacy of Prednisone for Treatment of Ocular Myasthenia; GMG, generalized myasthenia gravis; MG-QOL-15, 15-item Myasthenia Gravis Quality-of-Life Scale; MMS, minimal manifestation status; MSG, muscle study group; QMG, quantitative myasthenia gravis score; NEI-VFQ-25, 25-item National Eye Institute Visual Function Questionnaire; OMG, ocular myasthenia gravis; RCT, randomized, controlled trial; SAE, serious adverse event

Key words: clinical trial; ocular myasthenia; prednisone; neuromuscular; steroids

*See Appendix for listing of MSG participants.

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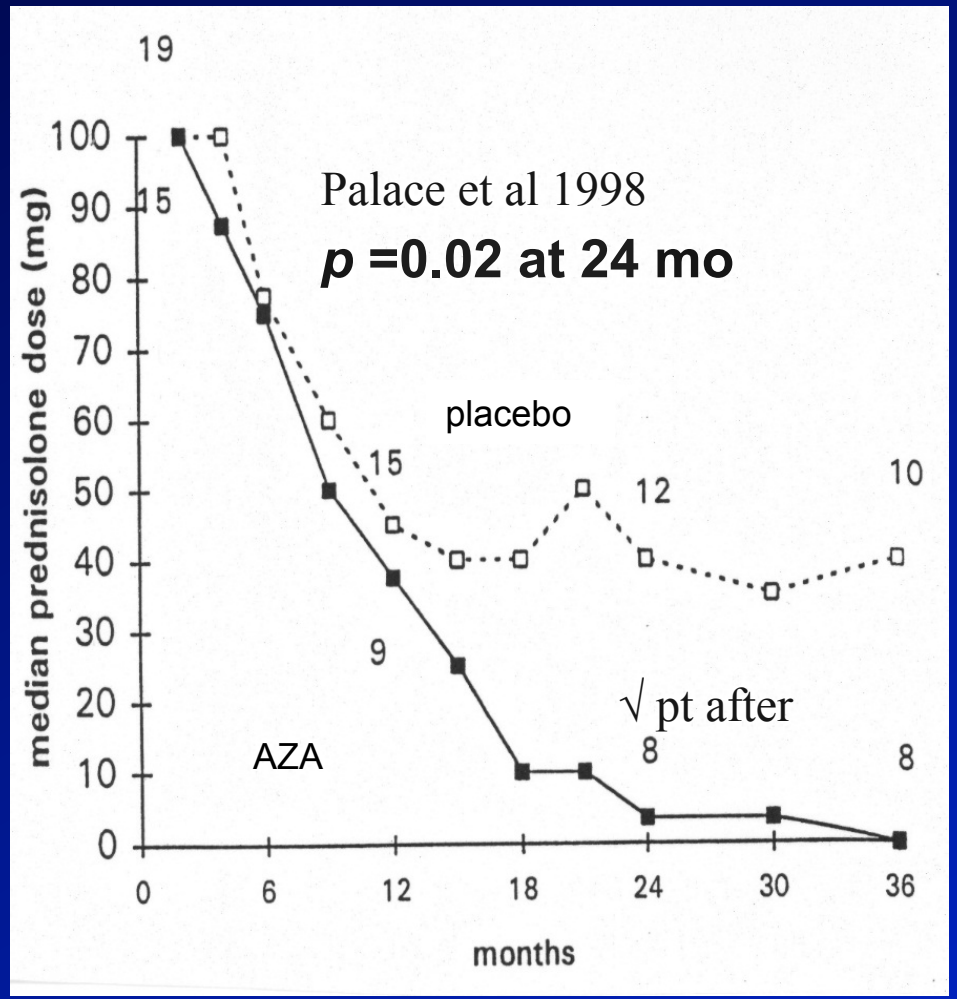
Benatar et al. Muscle Nerve. 2016; 53(3)363-9

Azathioprine (Imuran) Rx for MG

- Azathioprine: purine analog blocks DNA/RNA synthesis and cell proliferation
- Response is slow - up to 18 months
- Dose: Begin 50 mg/day x 1 week, Then, 2-3 mg/kg/day
- Typical dose 150 mg/day (single dose)
- Toxicity
  - Systemic “flu-like” reaction
  - Leukopenia
  - Hepatotoxicity
  - ? √ for TPMP def
  - Monthly CBC/LFT’s



