66° Congresso Nazionale
Società Nazionale di Neurofisiologia Clinica

Aggiornamenti in tema di miastenia

Lorenzo Maggi

U.O. Neurologia IV – Malattie Neuromuscolari e Neuroimmunologia

Disclosures

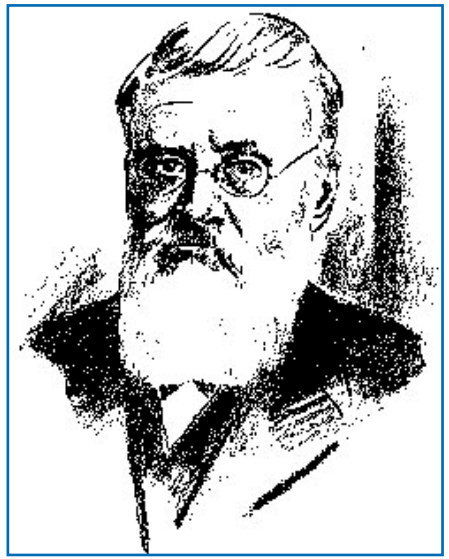
Sanofi-Genzyme, Biogen, Roche, Catalyst Pharmaceuticals

Dichiaro l’assoluta autonomia dei contenuti scientifici del mio intervento ed indipendenza da interessi economici commerciali con possibili aziende sponsorizzatrici l’evento.

Myasthenia gravis

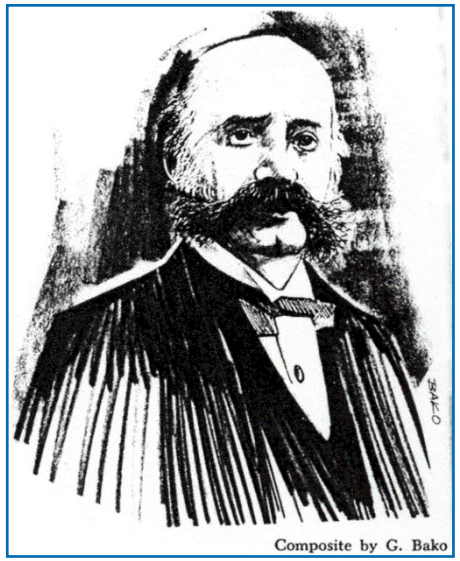
Myasthenia gravis (MG) is a **neuromuscular disease**, recognised as a clinical entity more than a century ago, for the fluctuating weakness and fatigability of both cranial, limb and axial muscles.

Thomas Willis (1621-1675), English physician, wrote of "**a woman who temporarily lost her power of speech and became 'mute as a fish.**" The **first written description of MG**



A.Y. Kozhevnikov (1836-1902), Russian physician – **Early description of MG**

W.H. Erb (1841-1921), German Neurologist – **Delineation of MG**

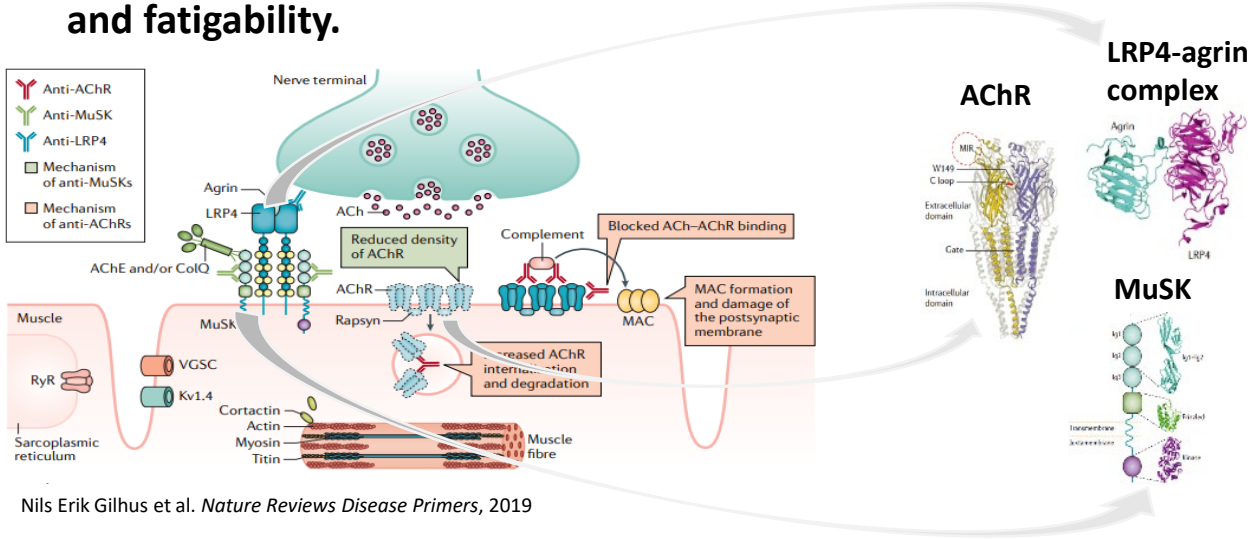


C. Weigert (1845-1904), German Pathologist – **MG and hypertrophy of thymus**

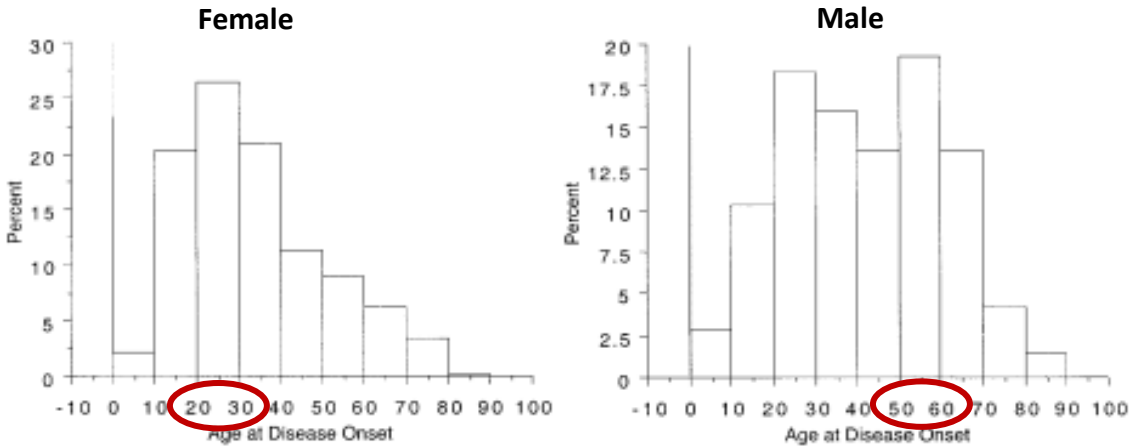
Mary Walker(1888-1974), British physician– **prostigmine temporary improvement on MG (1934).**

Definition and Epidemiology

- MG is caused by autoantibodies directed against components of the postsynaptic membrane at the NMJ **causing muscle weakness and fatigability.**



Nils Erik Gilhus et al. *Nature Reviews Disease Primers*, 2019



Mantegazza R, et al. *Ann N Y Acad Sci*. 2003

- **Myasthenia Gravis (MG)** is a rare autoimmune disorder
- **Prevalence**: 100-350 cases per 1 million
- **Annual incidence**: 10-29 cases per million people
- **Factors influencing prevalence and incidence**:
  - Age
  - Gender
  - Ethnicity

	Incidence (per 1 million people per year)	Prevalence (per 1 million people)	Subgroup(s)	Study years
England[17]	17·6	..	All myasthenia gravis	2014–18
USA[18]	22	..	Ocular myasthenia gravis	1990–2017
Sweden[5]	29	361	All myasthenia gravis	2006–16
Slovakia[4]	17·4	247	All myasthenia gravis	2010–15
Latvia[6]	Approximately 10	114	All myasthenia gravis	2010–15
Finland[19]	..	290	All myasthenia gravis	2004–14
South Korea[5]	24·4	100	All myasthenia gravis	2010–13
Israel[20]	18·4	..	Acetylcholine receptor-positive myasthenia gravis	2004–13
Canada[2]	23	263	All myasthenia gravis	1996–2013
Portugal[21]	6·3	117	All myasthenia gravis	2013
South Africa[22]	8·5	..	Acetylcholine receptor-positive myasthenia gravis	2011–12
Norway and Netherlands[23]	..	138 for Norway, 167 for Netherlands	All myasthenia gravis	2009–10 for Norway, 2011–12 for Netherlands
Australia[3]	24·9	117	All myasthenia gravis	2009
Denmark[24]	4·2 for early-onset, 19 for late-onset	..	Early-onset and late-onset myasthenia gravis	1996–2009

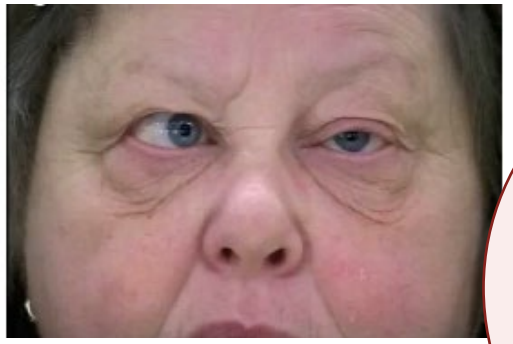
Studies are listed in time order (most recent first).

Punga A, et al. Lancet Neurol. 2022.

Clinical features of Myasthenia Gravis

Although many pts present with ocular manifestations alone, 17–50% develop generalised MG within 6 months to 1 year of symptom onset, 61–85% within 2 years.

Myasthenic crisis in around 15% of pts, mostly during the early years, but possible at any age and in all generalised MG subgroups, mostly in MuSK-MG, thymoma-MG and AChR-Ab late-onset MG.

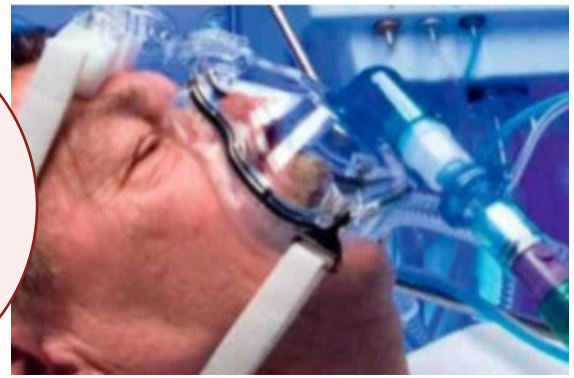


Ocular symptoms

- Dropping eyelid
- Diplopia
- Ophtalmoparesis

Fluctuations

Respiratory symptoms



Bulbar symptoms

- Dysphagia
- -Dysphonia
- Dysartria
- Tongue weakness

Generalized symptoms

- Dropping head
- Fatigue
- -Weakness of facial muscles
- Weakness of upper and lower limbs
- Weakness of axial muscles

Myasthenia Gravis classifications

Table 1 MGFA Clinical Classification

Class I	Any ocular muscle weakness May have weakness of eye closure All other muscle strength is normal
Class II	Mild weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class III	Moderate weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb, axial muscles, or both May also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class IV	Severe weakness affecting other than ocular muscles May also have ocular muscle weakness of any severity
IVa:	Predominantly affecting limb and/or axial muscles May also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal, respiratory muscles, or both May also have lesser or equal involvement of limb, axial muscles, or both
Class V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

(Jaretzki A et al Neurology 2000)

MG stratification may be relevant to prognosis and treatment response (functional to a personalized approach).

Antibody-based

AchR-Ab
- ✓highly specific for MG,
- ✓IgG1, bind C'
- ✓85% generalized MG

Musk-Ab
- ✓IgG4, do not bind C'
- ✓interference w Musk
- ✓«Oculobulbar MG»
- ✓respiratory insufficiency

LRP4-Ab
- ✓IgG1
- ✓receptor for nerve agrin
- ✓loss of agrin-LRP4 interaction
- ✓altered AChR clustering

Other antibodies
- ✓agrin,
- ✓cortactin,
- ✓titin & RyR

Clinico-biological

Early onset MG with AChR-Ab
- ✓ Onset < 50 years
- ✓ Follicular hyperplasia of the thymus
- ✓ Female > Males

Late onset MG with AChR-Ab
- ✓ Onset > 50 years
- ✓ Atrophic thymus

Thymoma-associated MG
- ✓ AChR+, 10-20 % of MG patients
- ✓ Thymoma associated disorders

MuSK-associated MG
- ✓ Thymoma not reported
- ✓ Cranial and bulbar muscles
- ✓ Respiratory crises

LRP4-associated MG
- ✓ 2-30% of AChR/MuSK DN MG
- ✓ Females
- ✓ ocular/generalized MG

Ocular MG
- ✓ No symptoms/signs of gen. MG

Seronegative MG - Triple neg?
- ✓ No differential clinical features

Age

Onset during childhood, at age 18 years or younger, is defined as **juvenile-onset myasthenia gravis**.

Patients with **early-onset disease** (19–50 years of age) are often young women, AChR-Ab positive, thymus hyperplasia, and HLA-A1B8DR3.

Late-onset MG (age >50 years) is typically more common in men with atrophic thymus and HLA-DRB1*15:01.

