Myasthenia Gravis News

Dr H. Ayromlou

Professor of neurology

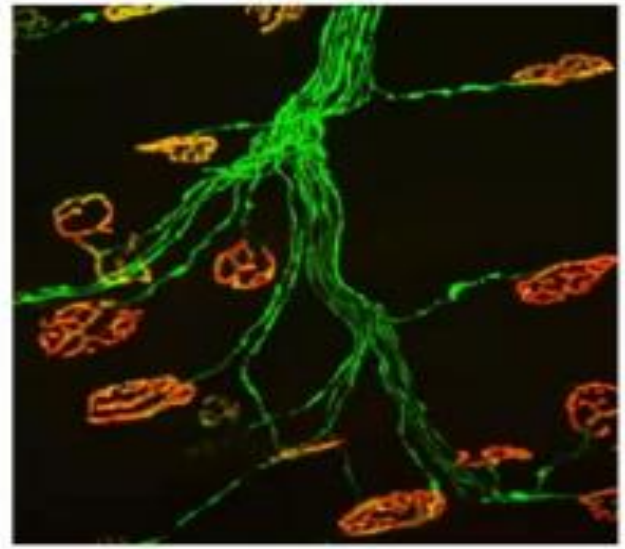
Tabriz University of Medical Sciences

Introduction

- Myasthenia gravis forms the largest disease group of neuromuscular junction disorders and is caused by *pathogenic autoantibodies to components of the postsynaptic muscle endplate*
- Patients with MG should be classified into *subgroups, with implications for diagnosis, optimum therapy, and prognosis*
- Most patients with *mild to moderate* symptoms: *full remission or substantial improvement*
- *Severe* cases: *Full remission is rare*, some variation over time is common, and steady progression is unusual
- ***In 10–15% patients***: full control of the disease is not possible or is only at the cost of severe side effects of immunosuppressive therapy