- High dropout (34 to 18))
- Take at least a year to have an effect

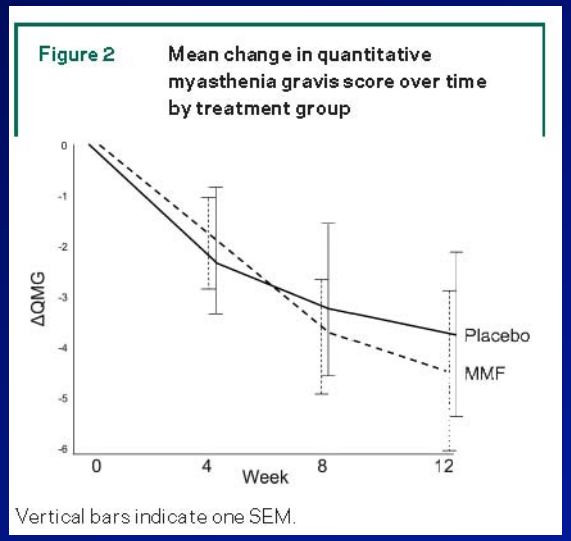
Cyclosporine in MG

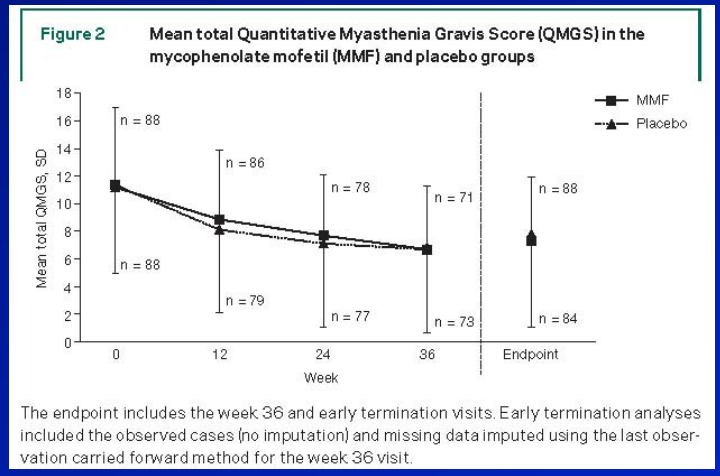
- Selective/reversible on T-cells
  - Inhibit IL-2 and interferon γ
  - Inhibits cytotoxic T cells / express supp T cells
- 1987 - CSA Effective in non-immunosuppressed MG
  - 20 patients
- 1993 - CSA Effective in Steroid-Dep MG
  - 39 patients
- QMG - Primary End-Point
- In 1993 Study:
  - Mean Dec QMG 3.5 in CSA
  - Mean Dec QMG 0 in Placebo
- Sandoz industry study: results never released

Tindall et al 1987 & 1993

Mycophenolate Mofetil Rand/Control Trials in MG

- **Sanders & colleagues** (MSG *Neurology* 2008;71:394)
  - Investigator initiated funded by FDA-ODG
  - Must be AChR-Ab pos
  - No prior IS Rx
  - 2.5 gm MM vs. plac
  - All placed on pred 20
  - 1º – QMG 3 mos
  - 2º – MMT, MG-ADL
  - AChR-Ab, SFEMG
  - 80 subjects
- **Aspreva sponsored-138 subjects** (Sanders et al *Neurol* 2008;71:400)
  - Can already be on prednisone
  - 9 month trial





RESULTS FOR BOTH:
NO SIGNIFICANT DIFFERENCE!

IV Immunoglobulin in Patients with Myasthenia Gravis

- 51 pts IVIg vs. placebo
- QMG: Sig dif at day 14 (p=0.047)
- Persisted at day 28
- Change in
  - IVIg: -2.54
  - Placebo: -0.89

Table 3 Mean change in QMG Score for Disease Severity on day 14 in patients with mild and moderate to severe MG

Baseline severity treatment group	LS means	LS mean difference (95% CI)	*p* Value
Mild MG (QMG Score <10.5)			
IVIG, n = 11	−0.97	−0.10 (−2.03–1.83)	0.914
Placebo, n = 12	−0.86		
Moderate to severe MG (QMG Score >10.5)			
IVIG, n = 13	−4.10	−3.39 (−5.88–0.90)	0.010*
Placebo, n = 15	−0.71		

- Post intervention status at day 14
  - IVIg imp 25%
  - Placebo imp 6%
- RNS/SFEMG-no sig diff
- Meriggioli editorial:
  - Getting enough “bang for the buck”

Zinman, Eduardo, Bril Neurology 2007; 68:837-881

RCT of IVIG & PLASMA EXCHANGE in MG

- 84 pts: IVIG 1g/kg/d x 2 days (n=41) or PLEX x 5 (n=43)
- AChR Ab+ in all but 4 MuSK cases: 2 on IVIG & 2 on PLEX
- Moderate to severe MG: QMG≥11 and "worsening"