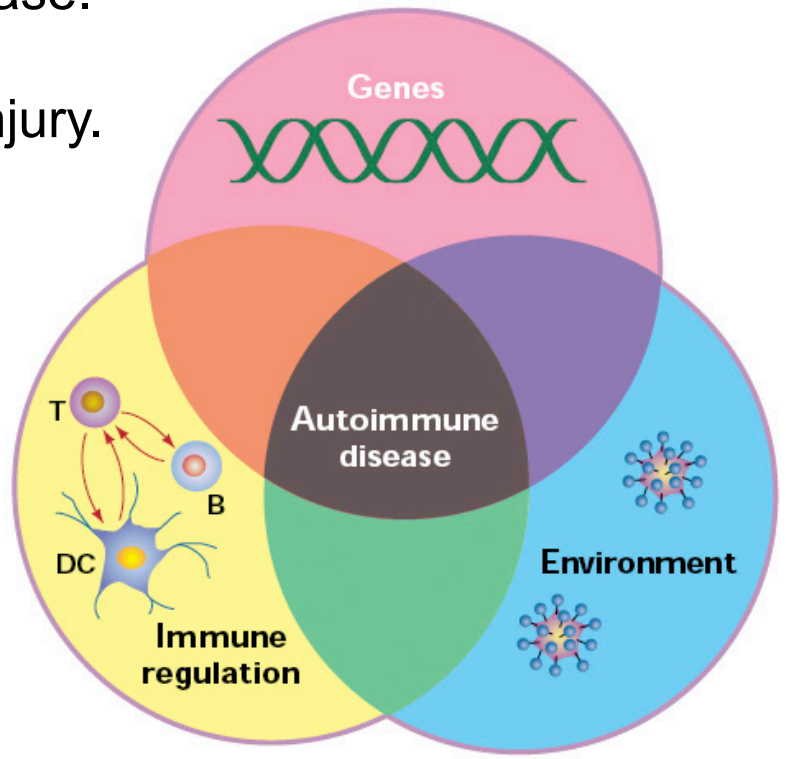
A **very late-onset** subgroup of MG (onset at ≥65 years) recently described and characterised by more-frequent life-threatening symptoms at presentation, AChR-Ab positive, while not associated with thymoma.

AUTOIMMUNITY: Triggering factors

Genetic: Crucial determinants of susceptibility to autoimmune disease.

Environmental: Viruses, bacteria, other infectious agents; tissue injury.

Immune (dys)regulation:
Altered B , T cell activation or suppression.



Ermann J et al. *Nature Immunol* 2001;2:759-766

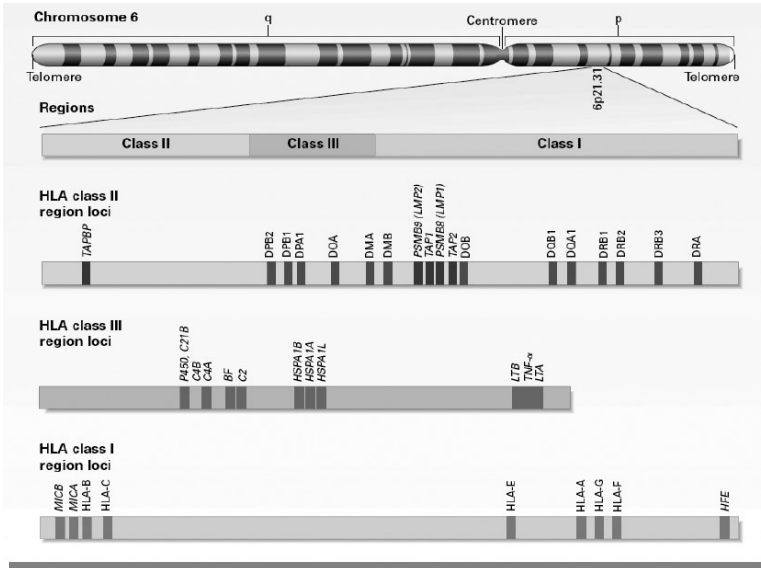
Genetic factors in MG

A multifactorial disease, markedly influenced by genetic factors, even if with a limited heritability.

The major histocompatibility complex (MHC) is the first and most important genetic factor involved in MG

- ✓ **HLA A1-B8-DR3 (8.1)** haplotype is mainly associated with AChR-EOMG;
- ✓ **HLA DR14-DQw5** is mainly associated with MuSK-MG.

There are many non-HLA genes associated with MG (i.e. IFN-gamma, IL-10, IL-1 beta, AChR subunits, immunoglobulin chains).



Bartoccioni, E et al. *Neurology* 2009;72:195-197

All the elements necessary for autoimmune response are present in MG thymus for:

MG triggering

AChR subunit expression on muscle-like myoid cells in close contact with:

- HLA-class II positive antigen-presenting cells (TECs and DCs)
- AChR-specific T cells

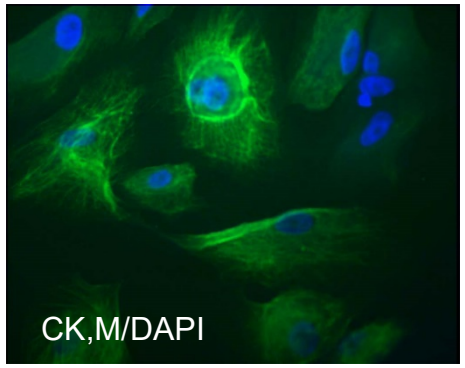
MG perpetuation

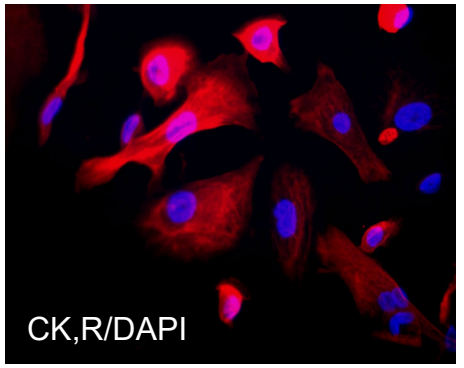
- Presence of germinal centers (GC) containing AChR-specific B cells which secrete anti-AChR antibodies
- Medullary AChR-specific T cells in close contact with follicular dendritic cells (APC)

Hypothesis of virus-mediated autoimmunity in MG

An exogenous or endogenous “danger signal” (i.e. **viral infection** of the **thymus**) might activate the **innate immune system** originating on susceptible backgrounds pathogenic pathways triggering the **autoimmune response**.

Studies in vitro to analyse TLR4-mediated pathways in TECs isolated from MG thymus





Increased expression of TLR4, IL-6, biglican (BGN), CCL22 and AChR alpha subunit in MG TECs treated with LPS to induce TLR4-mediated pathways.

Comments on EBV in MG thymus

Epstein-Barr Virus Persistence and Reactivation in Myasthenia Gravis Thymus

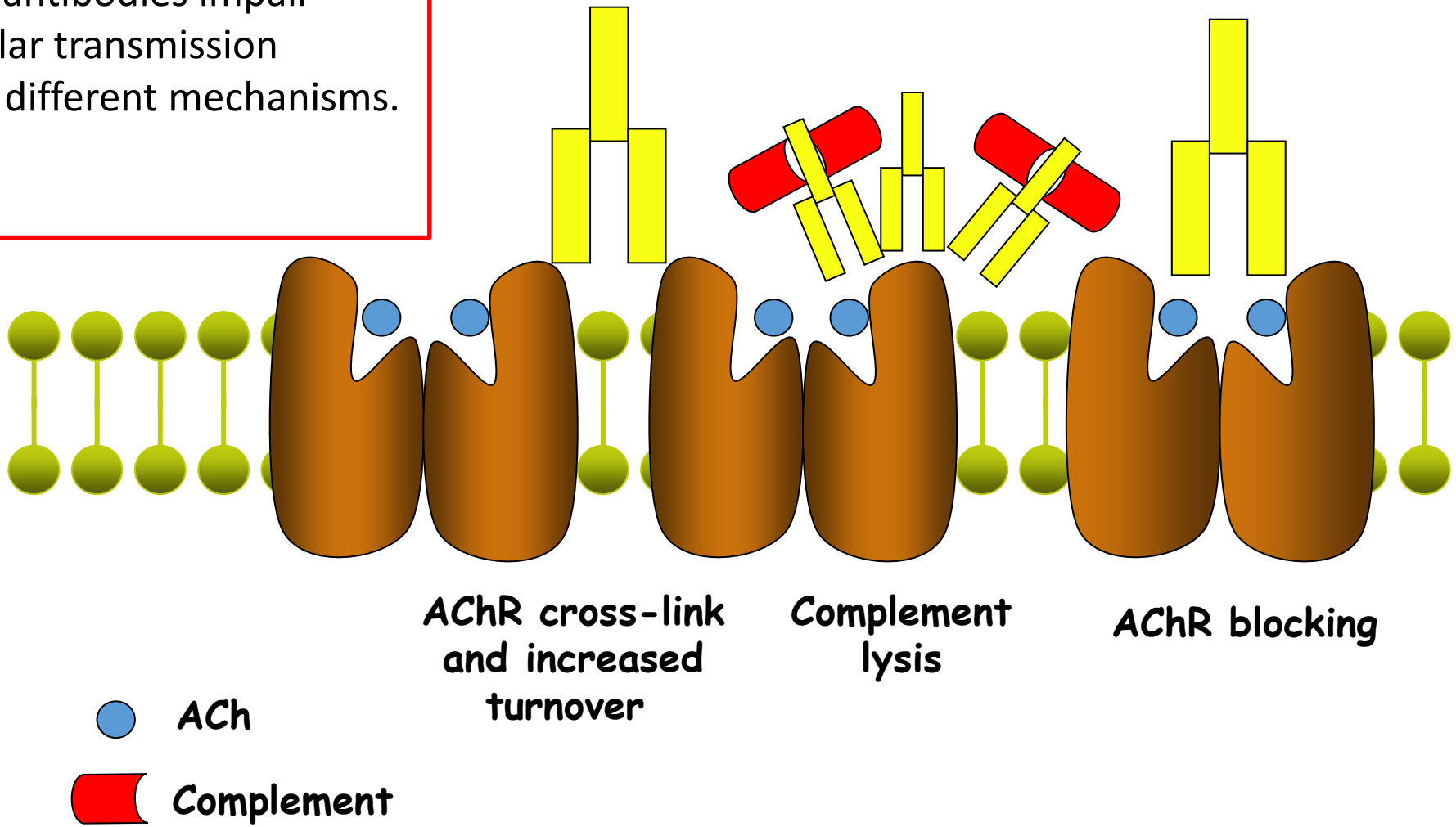
Paola Cavalcante, PhD,[1] Barbara Serafini, PhD,[2] Barbara Rosicarelli, PhD,[2] Lorenzo Maggi, MD,[1] Massimo Barberis, MD,[3] Carlo Antozzi, MD,[1] Sonia Berrih-Aknin, PhD,[4] Pia Bernasconi, PhD,[1] Francesca Aloisi, PhD,[2] and Renato Mantegazza, MD[1]

- EBV gene expression is aberrantly regulated in MG thymus
- An abnormal viral load in the thymus might contribute to the chronic B cell activation observed in this organ in MG.
- Similarity between the MG thymus and the MS brain, with respect to the high proportion of tissue-infiltrating EBV-infected B cells and the formation of EBV-enriched ectopic lymphoid tissue, supports the idea that EBV might be pathologically relevant for autoimmune diseases characterized by B cell abnormalities.

Dysregulated **EBV infection** in the pathological thymus is a **common feature in MG** and could contribute to the immunological alterations initiating and/or perpetuating the disease

Mechanisms of anti-AChR antibodies in MG

- Specific autoantibodies impair neuromuscular transmission according to different mechanisms.
- Mainly IgG1

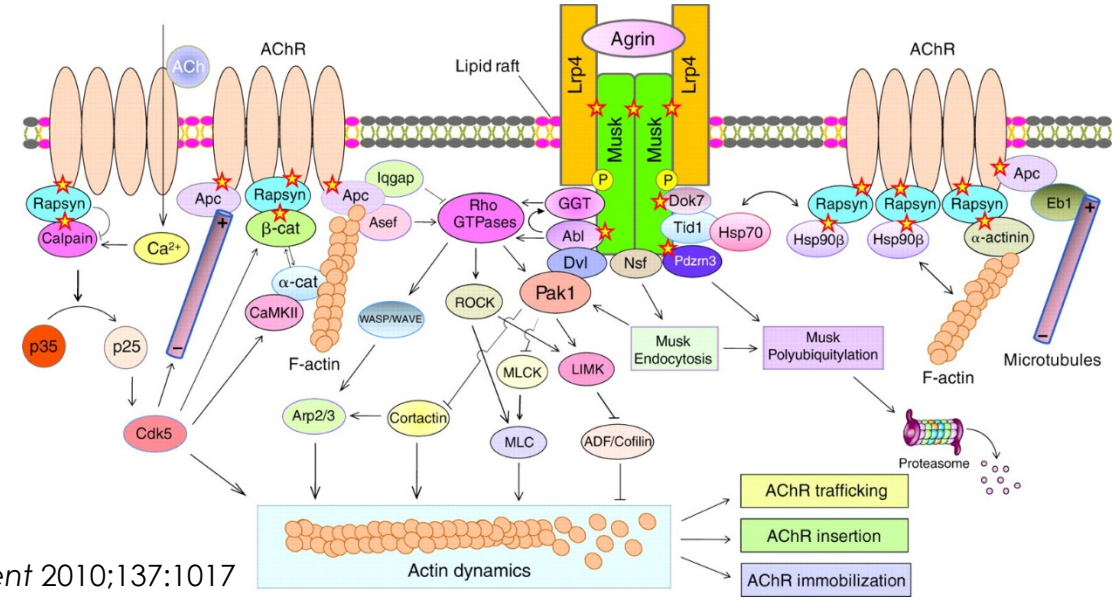


Mechanisms of anti-MuSK antibodies in MG

✓ Anti-MuSK Abs **do not reduce the number of MuSK molecules** and do not alter MuSK or AChR subunit mRNA synthesis;

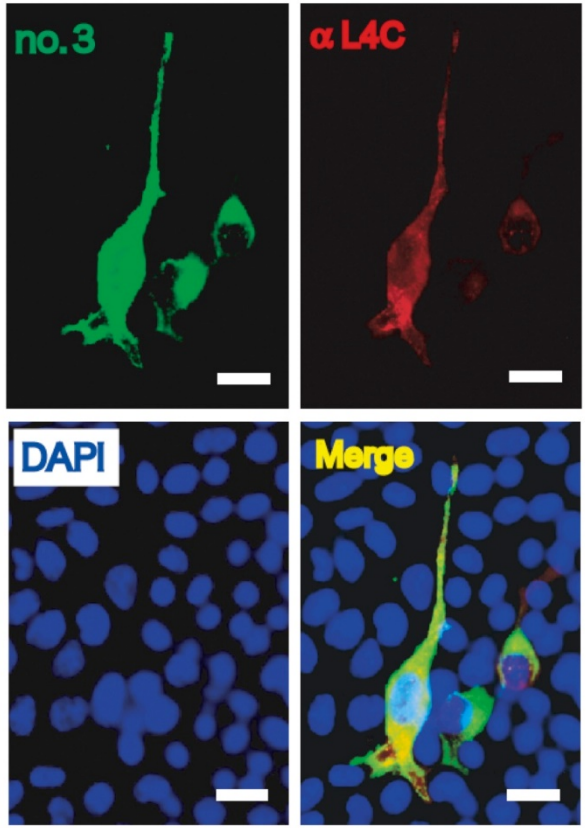
✓ Anti-MuSK Abs **cause a 20% decrease of AChR numbers** on the surface of the post-synaptic membrane, not due to AChR internalization;

✓ Anti-MuSK Abs **might interfere** directly with the MuSk function(s) by hampering the interaction of MuSK **with the lrp4-agrin-MuSK-rapsyn-AChR** pathway causing degeneration of NMJs and disturbance of AChR turnover.