Autouimmune disorders at the neuromuscular junction

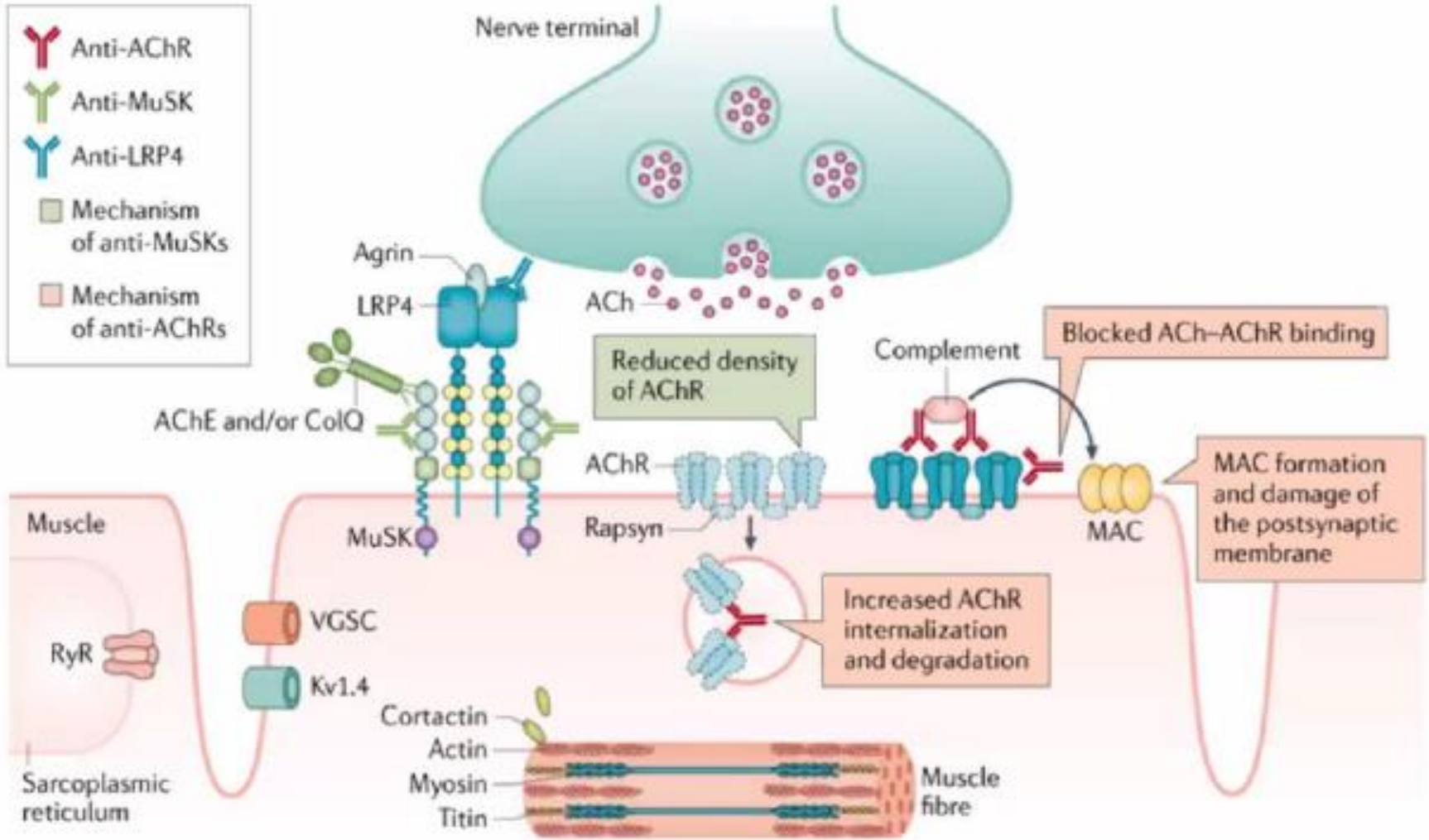
- Myasthenia gravis
  - Early onset thymic hyperplasia – AChR ab.
  - Late onset normal thymus - AChR ab.
  - Thymoma - AChR ab.
  - MuSK autoantibodies
  - LRP4 autoantibodies
  - No detectable autoantibody
    - Low affinity
    - Unknown antibody
    - No antibody
  - Ocular - AChR ab. / No detectable



- Lambert-Eaton myasthenic syndrome (LEMS)
  - Paraneoplastic - VGCC ab.
  - Non-paraneoplastic - VGCC ab.

- Neuromyotonia (Isaac's syndrome)
  - Paraneoplastic (thymoma, small cell lung carcinoma) - VGKC ab.
  - Non-paraneoplastic - VGKC ab.