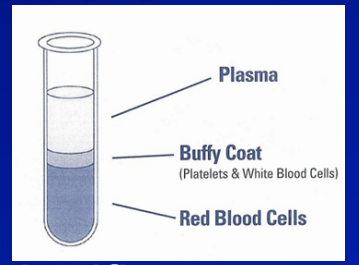
	IVIG QMG MEAN (SD)	PLEX QMG MEAN (SD)	P
Baseline	14.2 (4)	14.4 (3.8)	**0.83**
Day 0-14*	3.2 (4.1)	4.7 (4.9)	**0.13**
Day 0-21	3.3 (3.6)	5.3 (5.5)	**0.07**
Day 0-28	2.6 (4.0)	4.7 (5.7)	**0.08**

Improved post-intervention status: 69% IVIG and 65% PLEX
Conclusion: IVIG & PLEX both effective Rx, well tolerated with similar effect durability

Barth et al. Neurology. 2011;76(23):2017-23

PLASMA EXCHANGE

- PLEX removes 3-6 liters of plasma over several hours
- Replace with albumin or purified protein fraction (PPF)
- Directly removes humoral factors such as autoantibodies, immune complexes, complement & inflammatory mediators
- Each PLEX reduces IgG by 45%, or 90% by PLEX 3-5
- Use in MG:
  - Crisis (respiratory insufficiency or severe dysphagia)
  - Pre-surgery / thymectomy particularly in patients with significant bulbar dysfunction or low FVC
  - Severe MG (not in crises) while initiating or increasing oral immunosuppressive drugs
  - When rapid response is needed
  - Chronic Rx for refractory cases



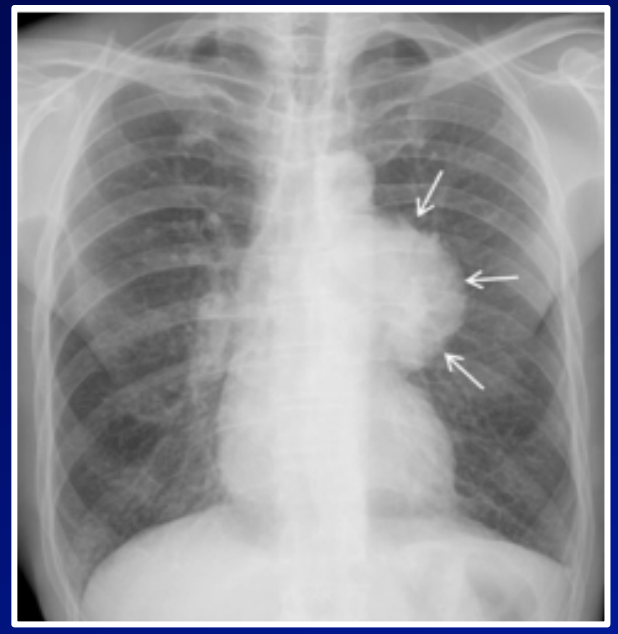
Neurol Clin. 2018 May;36(2):311-337

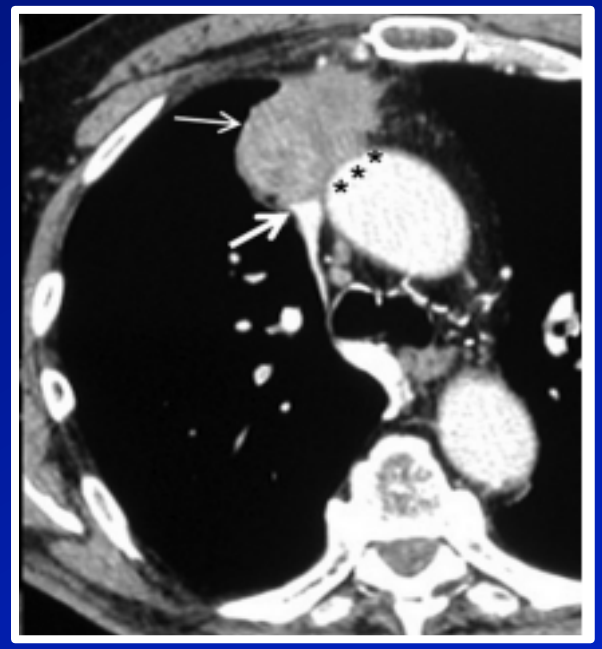
Phase II Trial of Methotrexate in MG
Barohn and Muscle Study Group
FDA OPD R01 FD003538/IND #101,306

- A randomized, double-blind, placebo-controlled study
- 50 patients
  - 25 receiving MTX; 20mg/week
  - 25 receiving placebo/12 mo study
- Hypothesis – adding MTX therapy will improve the MG manifestations so that prednisone dose can be reduced and clinical measures of MG severity will improve
- The primary measure of efficacy will be the 9-month prednisone area under the curve (AUC)
- Secondary: QMG, MG ADL, MG Comp, MG QOL15
- 20 sites – KUMC, UTSW, UTSCSA, UC-Irvine, OSU, U. North Carolina, U. Virginia, UCSF – Fresno, U. Miami, U. Indiana, MGH, CPMC, U. Iowa, Toronto, Phoenix, Methodist, NM Center Houston, Penn State, U. Florida, U. Toronto
- **Conclusion: NEGATIVE STUDY; but some data suggests it helps some patients. Considering new trial.** *Pasnoor et al. Neurology 2016;87:57-64*