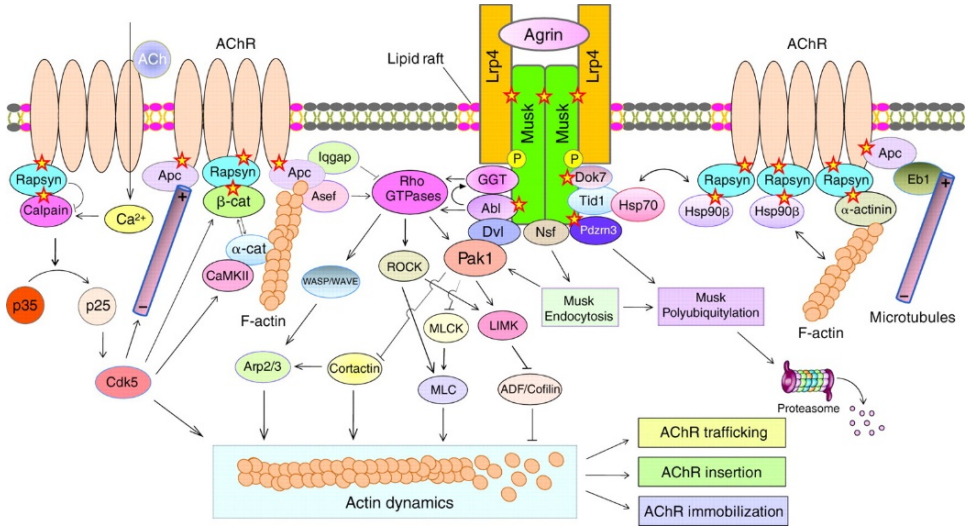
Wu H et al. *Development* 2010;137:1017

Autoantibodies to low-density lipoprotein receptor-related protein (Lrp4)



Higuchi et al. *Ann Neurol* 2011;69:418-422

- ✓ 1–2% of total MG cases of the disease;
- ✓ Predominantly female pts with mild generalised or ocular, early-onset disease.
- ✓ The frequency of LRP4 antibodies in SNMG varies from around 1% to 54% (probably due to geographical differences, with lower prevalence in Asia).
- ✓ These antibodies are mainly **IgG1**;
- ✓ They potentially inhibit the interaction between neural agrin and the extracellular portion of Lrp4;
- ✓ Probably involvement of the complement system and reduced agrin-Lrp4-MuSK signaling.



Wu H et al. *Development* 2010;137:1017

Autoantibody testing as specific diagnostic tool

- Determination of anti-AChR antibodies (positive in 80% of patients) is the first assay to be performed; if negative anti-MuSK antibodies (positive in 5–8%).
- Anti-LRP4 antibodies,
  - should be tested in double AChR/MuSK-negative patients.
  - rarely found in anti-AChR or anti-MuSK Ab positive pts, possibly representing a subgroup more severely affected at onset.
  - Antibodies to LRP4 were occasionally found in ALS, in DOK7 gene CMS and in pts with a weak response to PD.
- The most sensible diagnostic assay for anti- AChR and anti-MuSK antibodies is radioimmunoassay (RIA).
- The introduction of Cell-based assays (CBA) has significantly increased the chance to identify Ab to low affinity clustered AChR, MuSK and LRP4, thus improving MG diagnosis, although commercial kits are not available.
- Cell-based assays, based on autoantigen-transfected cells, represent the future development of diagnostic assays for myasthenia gravis because of their high sensitivity and ability to reflect antibody binding as in pathophysiological context.
- Detection of Ab to titin by ELISA and to RyR by western blot is suggestive of thymoma but also present in late-onset MG.
- Reduced titres of AChR-Ab often reported alongside clinical improvement after immunosuppressive treatment and thymectomy; however, absolute antibody titres do not predict individual disease severity or therapeutic response. Serial measurement of MuSK antibodies can be more useful.

MG Guidelines/Consensus/Recommendations

Donald B. Sanders, MD*
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Amelia Evoli, MD
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Janice M. Massey, MD
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International consensus guidance for management of myasthenia gravis

Executive summary

Neurology® 2016;87:419-425

European Journal of Neurology 2010, **17:** 893–902 doi:10.1111/j.1468-1331.2010.03019.x

EFNS GUIDELINES/CME ARTICLE

Guidelines for treatment of autoimmune neuromuscular transmission disorders

G. O. Skeie[a], S. Apostolski[b], A. Evoli[c], N. E. Gilhus[d], I. Illa[e], L. Harms[f], D. Hilton-Jones[g], A. Melms[h], J. Verschuuren[i] and H. W. Horge[j]

European Journal of Neurology 2014, **21:** 687–693 doi:10.1111/ene.12359

EFNS/ENS GUIDELINES / CME ARTICLE

EFNS/ENS Guidelines for the treatment of ocular myasthenia

E. Kerty[a,b*], A. Elsais[a,b*], Z. Argov[c], A. Evoli[d] and N. E. Gilhus[e,f]

International Consensus Guidance for Management of Myasthenia Gravis

2020 Update

Pushpa Narayanaswami, MBBS, DM, Donald B. Sanders, MD, Gil Wolfe, MD, Michael Benatar, MD, Gabriel Cea, MD, Amelia Evoli, MD, Nils Erik Gilhus, MD, Isabel Illa, MD, Nancy L. Kuntz, MD, Janice Massey, MD, Arthur Melms, MD, Hiroyuki Murai, MD, Michael Nicolle, MD, Jacqueline Palace, MD, David Richman, MD, and Jan Verschuuren, MD

Neurology® 2021;96:114-122. doi:10.1212/WNL.0000000000011124

Neurological Sciences (2019) 40:1111–1124
https://doi.org/10.1007/s10072-019-03746-1

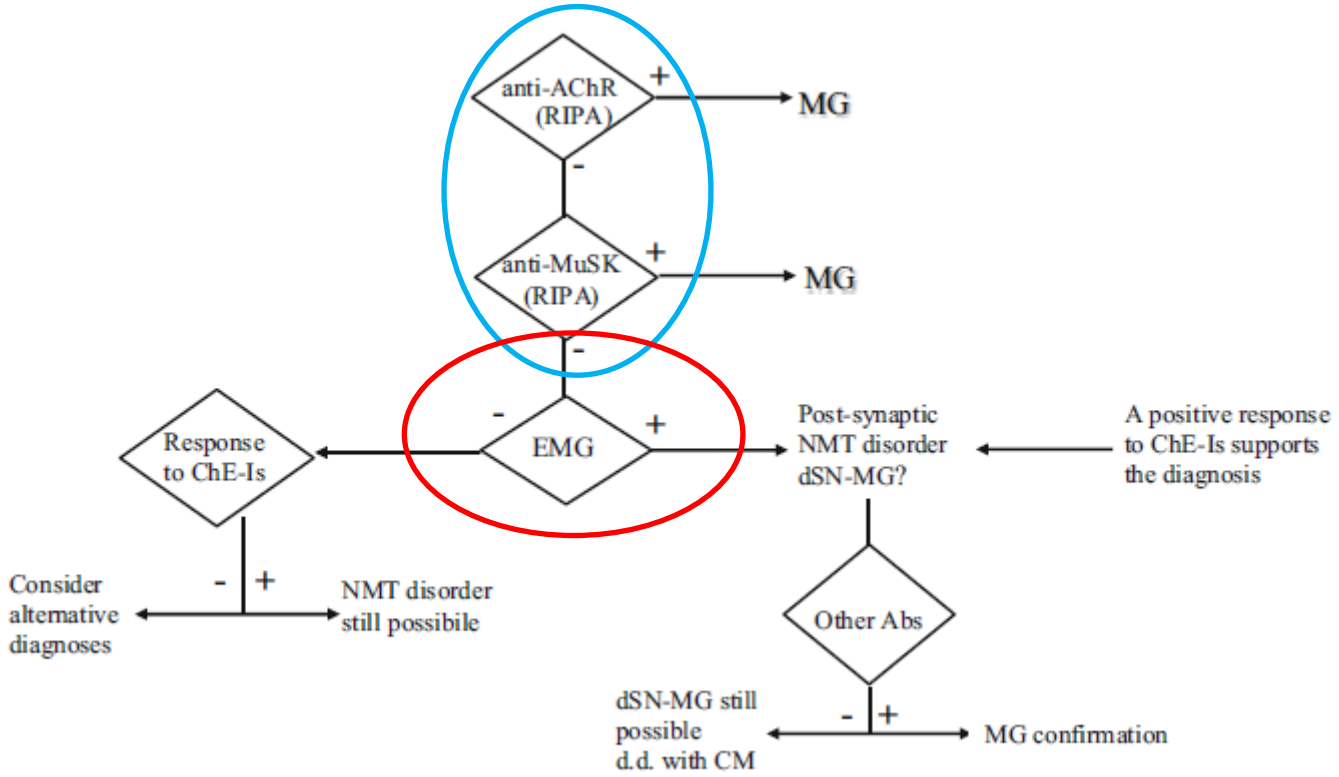
REVIEW ARTICLE

Italian recommendations for the diagnosis and treatment of myasthenia gravis

Amelia Evoli[1,2] · Giovanni Antonini[3] · Carlo Antozzi[4] · Antonio DiMuzio[5] · Francesco Habetswallner[6] · Cesare Iani[7] · Maurizio Inghilleri[8] · Rocco Liguori[9,10] · Renato Mantegazza[4] · Roberto Massa[11] · Elena Pegoraro[12] · Roberta Ricciardi[13] · Carmelo Rodolico[14]

Diagnostic algorithm for myasthenia gravis

- Serum Ab determination is considered the most specific diagnostic tool for the disease.
- (EMG) and clinical response to cholinesterase inhibitors are important for diagnosis confirmation, particularly for seronegative pts, who need differential diagnosis to distinguish MG from other neuromuscular disorders, including LEMS.
- However, RNS and SF-EMG still fundamental for diagnostic purposes in MG.

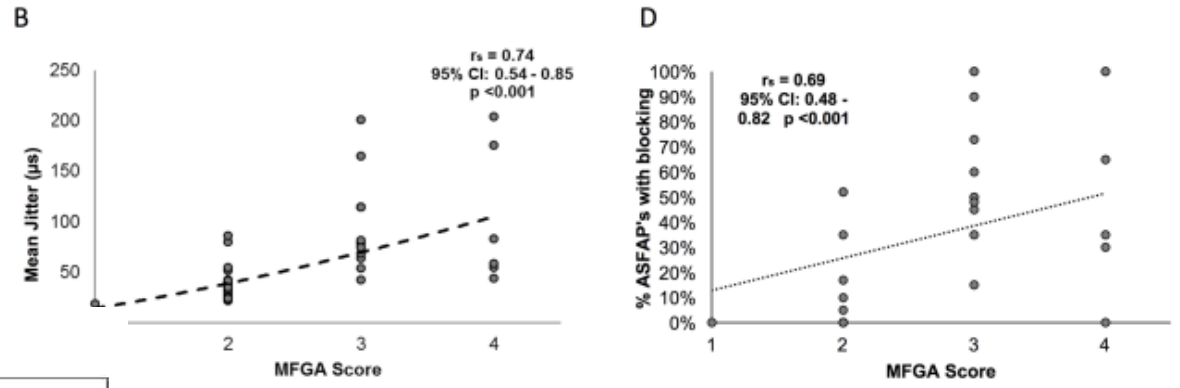


Evoli et al., Neurol Sci. 2019

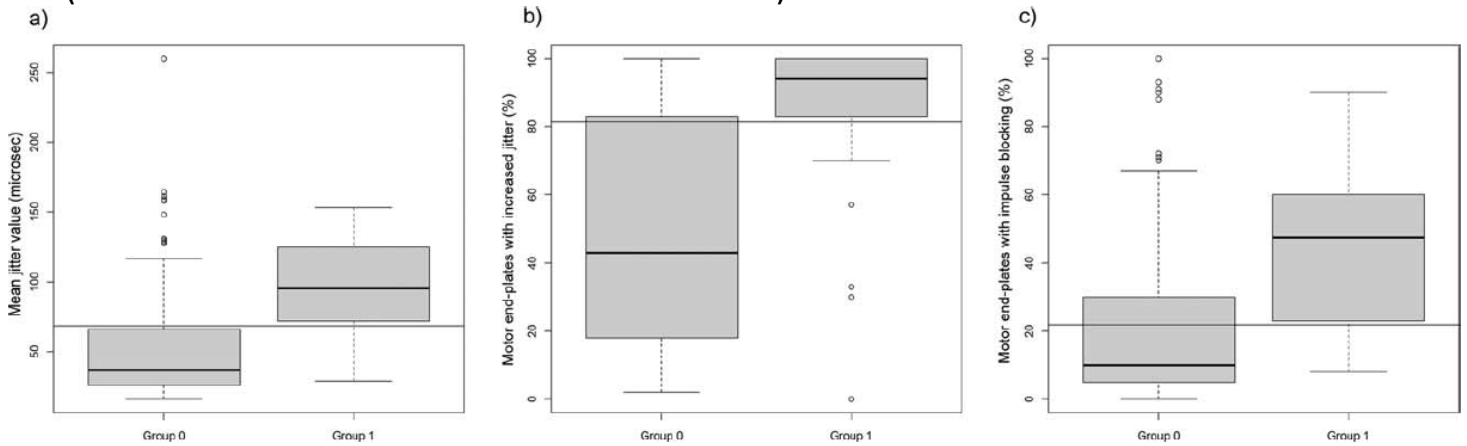
Jitter as outcome measure in MG?