Pathophysiology of MG at the neuromuscular junction



Gilhus, N. E. et al. (2019) Myasthenia gravis. *Nature Rev. Dis. Primers*

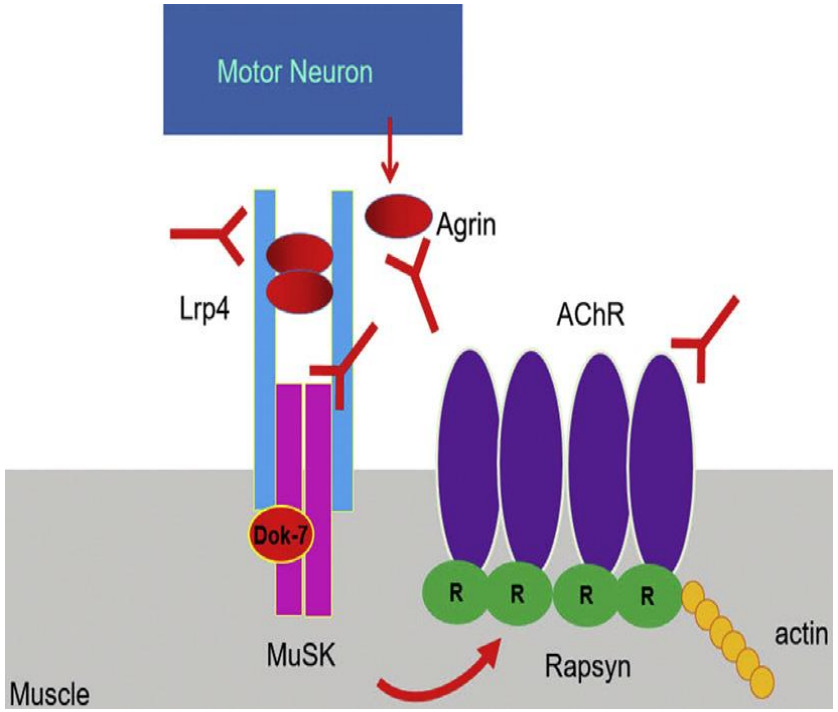
Classification of MG

Due to implications for management, myasthenia gravis could be classified by:

- Clinical status (ocular vs generalized disease),
- Disease severity
- **Antibody type**
- Associated thymic pathology (thymoma, thymic hyperplasia)
- Response to treatment

Autoantibody targets defining MG subtypes

- **Stratification based on autoantibody is of great relevance as therapeutic approaches may vary accordingly.**
- **Anti-acetylcholine receptor (AChR) antibodies have been described in the seventies**
- **Since 2001 and 2011, 2 new subgroups of patients have been characterized with autoantibodies against other components of the NMJ:**
  - **muscle-specific kinase (MuSK)**
  - **low-density lipoprotein- related protein 4 (LRP4)**