MG and Thymoma

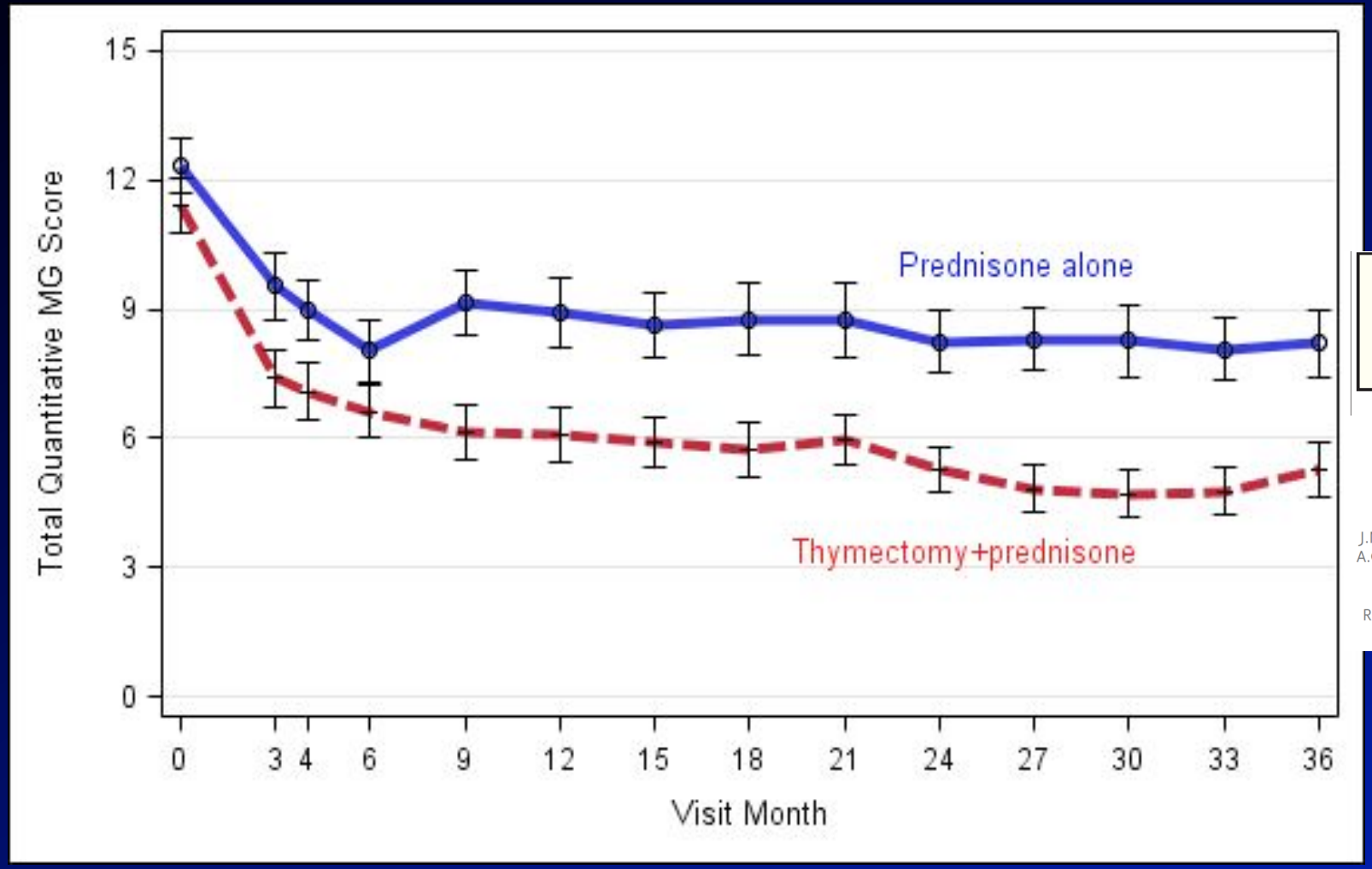
- 15% of MG patients
- Mostly in MG patients > 30 years
- Reason for chest CT in all new MG patients
- If thymoma patient, thymectomy has to be done.
  - But also still have to treat MG with medication
  - Taking out thymoma often doesn't stop MG symptoms