- SF-EMG is considered the most sensitive tool for MG diagnosis.
- The sensitivity and specificity depend on the tested muscle and is highest for the orbicularis oculi muscle, with sensitivity of 94–99% and specificity of 85–98%.
- In most MG patients, disease severity correlates with SFEMG jitter and impulse blocking, but opinions differ regarding the prognostic value of the initial SFEMG data for the long term clinical course.

Bhatia et al., Muscle Nerve, 2018



Group 0,benign clinical course (worst MGFA clinical classification score of I-III); Group 1, severe clinical course (worst MGFA clinical classification score of IV-V).

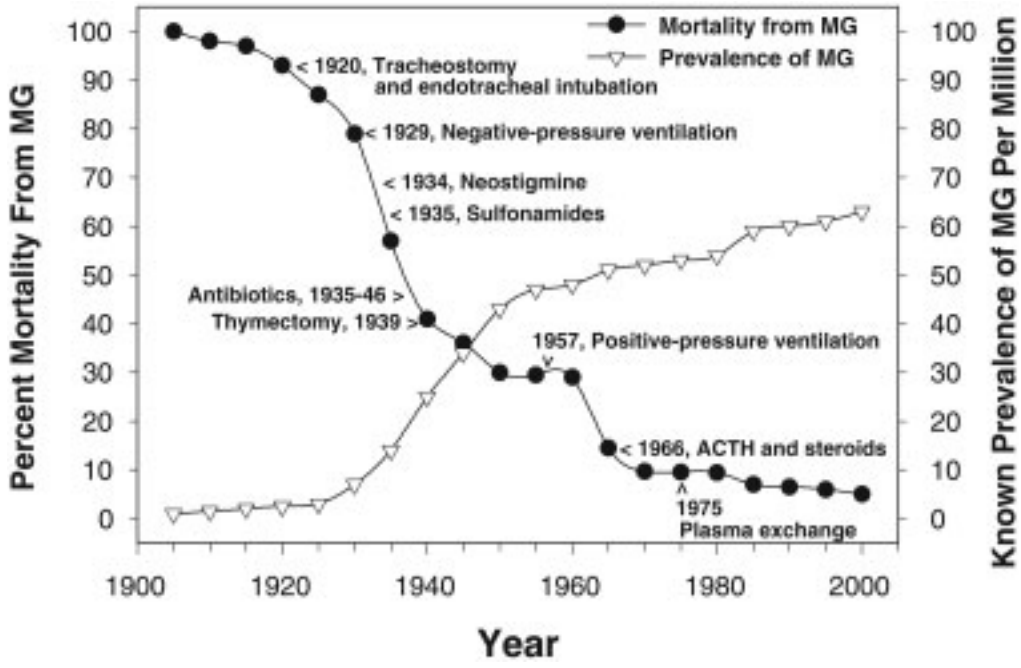


Baruca et al., Muscle Nerve, 2016

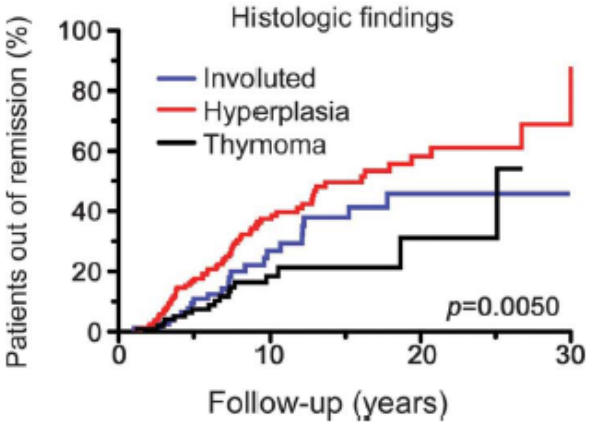
Only patients (n=232) who presented with mild disease and had SFEMG of the OOc at the time of diagnosis were included in the retrospective study.

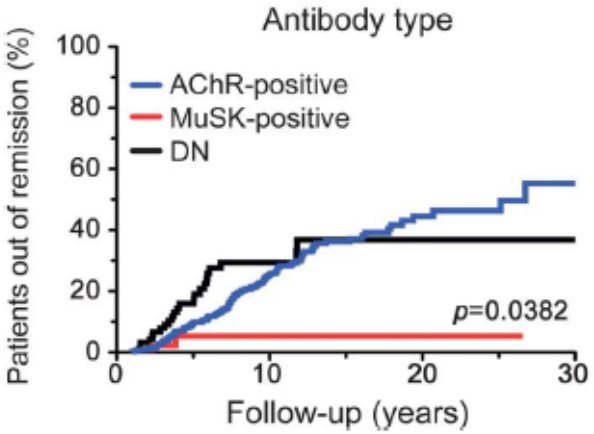
MG prognosis

- Over the years substantial reduction in mortality attributable to MG (Grob, 2008).
- Mortality is low in early-onset disease and increases progressively after age 50 years (Cortes-Vicente, 2020).



- In a recent case series of 677 MG pts approximately 2% died of MG-associated causes (Baggi, 2013).





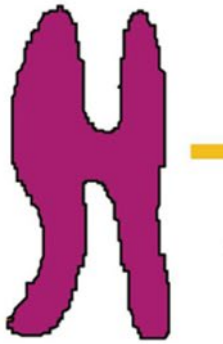
- MuSK-MG less responsive to common treatment than AChR-MG, similarly thymomatous MG is less responsive than non thymomatous AChR-MG (Baggi, 2013).

MG-TREATMENT:

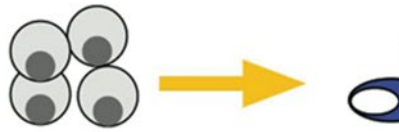
Treatment in MG is strictly associated with pathogenetic mechanisms

Rescue/short-term treatments

- IVIg
- PLEX
- Immunoadsorbtion

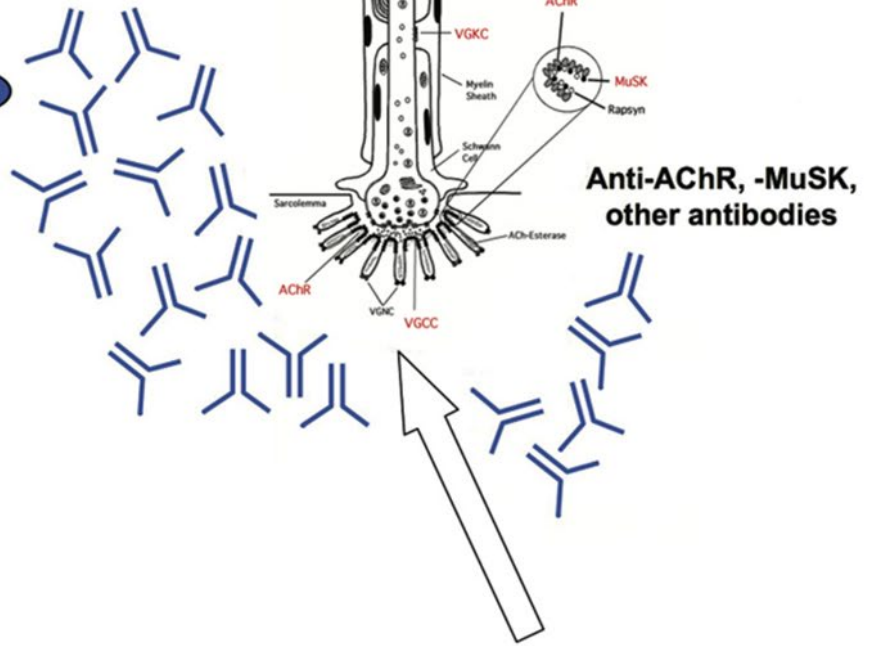


Thymus



Autoreactive T cells

B cells



Anti-AChR, -MuSK, other antibodies

Steroids

Conventional immunosuppressants

Thymectomy

Disease modifying treatments

Biologicals

Symptomatic treatments:

- AchE inhibitors
- 3,4 DAP?

Some issues

- Ideal treatment goal of establishing complete stable remission (CSR) or in clinical practice achievement of minimal manifestations (MM) or pharmacological remission (PR) with no greater than mild adverse events.
- It should be noted that prospectively designed, controlled studies have historically not been the norm in MG.
- Rare disease, making difficult adequate recruitment of patients for clinical trials.
- Therapy of MG, is still largely based on symptomatic treatment and non-specific immunosuppression.
- Primary outcomes often not well defined.
- Long latency before onset of effect of most of immunosoppressive treatment.
- Disease heterogeneity (age at onset, ocular vs generalized, antibody pattern, thymic histology).
- Comparator: placebo not ethical and concomitant immunosuppressive treatment may have unpredictable effect (as in mycophenolate mofetil and methotrexate clinical trials).
- **Has been MG natural history completely clarified?**

Corticosteroids (CST) in MG

- Since 1972 (*Jenkins RB Lancet;I: 765-7*).
- Few randomized controlled trials:

-Pred vs. placebo	(Howard, 1976)
-Pred vs. Aza	(Gajdos, 1993)
-Prednisolone with Aza	(Palace, 1998)
-*M*-Pred vs. IVIG	(Schuchardt, 2004)

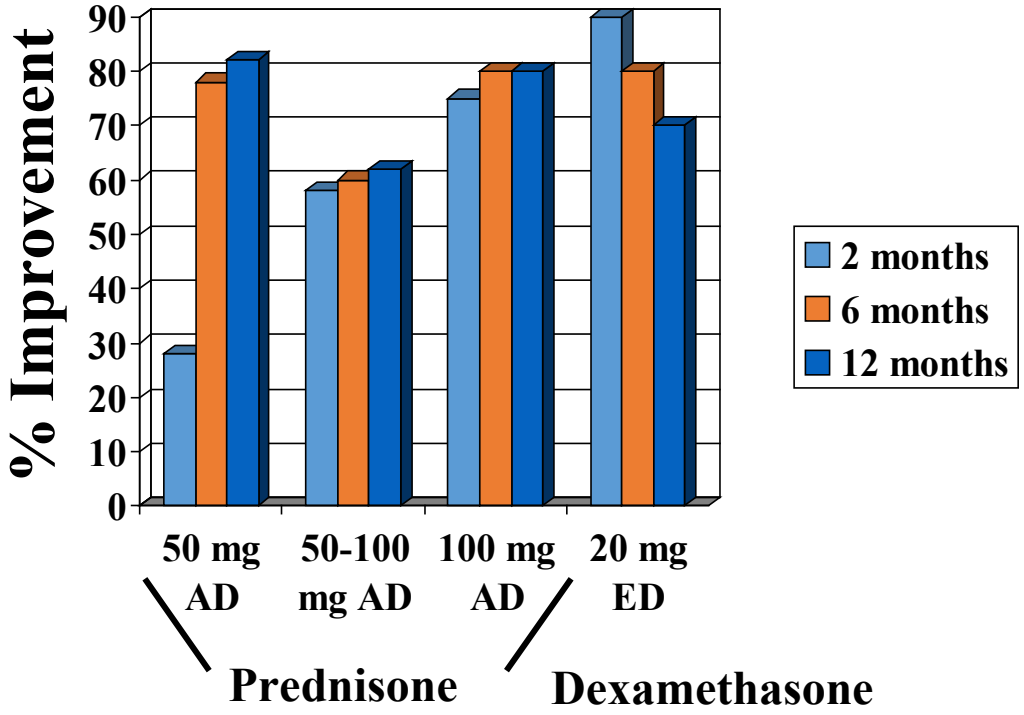
- Clinical efficacy: about 70% of patients improve (**still the most effective treatment**).
- First therapy when immunosuppressive drugs are needed.
- In ocular MG CST may prevent the progression to generalized MG (EFNS/ENS guidelines for ocular MG, 2014), but still poor evidence.
- Improvement: within 1–2 months.
- Chronic administration (years!), hence long-term monitoring of side effects.
- Monotherapy in about 60% of patients.

Controversies about the treatment of myasthenia gravis

LP Rowland *Journal of Neurology, Neurosurgery, and Psychiatry, 1980; 43: 644-659*

1. Is prednisone of *proven* value in treating Myasthenia Gravis?
2. Is one corticosteroid preferable to another?
3. What dosage should be used? For how long?
4. If there is no improvement, how long should steroid therapy be continued before deeming the trial a failure?
5. Are steroids safer or more hazardous than azathioprine?
6. How should properly informed consent be obtained before a patient embarks upon prolonged steroid therapy?
7. Are immunosuppressive drugs of proven value in treating Myasthenia Gravis?
8. Is any one immunosuppressive drug preferable to another?
9. Should immunosuppressive drugs be given before, after, or with steroid drugs?
10. What dosage should be used? Should it be arbitrary, according to body weight, or should mild leucopenia be induced?