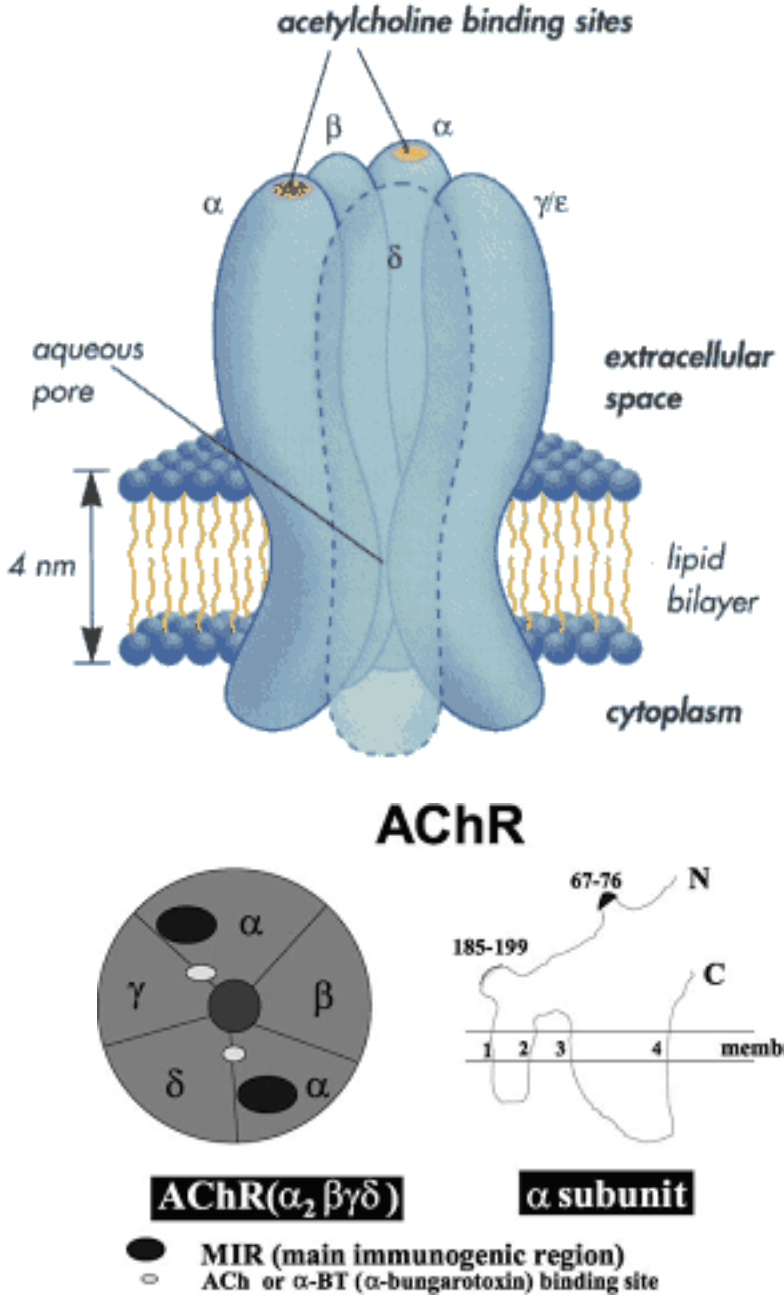


Myasthenia gravis subgroups

- ***Early-onset MG with AChR antibodies***
- ***Late-onset MG with AChR antibodies***
- ***Thymoma-associated MG***
- ***MUSK-associated MG***
- ***LRP4-associated MG***
- ***Antibody-negative generalized MG***
- ***Ocular MG***