A.M. Priola, S.M. Priola / Clinical Radiology 69 (2014) e230-e235

QMG Score (Mean±SE) by Treatment Group



The NEW ENGLAND JOURNAL of MEDICINE

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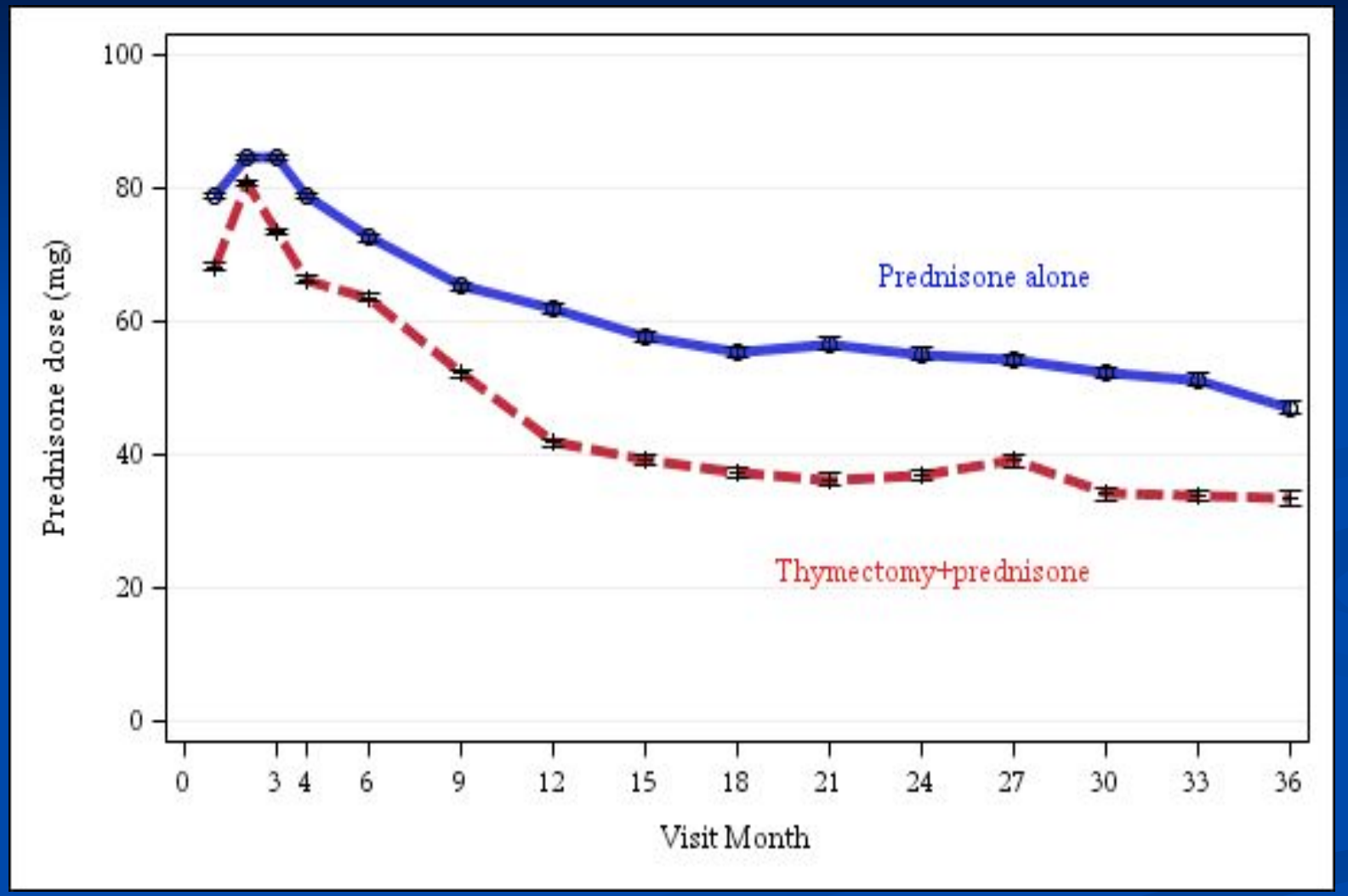
Randomized Trial of Thymectomy in Myasthenia Gravis

G.I. Wolfe, H.J. Kaminski, I.B. Aban, G. Minisman, H.-C. Kuo, A. Marx, P. Ströbel, C. Mazia, J. Oger, J.G. Cea, J.M. Heckmann, A. Evoli, W. Nix, E. Ciafaloni, G. Antonini, R. Witoonpanich, J.O. King, S.R. Beydoun, C.H. Chalk, A.C. Barboi, A.A. Amato, A.I. Shaibani, B. Katirji, B.R.F. Lecky, C. Buckley, A. Vincent, E. Dias-Tosta, H. Yoshikawa, M. Waddington-Cruz, M.T. Pulley, M.H. Rivner, A. Kostera-Pruszczyk, R.M. Pascuzzi, C.E. Jackson, G.S. Garcia Ramos, J.J.G.M. Verschuuren, J.M. Massey, J.T. Kissel, L.C. Werneck, M. Benatar, R.J. Barohn, R. Tandan, T. Mozaffar, R. Conwit, J. Odenkirchen, J.R. Sonett, A. Jaretzki, III, J. Newsom-Davis, and G.R. Cutter, for the MGTX Study Group*