Different CST regimens



- Most of the studies used prednisone or prednisolone, few data on deflazacort and dexatethasone or comparison between different CSTs.
- Short courses of high dose intravenous MP may be useful for exacerbations (Arsura, 1985).

Schedule for steroid treatment

- **"High dose"**

  Prednisone: 75–100 mg according to body weight every day for 6–8 weeks (time to maximum improvement) shift to alternate days slow tapering.

- **"Slowly-increasing dose"**

  Prednisone: 30 mg on alternate days (AD), increase with 10 mg AD up to maximum improvement.

- **Evidence of reduced side effects by the alternate-day regimen is weak (Gilhus, 2015).**
- Caution to initial exacerbation and possible clinical worsening when increasing dosages (hospitalization, especially if bulbar symptoms).

If there is no improvement, how long should steroid therapy be continued before deeming the trial a failure?

- **No definitive answer since no controlled studies have been conducted**
- **Uncontrolled clinical studies on steroid usage pointed out that starting treatment with high dose steroid maximal benefit is reached within 30–40 days**
- **More difficult to say using the slow increasing dosage schedule**
- **Based on clinical practice, it is reasonable to say that no clinical benefit after 2 months of high dose steroid treatment suggests a potential treatment failure; at this point, association with an immunosuppressant should be strongly considered.**

Should immunosuppressive drugs be given before, after, or with steroid drugs?

• *Journal of Neurology, Neurosurgery, and Psychiatry, 1993; 56: 1157–1163*

A randomised clinical trial comparing prednisone and azathioprine in myasthenia gravis. Myasthenia Gravis Clinical Study Group. Gajdos P. et al

It appears that the most severe forms of the disease, often resistant to prednisone or azathioprine alone, could benefit from the combination of both drugs.

• *J Neurology 1988; 235:449–53*

Azathioprine as a single drug or in combination with steroids in the treatment of myasthenia gravis. Mantegazza R et al.

Positive responses were noted in 75% of patients on Aza alone and in 70% receiving the combined regimen. The clinical course of the two groups differed in terms of respiratory crisis and need for plasma exchange.

• *Neurology 1998; 50: 1778–1783.*

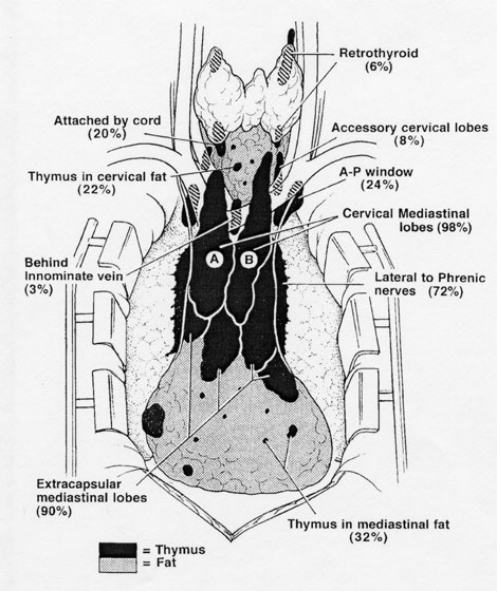
A randomized double-blind trial of prednisolone alone or with azathio- prine in myasthenia gravis. Myasthenia Gravis Study Group. Palace J, et al.

Azathioprine as an adjunct to alternate day prednisolone in the treatment of antibody-positive generalized MG reduces the maintenance dose of prednisolone and is associated with fewer treatment failures, longer remissions, and fewer side effects.

Prednisone and azathioprine should be started together in pts with progressive MG symptoms (EFNS guidelines for MG, 2010)

Thymectomy

Aim of thymectomy is to modify MG natural history with the idea of removing a site of autosensitization or perpetuation of the autoimmune attack.



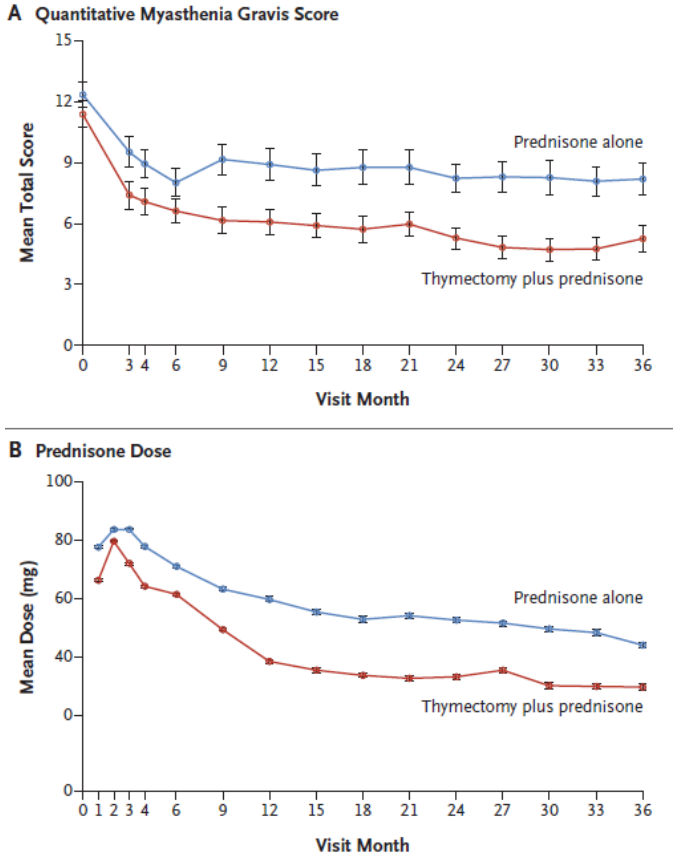
Jaretzki, et al., Neurology, 2000.

- In non-thymomatous generalized AChR-MG, thymectomy is performed to increase the chance to reach CSR or potentially avoid or minimize the dose or duration of immunotherapy.
- Should be performed early in the disease.
- Due to of the long delay in onset of effect, thymectomy for MG is an elective procedure.
- With rare exceptions (small thymoma in the elderly), all MG patients with thymoma should undergo thymectomy.
- No evidence supporting thymectomy in MuSK- or LRP4-MG.
- Less invasive (endoscopic and robotic) approaches appear to yield similar results to more aggressive approaches (transsternal thymectomy), although no data from randomized, controlled comparison studies.
- Thymectomy may be considered in patients with generalized SNMG or ocular MG if they fail to respond adequate to immunosuppressive (IS) therapy or to avoid/ minimize intolerable adverse effects from IS therapy (Narayanaswami, Neurology, 2020).

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 11, 2016 VOL. 375 NO. 6

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*



- 126 patients with **generalized AChR-MG <5 years duration between 18 and 65 years** of age randomized between 2006 and 2012.
- The authors compared compared extended transsternal thymectomy plus alternate-day prednisone with alternate- day prednisone alone.
- The primary outcomes were:
  - The time-weighted average QMG score over a 3-year period and
  - the time-weighted average required dose of prednisone over a 3-year period.

➢ Thymectomy was associated with a QMG score that was 2.85 points lower than that with medical therapy alone and considered clinically significant.

➢ Patients in the thymectomy group also had a lower average requirement for alternate-day prednisone (44 mgs vs. 60 mgs).

➢ A further observation from the 2-year extension study is that, even after thymectomy, MG still requires corticosteroids and immunosuppressive drugs for several years (Wolfe et al., Lancet Neurol. 2019).

Refractory MG

Definition of refractory MG. PIS is unchanged or worse **after corticosteroids and at least 2 other IS agents**, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by patient and physician.

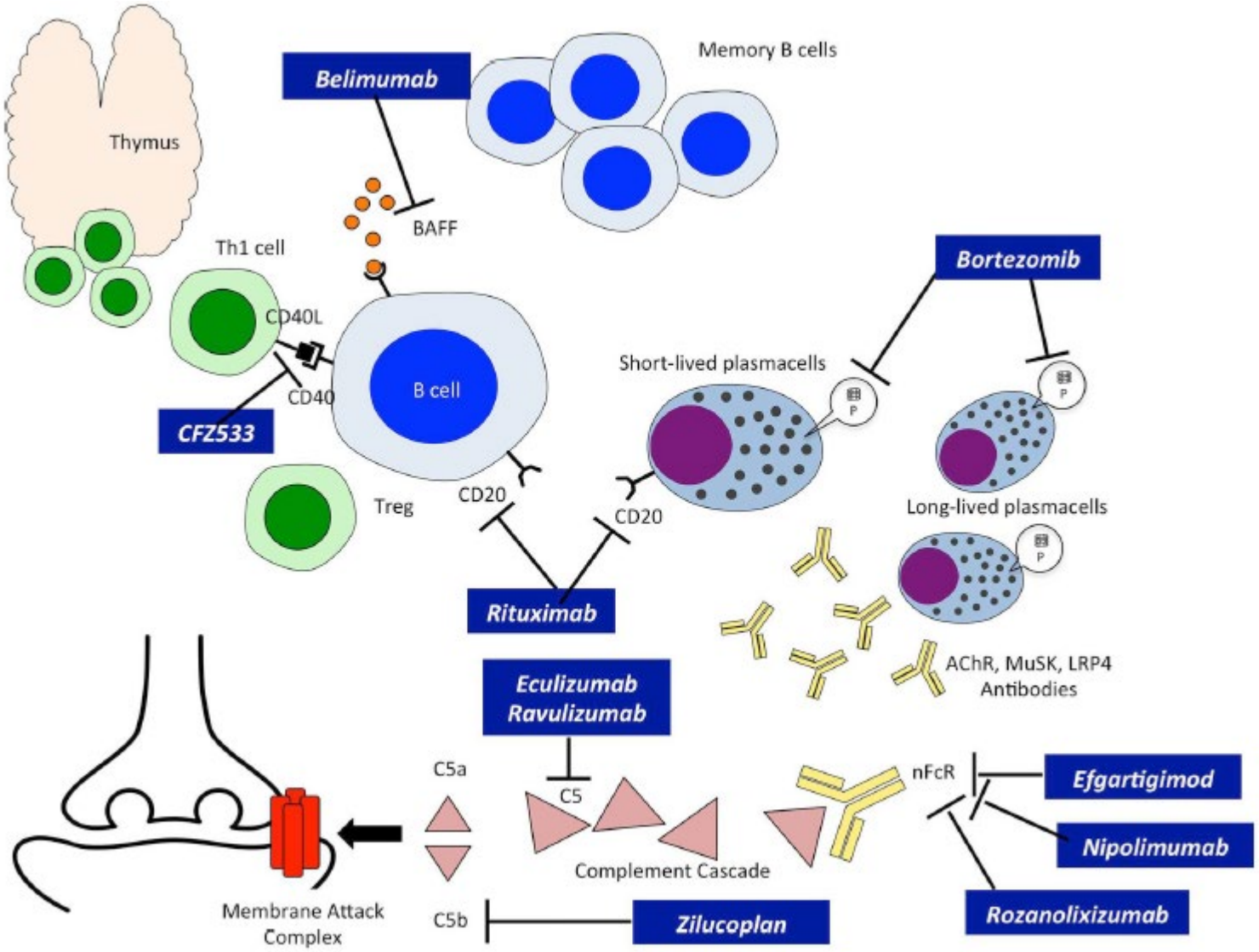
International consensus guidance for management of myasthenia gravis
Executive summary
Neurology® 2016;87:419-425

- A significant proportion of patients with MG struggle with refractory disease marked by persistent symptoms that may be severe, with the side effects of prolonged immunomodulatory treatment, or with the need for chronic rescue therapy.
- It also showed that improved treatment paradigms should be based on MG subtypes.
- **Factors associated with refractory MG:**
  - Musk-Ab (however, being AChR-MG much more frequent than MuSK-MG the total number of refractory AChR-MG is the highest);
  - Female;
  - Early onset;
  - Thymoma;
  - Thymectomy.

MG-TREATMENT: *BIOLOGICALS - PRECISION MEDICINE*

-The introduction of new biological compounds directed specifically against different steps of the MG autoimmune process has opened a new era.

-They belong to 3 major groups:
a. Complement inhibitors;
b. Neonatal Fc Receptor (nFcR) antagonists;
c. anti-B cell therapies.

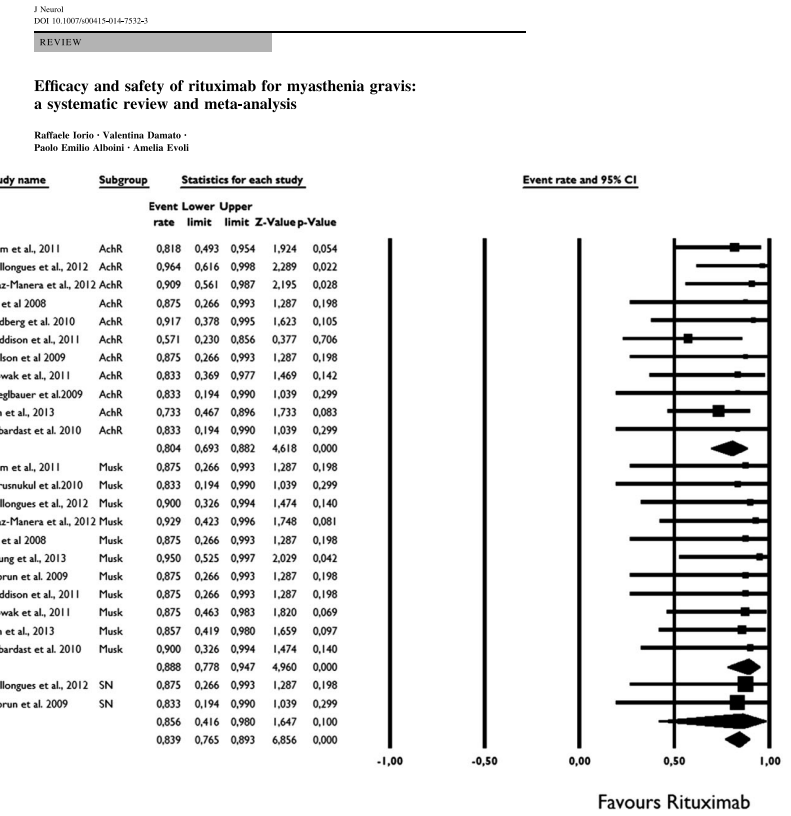


Mantegazza and Antozzi, Frontiers in Neurology, 2020

Rituximab

- Anti-CD20, chimeric, IgG1 monoclonal antibody.
- Targets the precursor of plasma cells, without any effect on long-lived plasma cells.
- Acts also on T-cell response (as a small subset of T lymphocytes expresses CD20).
- 375 mg/m^2 x 4 consecutive weekly infusions or 500 mg x 2 or 1000 mg x 2(the last regimen sufficient to induce rapid and near-complete depletion of CD19+ for more than 24 weeks).