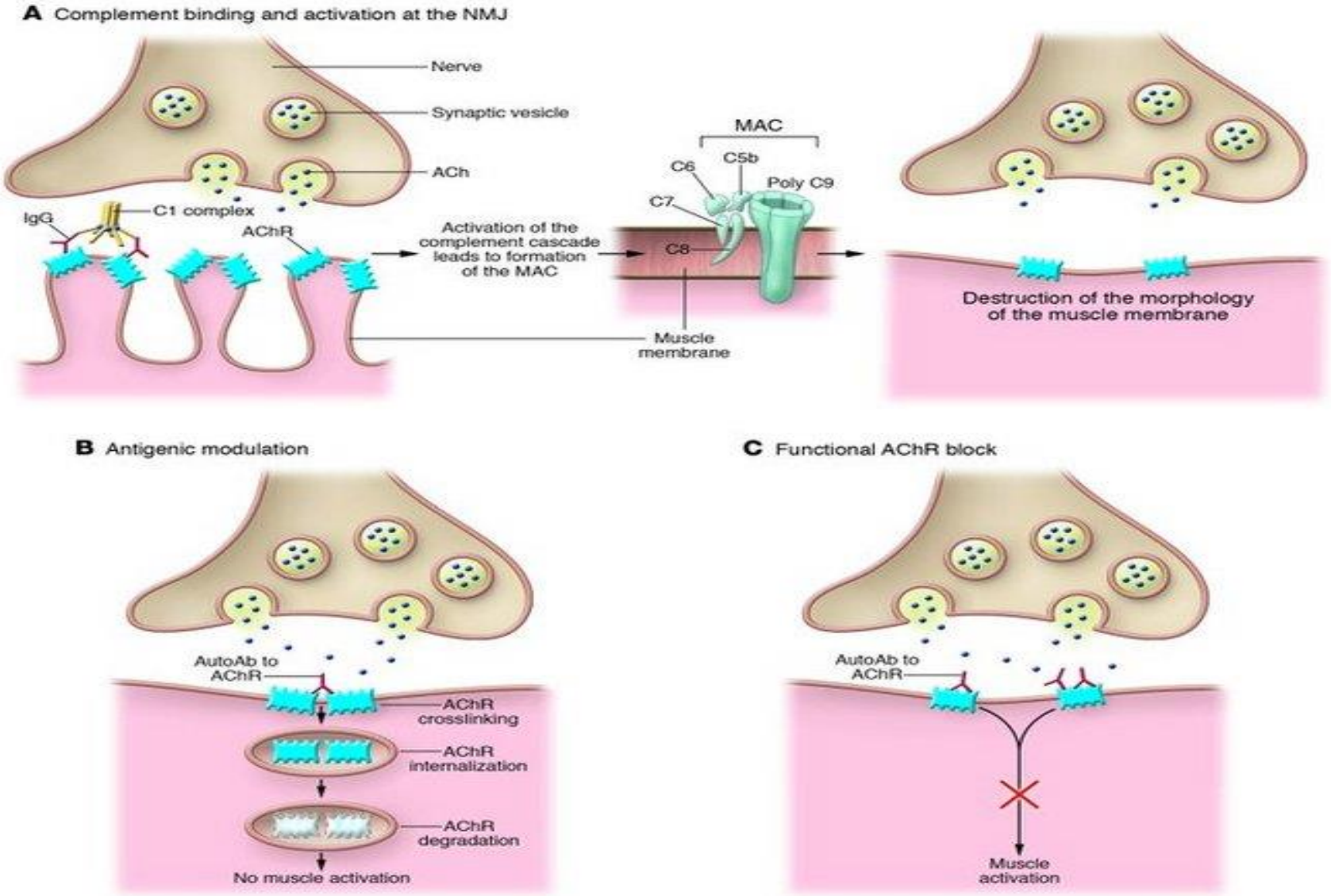
MG with anti-AChR ab

- The nicotinic AChR is composed of five protein subunits
- is concentrated on muscle cells at the NMJ.
- The anti-AChR ab target a region on the extracellular side of the α-subunit of the AChR called the MIR (main immunogenic region)

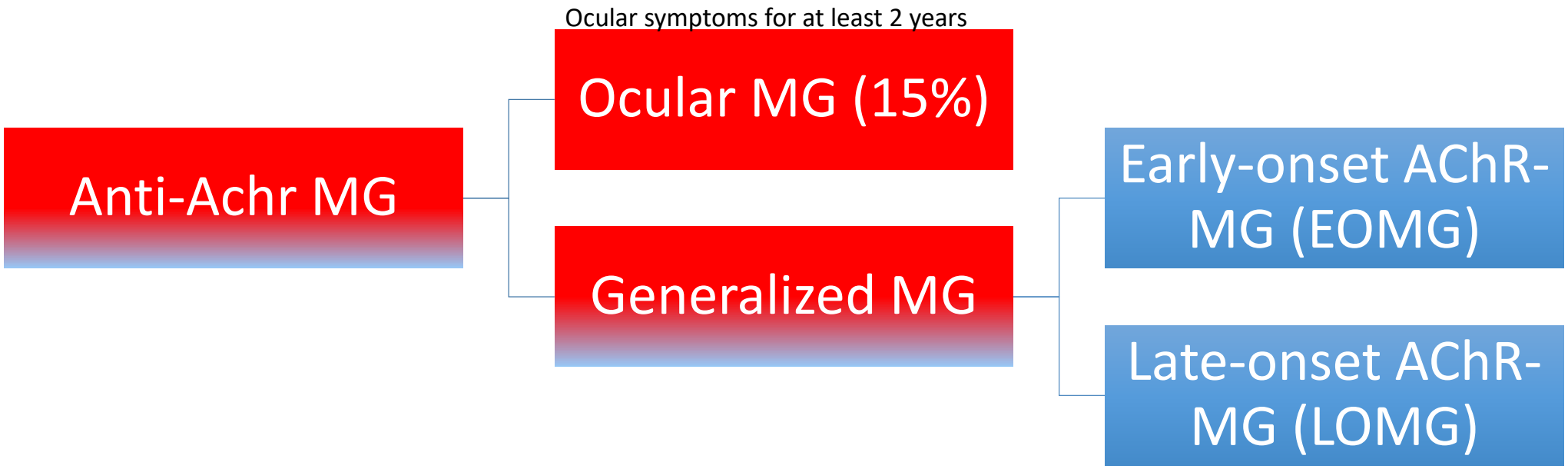


A number of mechanisms underlie the reduction of AChRs at the NMJ in MG patients

Classical complement pathway mainly involved



Main clinical subgroups of MG patients with anti-AChR antibodies



AChR antibody titers do not generally correlate with disease severity,

but titer decline is often observed when MG improves.