QMG difference: 2.85 pts (99.5% CI 0.47-5.22; p<0.001)

N Engl J Med. 2016 Aug 11;375(6):511-22

AD Prednisone Dose (Mean±SE) by Treatment Group



Time-weighted average AD prednisone dose difference: 32 mg vs 54 mg (95% CI 12-32 mg; p<0.001)

Summary of Adverse Events

	Prednisone Alone (N=60)	Thymectomy+ Prednisone (N=66)	P Value
Number of events[a]	93	48	< 0.001
Patients having ≥1 event– no.(%)[b]	33 (55)	25 (38)	0.05
Classification by patient no.(%)			
Life threatening[c]	7 (12)	1 (2)	0.03
Disability/Incapacity[†,c]	2 (3)	8 (12)	0.10
Required medical or surgical intervention[c]	5 (8)	9 (14)	0.40
Death[c]	1 (2)	0 (0)	0.48
Complication due to thymectomy	Not applicable	1 (2)	
Hospitalization[b]	31 (52)	15 (23)	< 0.001
Patients hospitalized for MG exacerbation[b]	22 (37)	6 (9)	< 0.001
Mean ± SD cumulative hospital days[*,d]	19.2 ± 24.5	8.4 ± 8.6	0.09
Hospitalization by MEDRA codes-no.(%)			
Gastrointestinal disorders[c]	2 (3)	2 (3)	~ 1
Hepatobiliary disorders[c]	1 (2)	0 (0)	0.48
Infections and infestations[c]	7 (12)	4 (6)	0.35
Injury, poisoning and procedure complications[c]	0 (0)	2 (3)	0.50
Metabolism and nutrition disorders[c]	0 (0)	1 (2)	~1
Nervous system disorders[b]	22 (37)	8 (12)	0.001
Respiratory, thoracic and mediastinal disorders[c]	2 (3)	1 (2)	0.60
Surgical and medical procedures[c]	7 (12)	0 (0)	0.005
Vascular disorders[c]	1 (2)	0 (0)	0.48

Disability/incapacity etiologies: for prednisone alone group, worsening swallowing difficulties and myasthenia gravis; in thymectomy+prednisone group, osteoporotic thoracic fracture, ocular muscle involvement due to relapsing MG, post-thymectomy diaphragmatic hemiparesis, rib fracture, impending myasthenic crisis, Pott's fracture, tear of left knee meniscus, and low back pain with possible stenosis.
MEDRA denotes medical dictionary for regulatory activities, MG myasthenia gravis.

N Engl J Med. 2016 Aug 11;375(6):511-22

Rituximab For AChR-Ab Positive Myasthenia Gravis - BeatMG

- Rituximab depletes B-cells that produce antibodies
- Study PI – R. Nowack (Yale) - CoPIs – J. Goldstein, M. Dimachkie, R. Barohn
- Funded by NeuroNext/NIH
- 50 pts - 1:1 randomization
- 21-90 yo, AChR-Ab+, n=50
- MGFA MG grades 2-5
- Prednisone ≥ 15 mg/day stable dose for 30d prior to screening
- Allowed non-steroid immunosuppressants with stable dose x 6 months
- Rituximab dose for trial: 375 mg/m^2 IV weekly x 4 Repeat in 6 months

NN103 BeatMG Rituximab Trial (Phase II)
AAN 2018

- Top-line results
  - n=52
    - Mean age: 53 RTX; 56 placebo
    - Mean prednisone dose: 24 mg RTX; 22 mg placebo
  - 1° outcome response rate (75% prednisone reduction in wks 48-52)
    - 60% RTX; 56% placebo → FUTILITY
  - 2° outcomes

	RTX	Placebo
ΔMGC (SD)	-5.7 (7.26)	-4.0 (4.1)
ΔQMG (SD)	-3.95 (5.43)	-1.7 (3.91)