- 168 patients.
- Response rate 83.9%.
- Higher in MuSK-MG (89%) than AChR-MG (80.4%), although not significant).
- Efficacious in all treatment regimen.
- Adverse event 7/168 (4%):
  -4 infection;
  -2 prolonged B cell depletion;
  -1 heart failure.



Phase 2 Trial of Rituximab in Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis

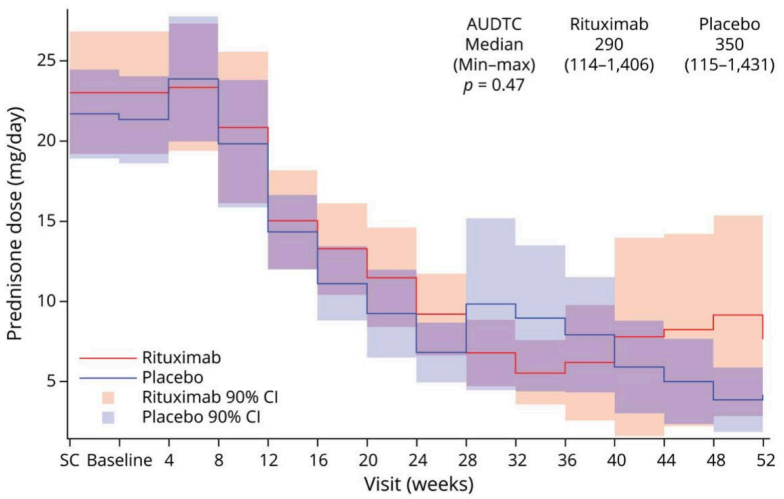
The BeatMG Study

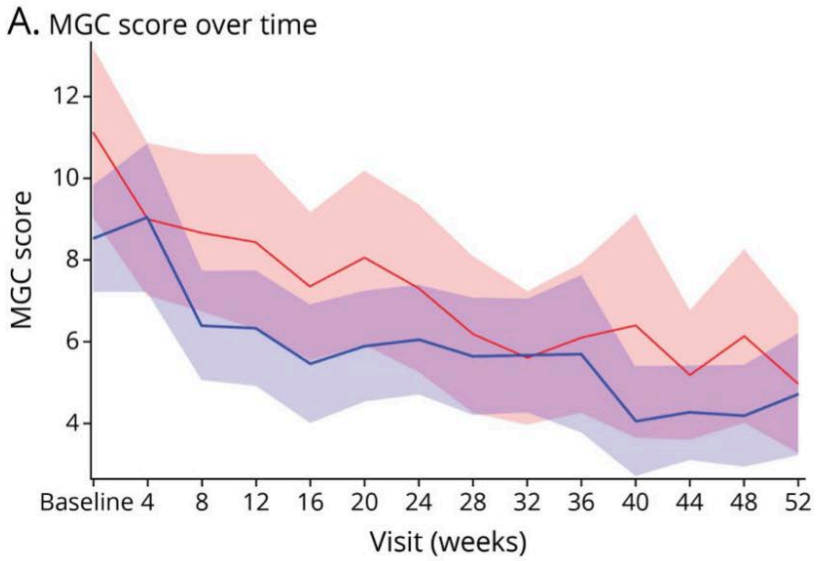
Richard J. Nowak, MD, Christopher S. Coffey, PhD, Jonathan M. Goldstein, MD, Mazen M. Dimachkie, MD, Michael Benatar, MD, PhD, John T. Kissel, MD, Gil I. Wolfe, MD, Ted M. Burns, MD, Miriam L. Freimer, MD, Sharon Nations, MD, Volkan Granit, MD, A. Gordon Smith, MD, David P. Richman, MD, Emma Ciafaloni, MD, Muhammad T. Al-Lozi, MD, Laura Ann Sams, MD, Dianna Quan, MD, Eroboghene Ubogu, MD, Brenda Pearson, BS, Aditi Sharma, MBBS, Jon W. Yankey, MS, Liz Uribe, MS, Michael Shy, MD, Anthony A. Amato, MD, Robin Conwit, MD, Kevin C. O'Connor, PhD, David A. Hafler, MD, Merit E. Cudkowicz, MD, and Richard J. Barohn, MD, on behalf of the NeuroNEXT NN103 BeatMG Study Team

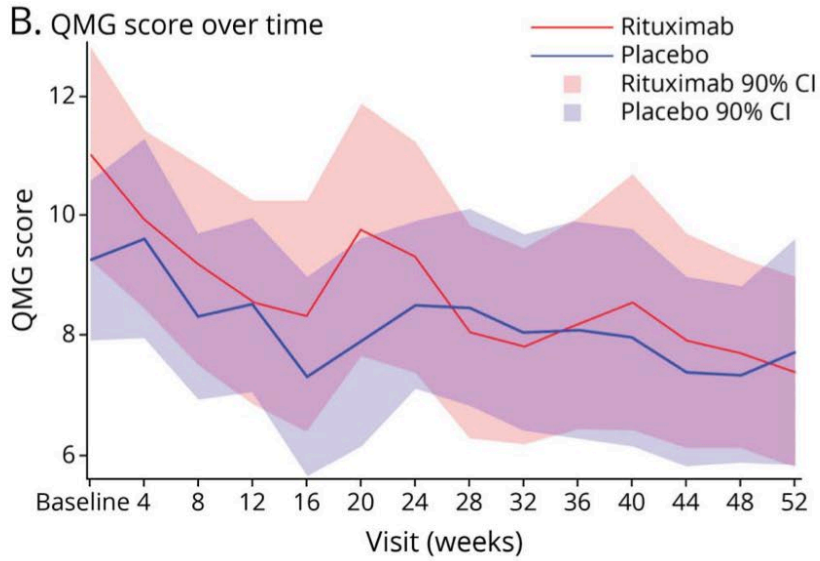
Correspondence
Dr. Nowak
richard.nowak@yale.edu

Neurology® 2022;98:e376-e389. doi:10.1212/WNL.0000000000013121

- 52 enrolled pts with generalized nonthymomatous AChR-Ab+ MG on a stable regimen of prednisone for 4 weeks;
- 2 cycles of RTX 6 months apart were compared to placebo with the primary outcome being a steroid-sparing effect (≥75% reduction in mean daily prednisone requirements).







- Preliminary results reported that the area under the curve for prednisone was not significantly different between RTX and placebo groups, with 60% on RTX and 56% on placebo achieving the primary outcome.
- No significant differences in mean QMG or MG-composite (MGC) changes between the groups.
- **<u>The study suggests that in mildly to moderately symptomatic generalized AChR-Ab+ MG, RTX is unlikely to have a clinically meaningful steroid-sparing effect over 12 months.</u>**

Responsiveness to low-dose rituximab in refractory generalized myasthenia gravis

Sisi Jing[a,b,1], Yang Song[c,1], Jie Song[b], Song Pang[d], Chao Quan[b], Lei Zhou[b], Yuyuan Huang[b], Jiahong Lu[b], Jianying Xi[b,*], Chongbo Zhao[a,b,**]

- Rituximab 600 mg (100 mg on first day plus 500 mg the following day), sufficient to deplete B cells and maintain low B-cell counts until 6 months after infusion.
- Maintaining low CD19+/CD20+ B cell counts (< 1%) could not prevent clinical relapse.

Recommendations unchanged from the 2016 consensus guidance (Narayanaswami, Neurology, 2020):

1. Rituximab should be considered as an early therapeutic option in patients with MuSK-Ab+ MG who have an unsatisfactory response to initial immunotherapy.

2. The efficacy of RTX in refractory AChR-Ab+ MG is uncertain. It is an option if patients fail or do not tolerate other IS agents.

Eculizumab (Soliris)

- Eculizumab is a fully humanized monoclonal antibody targeting complement component C5 inhibiting its conversion to C5a e C5b, hence blocking terminal complement activation and MAC complex formation, which plays an essential role in MG pathogenesis.
- Approved in Italy for refractory MG.

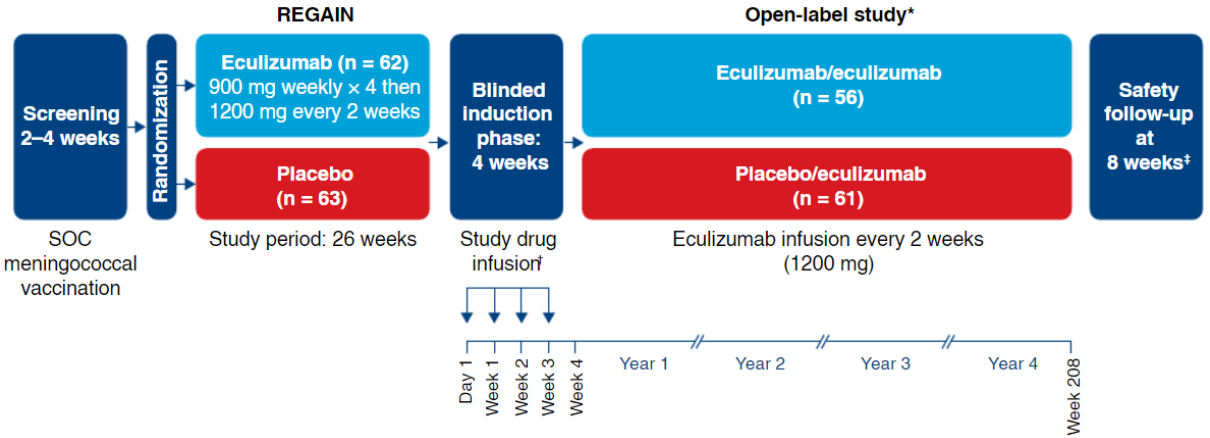
Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study

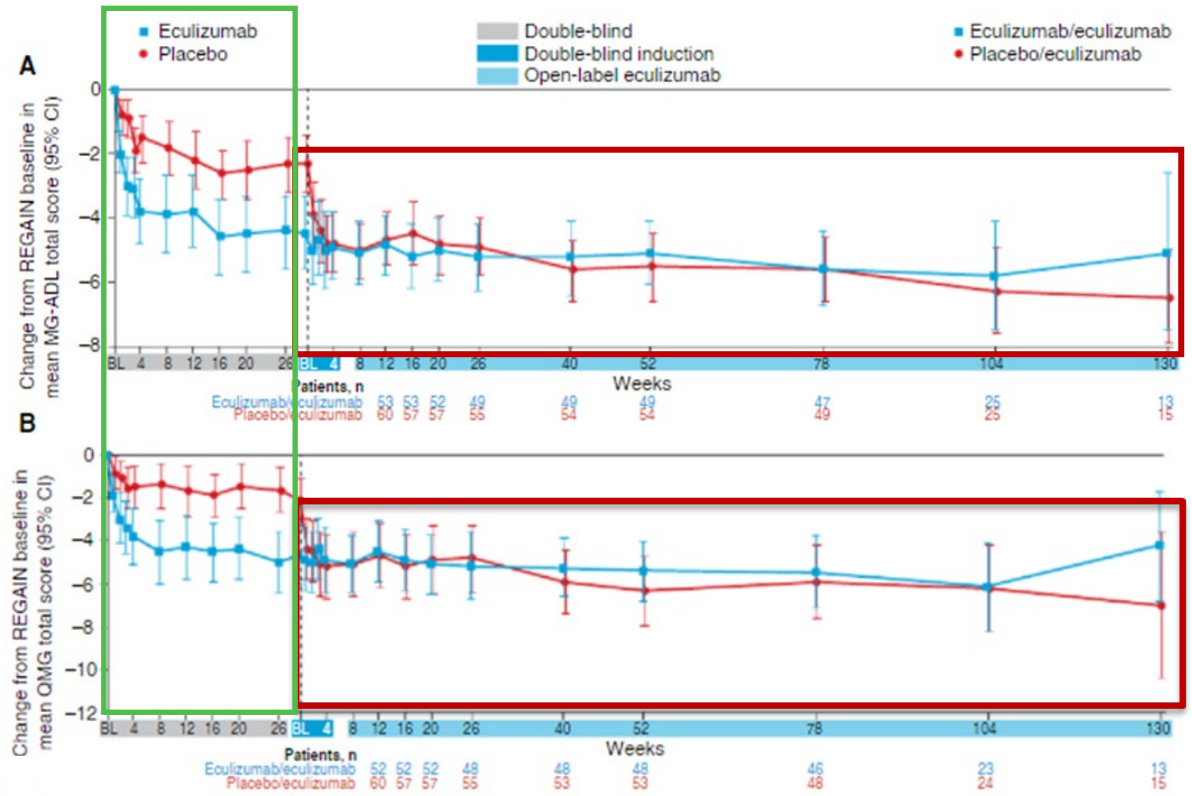
*James F Howard Jr, Kimiaki Utsugisawa, Michael Benatar, Hiroyuki Murai, Richard J Barohn, Isabel Illa, Saiju Jacob, John Vissing, Ted M Burns, John T Kissel, Srikanth Muppidi, Richard J Nowak, Fanny O'Brien, Jing-Jing Wang, Renato Mantegazza, in collaboration with the REGAIN Study Group**

Lancet Neurol 2017; 16: 976–86

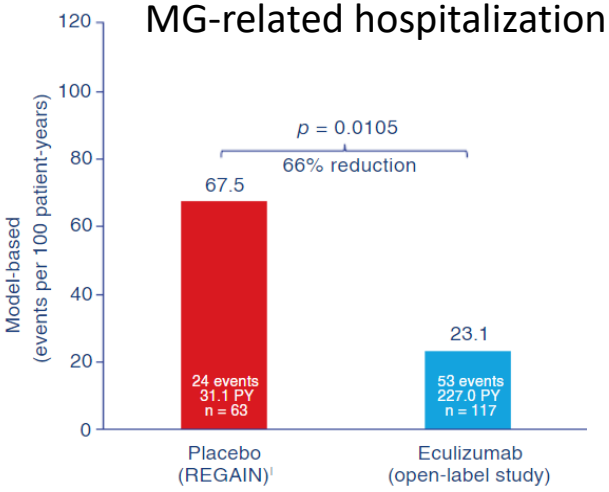
- 126 patients with refractory generalized MG (no thymoma).
- Intravenous administration.
- Induction dosing 900 mg on day 1 and weeks 1, 2, and 3; 1200 mg at week 4; and maintenance dosing 1200 mg every second week thereafter.
- Treatment time: 26 weeks.
- The primary efficacy endpoint was the change in MG-ADL total score from baseline to week 26 for eculizumab compared with placebo (not significant).