Behin et Le Panze, 2018

Early-onset AChR-MG (EOMG)

- Age of onset <45–50 y
- Most EOMG patients present a high level of anti-AChR antibodies often associated with thymic follicular hyperplasia
- > 80% of patients with follicular hyperplasia are women.

Late-onset AChR-MG (LOMG)

- Age of onset >45–50 y
- frequently associated with the presence of a thymoma
- **Very late-onset** form of AChR-MG defined by
  - males > females
  - > 60 y
  - not associated with a thymoma

Behin et Le Panze, 2018

Early-onset myasthenia gravis with AChR antibodies

- ***Definition: onset of their first symptom before age 50 years***
- ***Patients with a thymoma*** (detected on imaging or during surgery) excluded from this subgroup
- ***Thymic follicular hyperplasia*** (not a prerequisite)
- ***Responds to thymectomy***
- Female to male: ***3/1***
- ***HLA-DR3, HLA-B8, and other autoimmune risk genes***
- All autoimmune disorders: ***more widely reported in relatives of patients in this subgroup***

Late-onset myasthenia gravis with AChR antibodies

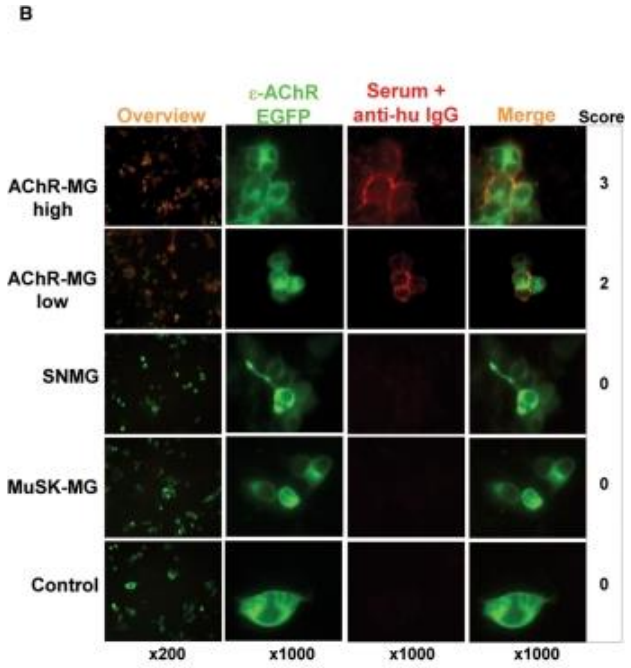
- ***Definition: onset of their first symptom after age 50 years***
- ***Thymoma is not evident*** (imaging or during surgery)
- ***Thymic hyperplasia occurs only rarely***
- Most often ***not respond to thymectomy***
- ***Slightly more frequently*** in males
- ***HLADR2, HLA-B7, and HLA-DRB1*15:01***

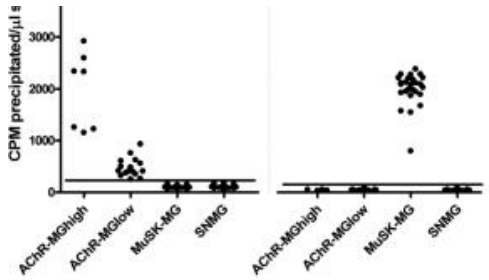
Thymoma-associated myasthenia gravis

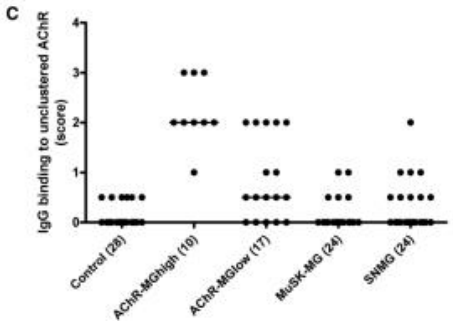
- ***A paraneoplastic disease***
- MG: ***most widely reported autoimmune disease*** associated with a thymoma (***pure red aplasia and neuromyotonia also associated***)
- Thymoma: in ***10–15%*** of all patients with MG
- ***Nearly all*** have AChR Abds & generalized disease
- ***About 30%*** of patients with a thymoma develop MG, ***and >30%*** have AChR Abds without MG