  - No significant safety issues

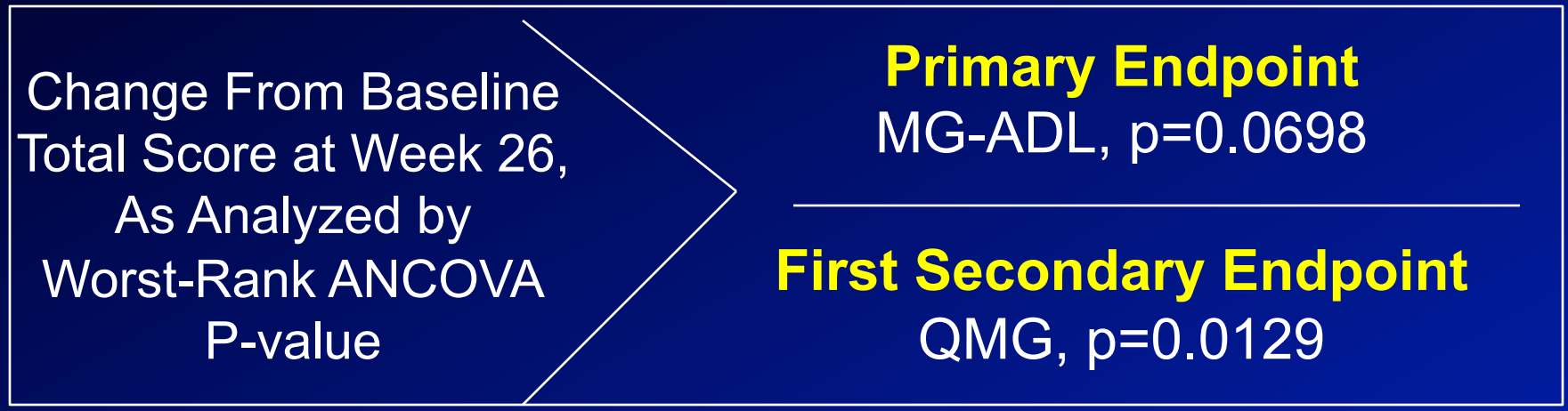
Eculizumab Phase 3 Trial MG Study REGAIN

- Intravenous complement inhibitor
- 62 eculizumab pts/63 placebo
- All AChR Ab+
- Meningococcal vaccination prior to starting drug/PBO
- Rx:
  - weekly IV 900mg x 4 weeks (Weeks 0 to 3) then
  - 1,200 mg every 2 weeks x 26 weeks
- Primary outcome measure – MGADL change from baseline at Week 26
- Secondary outcome measures – QMG, MG Composite, MG QOL

Howard JF, et. al. Safety and Efficacy of Eculizumab in Anti-acetylcholine Receptor Antibody-Positive Refractory Generalised Myasthenia Gravis (REGAIN): a phase 3, randomized, double-blind, placebo-controlled, multicenter study. Lancet Neurol. 2017;16(12):976-986.

Eculizumab Phase 3 Trial Results

MG-ADL and QMG Worst-Rank ANCOVA



- 3 of 4 prospectively defined sensitivity analyses to validate the primary endpoint of MG-ADL achieved p-value < 0.05
- For QMG, 4 of 4 prospectively defined sensitivity analyses achieved p-value <0.05
- US FDA approved for AChR+ generalized MG

Howard JF, et. al. Safety and Efficacy of Eculizumab in Anti-acetylcholine Receptor Antibody-Positive Refractory Generalised Myasthenia Gravis (REGAIN): a phase 3, randomized, double-blinde, placebo-controlled, multicenter study. Lancet Neurol. 2017;16(12):976-986.

Open Label Study of Subcutaneous Immunoglobulin in Myasthenia Gravis

- M Dimachkie PI
- Phase 2 multi-center study
- 25 participants in the IVIg screening phase (ISP)

- **Primary outcome:** % subjects ETP experiencing ≤ 3 points increase in **QMG** from Week 0 to Week 12
- **Secondary Outcomes**:
  - MG-ADL, MG-QOL-15, MGC & Treatment Satisfaction Questionnaire (TSQM)