MG-TREATMENT: *ECULIZUMAB (REGAIN trial and OLE)*





MG-related hospitalization

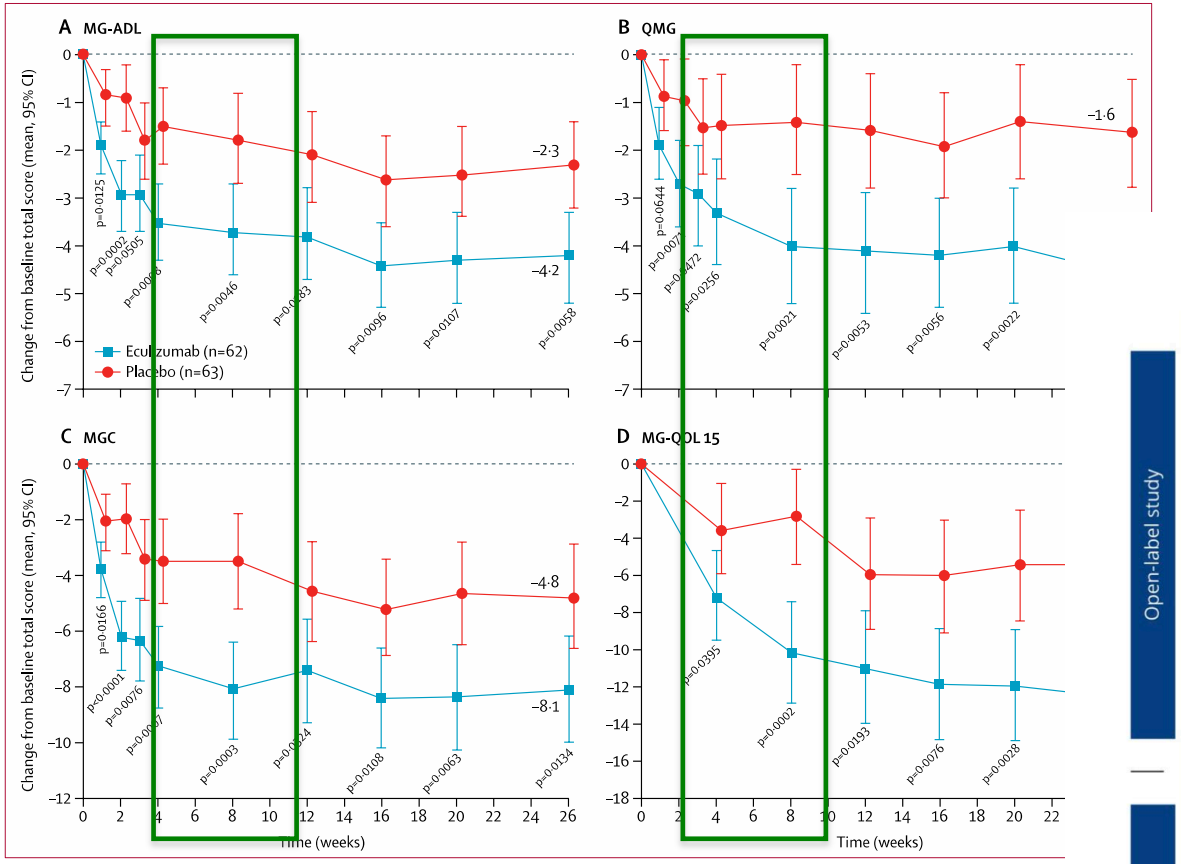


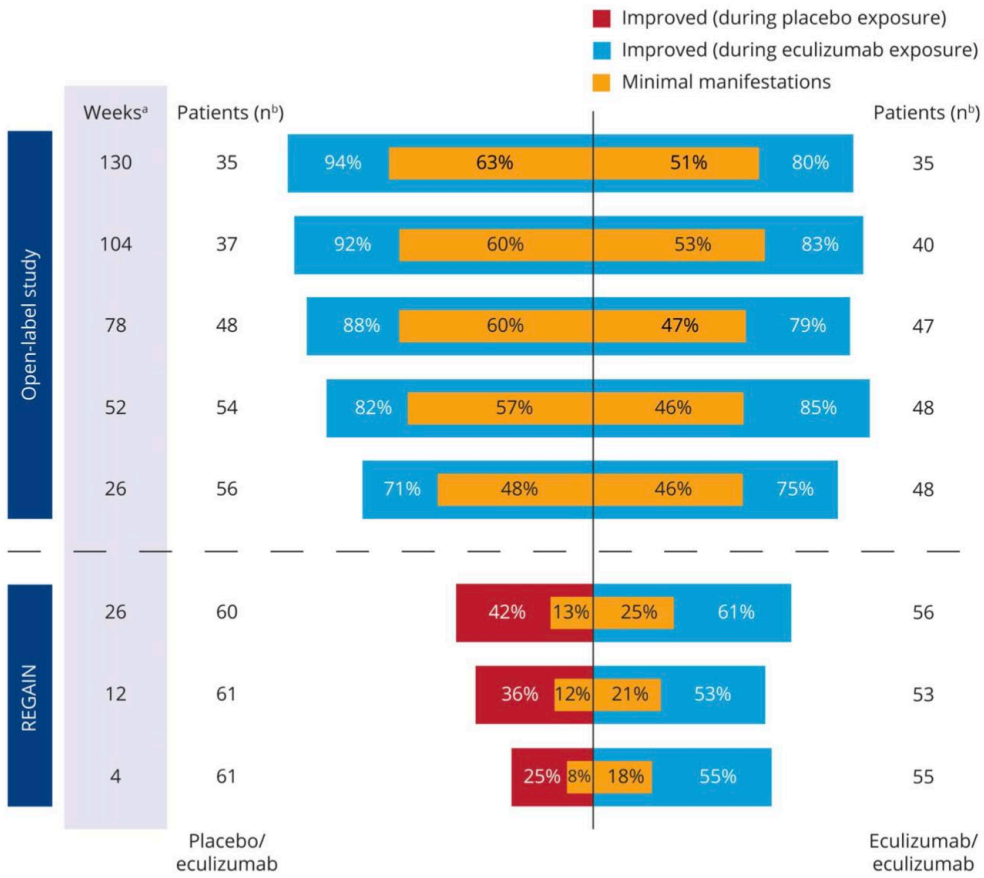
MG-ADL *p*= 0·0160
QMG *p*=0·0055
MGC *p*=0·0414
MG-QOL15 *p*=0·0134

*December 31, 2017 data cutoff point

Howard JF, et al. Lancet Neurol, 2017;
Muppidi S et al. Muscle&Nerve, 2019

Most of the treatment effect by week 12 (with initial effect by week 1 in MGC score)





Mantegazza et al., 2021

4 patients discontinued Eculizumab due to:
- MG crisis (1)
- bacteraemia, bowel perforation, and adenoK of prostate gland (3).

Most of the AE were mild to moderate in severity and unrelated to the study drug.

Complement Inhibitors

Eculizumab in treatment myasthenia gravis in has been authorised in the EU as Soliris since 14 August 2017.

Zilucoplan (s.c.)

RAISE

Randomized Trial of Zilucoplan in SubjEcts with Myasthenia Gravis

A Phase 3, Multicenter, Randomized, Double Blind, Placebo-Controlled Study to Confirm the Safety, Tolerability, and Efficacy of Zilucoplan in Subjects with Generalized Myasthenia Gravis

NCT04115293

Ravulizumab (e.v.)

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Ravulizumab in Complement-Inhibitor-Naïve Adult Patients With Generalized Myasthenia Gravis

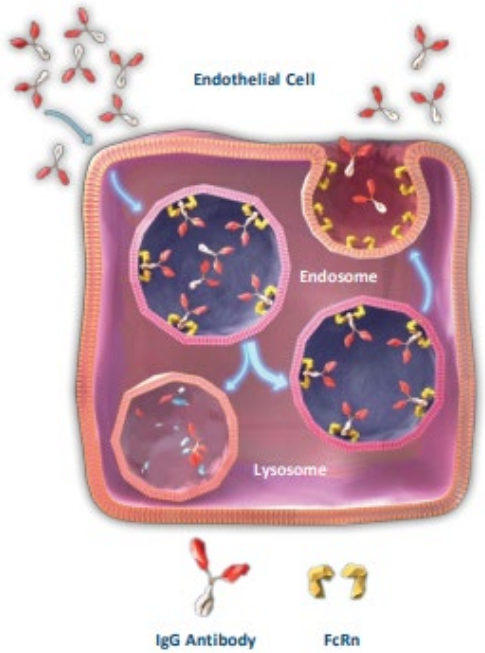
NCT03920293

https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141304

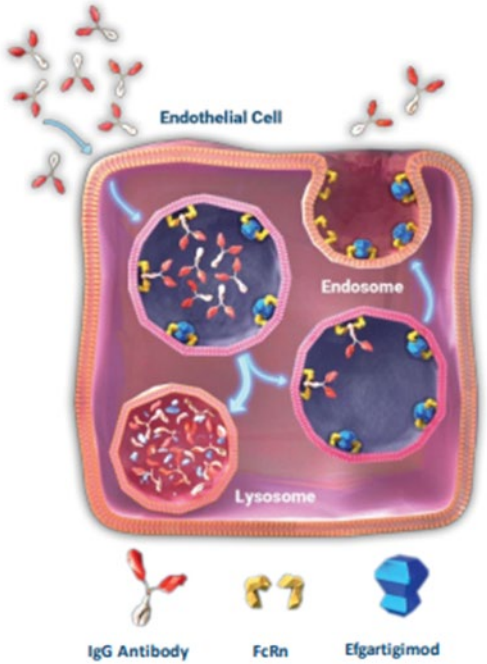
Neonatal FcRn Inhibitors

ARGX blocks IgG recycling and increases IgG clearance: faster remission and drastically reduced length and seriousness of acute autoimmune crisis.

- FcRn recycles IgG antibodies extending their abundancy



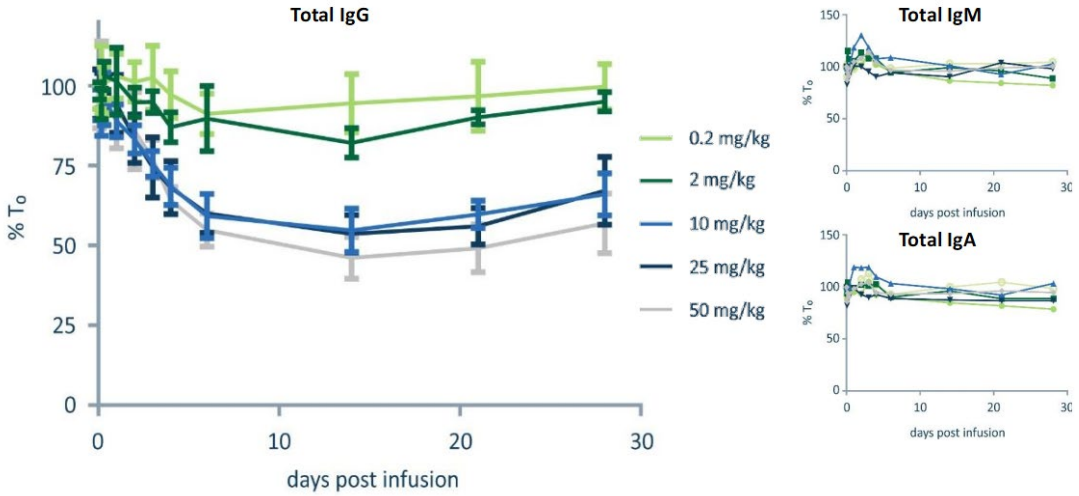
- Efgartigimod Blocks FcRn leading to IgG elimination



- Human IgG1 **Fc fragment** uniquely modulates FcRn, preserving characteristic pH dependent binding of endogenous IgG
- No impact on IgM, IgA or human serum albumin
- Does not affect IgG production, an important component to a vaccine response

https://www.argenx.com/pipeline/efgartigimod

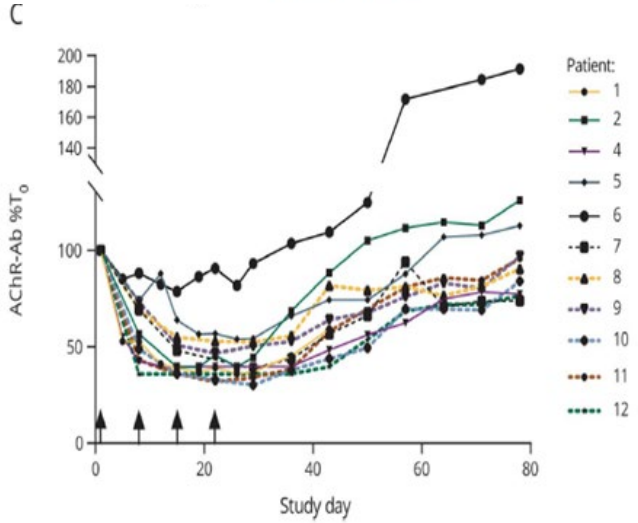
Ulrichts, poster MG conference, NY, 2017



A single intravenous infusion of ARGX-113 in healthy volunteers :

- Dose-dependent IgG reduction;
- up to 50% IgG reduction (6 days after infusion);
- Selective IgG reduction;
- Low IgG levels for more than four weeks.