Clustered-AChR

- Some anti-AChR ab are not detectable by the classical immunoprecipitation assay.
- These autoantibodies only recognize the AChR in its clustered configuration.
- These anti-AChR antibodies are predominantly of the IgG1 isotype and can also activate complement.
- Patients with isolated clustered AChR antibodies tend to be younger and have higher percentage of ocular MG, milder disease without respiratory failure, and better response to treatment.



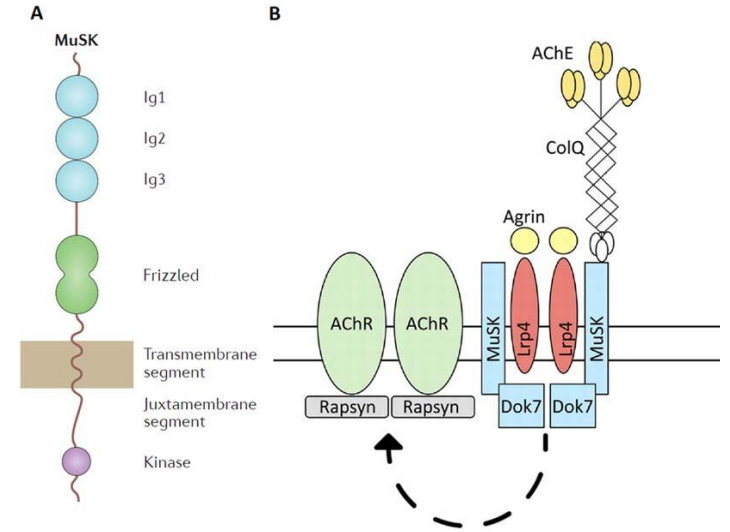


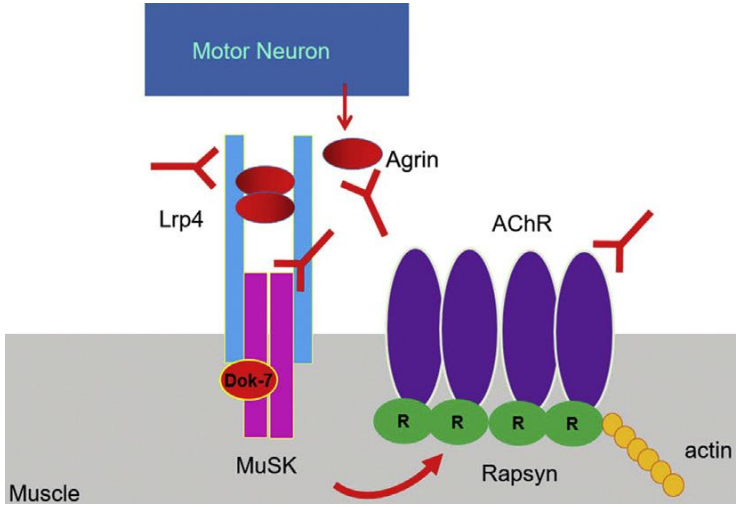