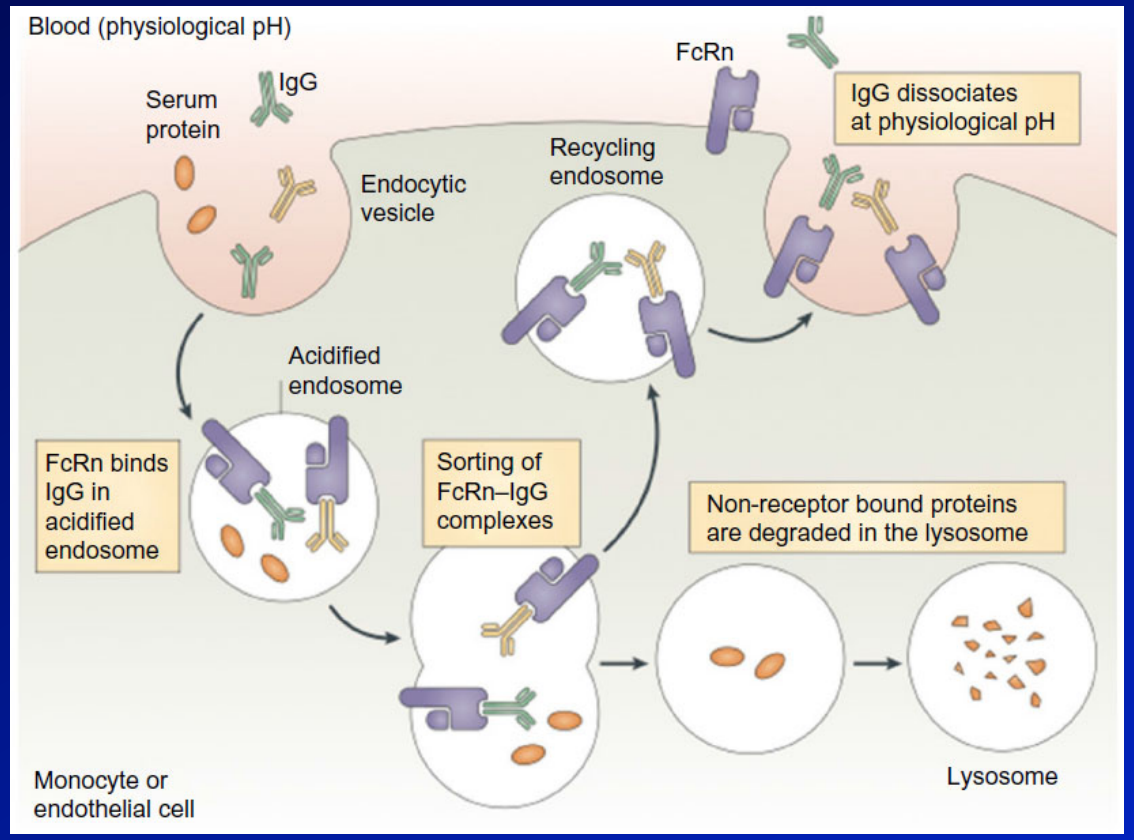
Emerging Therapies for MG

- **Subcutaneous immune globulin** (Dimachkie)
  - Completed- positive study
- **IVIg** - 3 studies (Grifols)
  - Awaiting results
- **Eculizumab** - complement inhibitor (Alexion)
  - completed-positive trial -FDA approved
- **Rituximab** - monoclonal Ab to B-cells
  - completed-negative trial
- **Belimumab (GSK)** -monoclonal to BLS
  - completed-negative trial
- **Ravulizumab** (Alexion) Phase 3 started to evaluate next C5 drug IV Q 8 wks in AChR+ MG
- **Ra Pharma** (Zilucoplan) -complement inhibitor/ SC in AChR + MG
  - Phase 2 study positive / Phase 3 starting
- **Argenx** (Efgartigimod) - Fc receptor blockade
  - IV Phase 2 done / Phase 3 started-Any MG
- **Momenta** -Fc receptor blockage
  - IV-Phase 2 started-AChR+ or MuSK+ MG
- **UCB** - (rozanolixizumab) Fc receptor blockade
  - SC-Phase 2 done/Phase 3-AChR+ or MuSK+
  - **Catalyst**- Firdapse for Musk MG started AChR+ or MuSK+ MG

https://www.centerwatch.com/clinical-trials/listings/217967/a-phase-3-randomized-double-blind-placebo-controlled-multicenter-study-to-evaluate-the-safety-and-efficacy-of-ravulizumab-in-complement-inhibitor-naive-adult-patients-with-generalized-myasthenia-gravis/

FcRn Blockers

- Binding FcRn (neonatal FcR), blocks IgG recycling (including disease causing autoantibodies) and increases IgG clearance



J Blood Med. 2015 Apr 24;6:131-41

Chronic MG Treatment Recommendations

- 1st Line: Pyridostigmine
  Corticosteroids
  Thymectomy
- 2nd Line: Azathioprine
  Cyclosporine
  IVIG
  Tacrolimus
- 3rd Line: Plasma exchange
  Eculizumab (immunization)
  Mycophenolate Mofetil
  Methotrexate
- 4th Line: Rituximab in MuSK may be 1st or second line
  Cyclophosphamide in non-MuSK
- 5th Line?: Autologous Hematopoietic SCT; Ruxolitinib; Tocilizumab; **Research (could be 3rd line!)**

Lindberg et al. Acta Neurol Scand. 1998:370-3

Palace et al. Neurology. 1998 50(6):1778-83

Tindall et al. Ann N Y Ac S. 1993 ;681:539-51
Yoshikawa et al. JNNP. 2011 Sep;82(9):970-7
Zinman et al. Neurology 2007; 68:837

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In green: consider in refractory MG

Sanders et al. Neurology. 2008;71(6):400-6
MSG. Neurology. 2008 ;71(6):394-9
Pasnoor et al. Neurology 2016;87:57-64

Drachman et al. Ann N Y Ac Sci. 2008:305-14

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