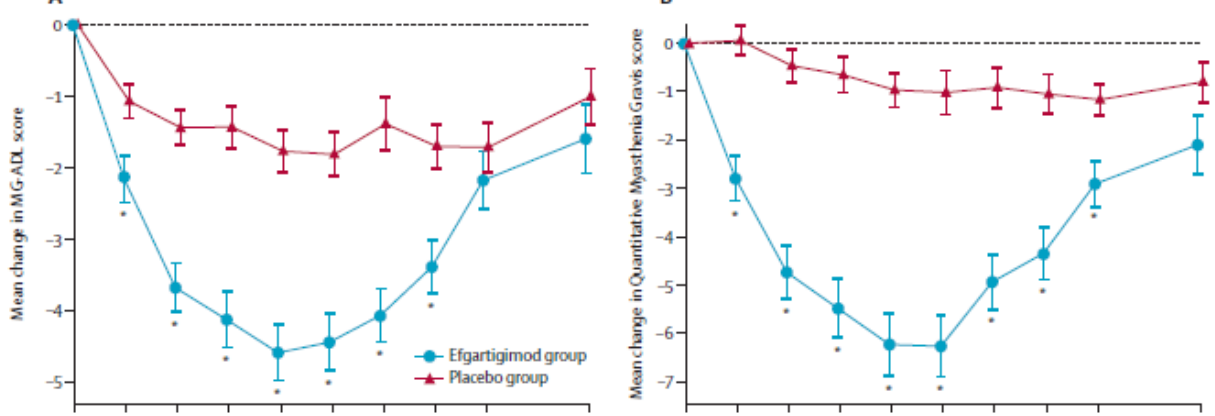
EFGARTIGIMOD (Adapt trial)



- Efgartigimod (10 mg/kg) vs placebo
- Anti-AChR+, anti-MuSK+ and seronegatives
- 4 infusions per cycle (one per week), repeated as needed depending on clinical response, no sooner than 4 weeks after the end of the previous cycle.

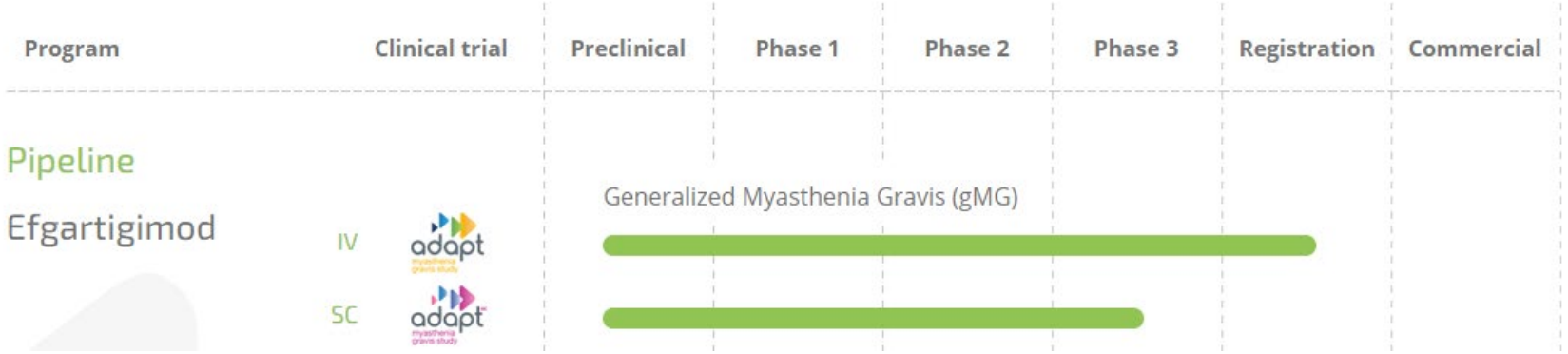
Favorable tolerability profile.

MG-ADL p <0.001
QMG p <0.001

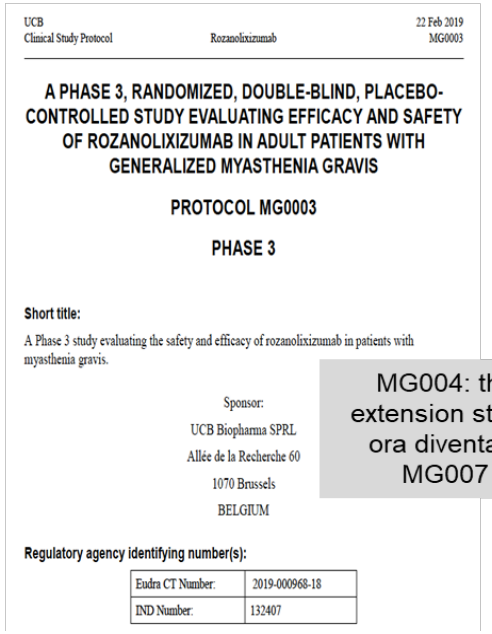


Howard JF, et al. Lancet Neurol, 2019, 2021

Neonatal FcRn Inhibitors



Phase 3 for Rozanolixizumab



UCB
Clinical Study Protocol
Rozanolixizumab
22 Feb 2019
MG0003

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING EFFICACY AND SAFETY OF ROZANOLIXIZUMAB IN ADULT PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

PROTOCOL MG0003

PHASE 3

Short title:

A Phase 3 study evaluating the safety and efficacy of rozanolixizumab in patients with myasthenia gravis.

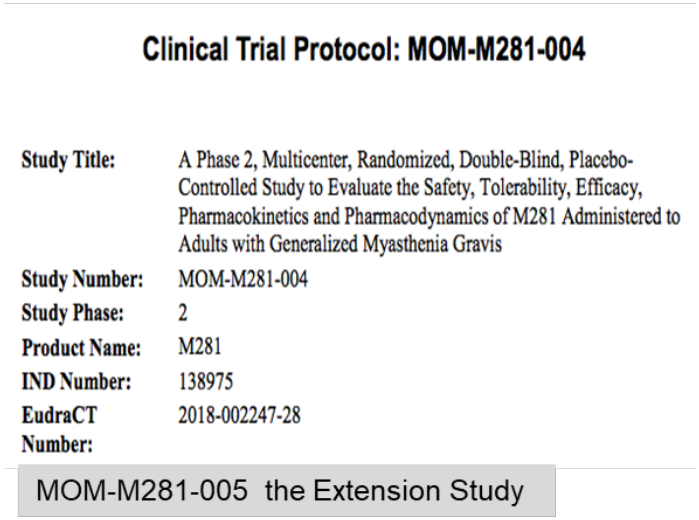
Sponsor:
UCB Biopharma SPRL
Allée de la Recherche 60
1070 Brussels
BELGIUM

Regulatory agency identifying number(s):

Eudra CT Number:	2019-000968-18
IND Number:	132407

MG004: the extension study, ora diventato MG007

Phase 2 for Nipocalimab



Clinical Trial Protocol: MOM-M281-004

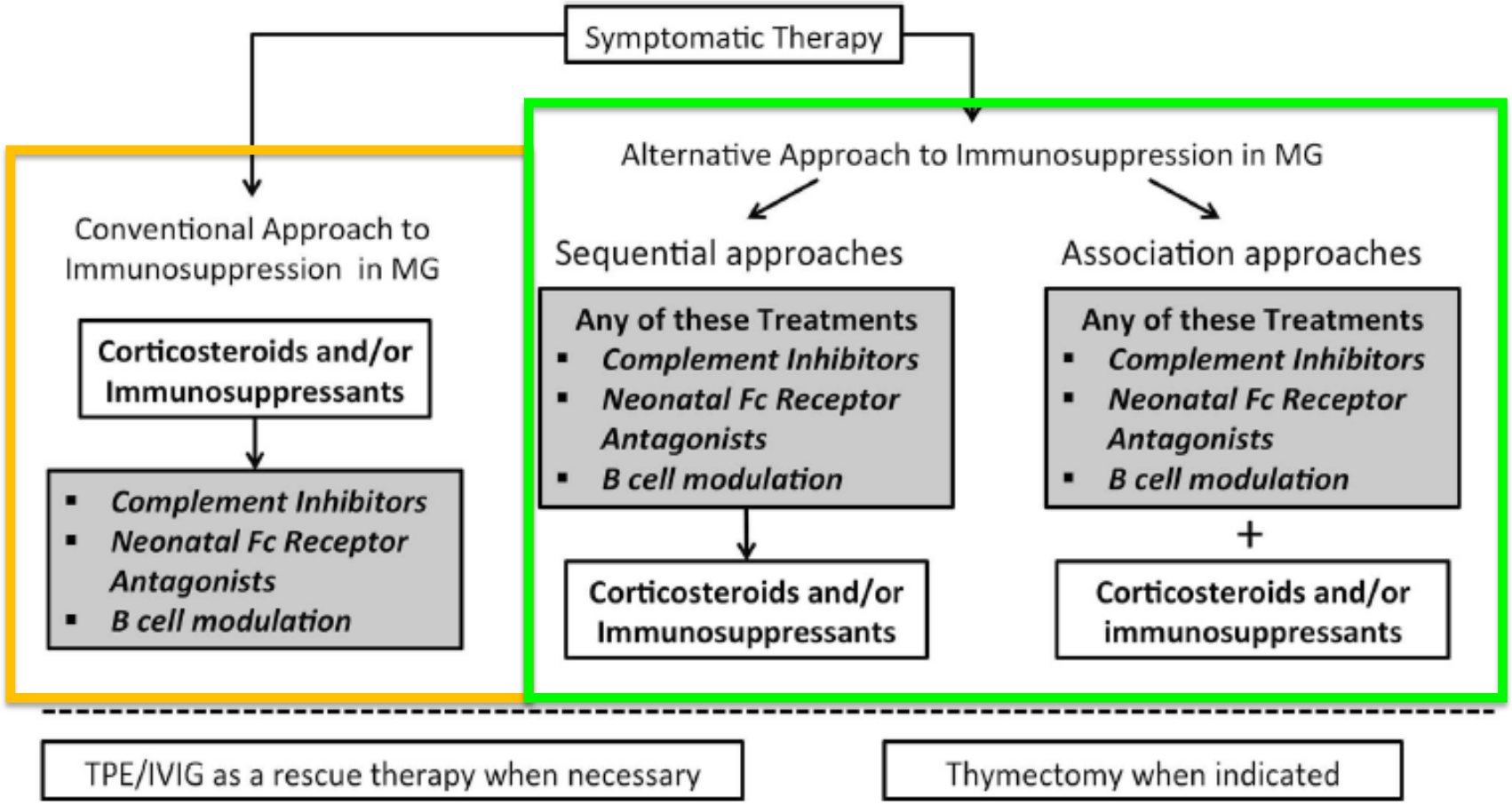
Study Title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics and Pharmacodynamics of M281 Administered to Adults with Generalized Myasthenia Gravis
Study Number:	MOM-M281-004
Study Phase:	2
Product Name:	M281
IND Number:	138975
EudraCT Number:	2018-002247-28

MOM-M281-005 the Extension Study

MG-ADL and RCTs in MG

RCT	Target/	Primary EndPoint
REGAIN & OLE	C5 (Eculizumab)	MG-ADL ≥ 3
ADAPT/ADAPT+	FCRn (Efgartigimod)	MG-ADL ≥ 3
CHAMPION	C5 (Ravulizumab)	MG-ADL ≥ 3
RAISE	C5 (Zilucoplan)	MG-ADL ≥ 3
MycarinG	FcRn (Rozanolixizumab)	MG-ADL ≥ 2
MINT	CD19 (Inebilizumab)	MG-ADL ≥ 3
ASCEND	FcRn (IMVT-401 mAb)	Anti AChR Ab
MOM-M281-04	FcRn (Nipocalimab)	MG-ADL ≥ 3
REGENERON	C5+siRNA (Pozelimab+Cemdisiran)	MG-ADL ≥ 3
Luminesce	IL6R (Satralizumab)	MG-ADL ≥ 2
SAR442168	Bruton Kinase (Tolebrutinib)	MG-ADL ≥ 2

CONVENTIONAL vs NEW THERAPEUTIC ALGORITHMS



Mantegazza R and Antozzi C, Front Neurol 2020

New horizons in MG

"Even with today's knowledge and available treatments, it is a challenge to find the optimal treatment for the individual patient"
Gilhus, NEJM, 2017

- New drugs available for refractory MG and targeted therapies for specific MG subgroups.
- Their safety over the years and in large cohorts?
- Pediatric population?
- Impact of Covid-19 on MG?
- Need to better understanding MG pathogenesis, factors predicting response to treatment and disease worsening.
- Fatigue vs fatigability?

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Immunodegenerative
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