Leite et al, 2008; Rodriguez-Cruz et al, 2015

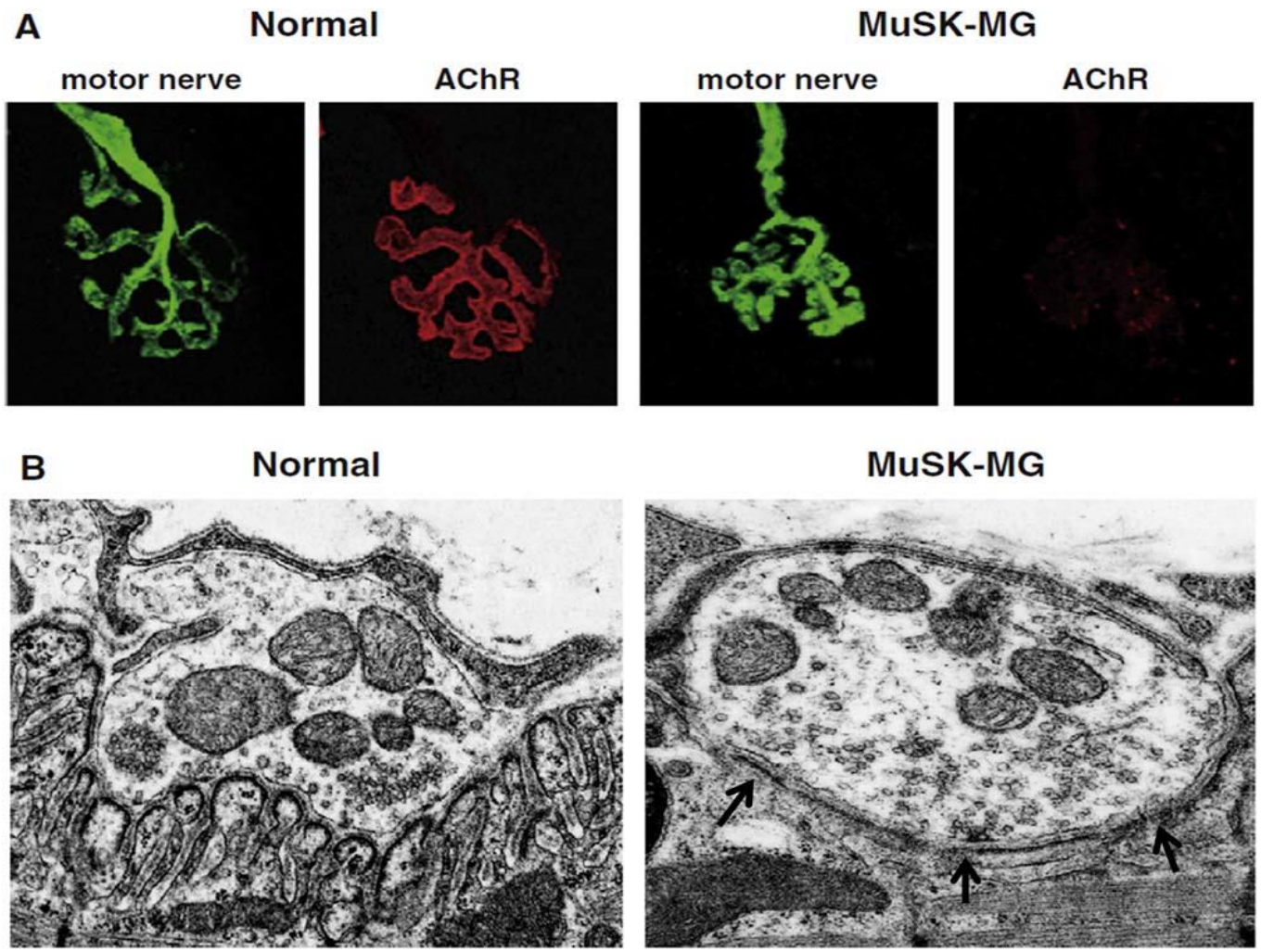
MG with anti- MuSK antibodies

- **MuSK is a transmembrane tyrosine kinase**
- **Expressed predominantly at the postsynaptic membrane of the NMJ.**
- **Essential for the development and maintenance of the NMJ.**
- **Agrin released from the motor nerve interacts with LRP4, which then binds to MuSK and facilitates MuSK dimerization and MuSK autophosphorylation in the kinase domain.**
- **This recruits DOK7, an adaptor protein, to MuSK,which initiates the intracellular pathway that leads to clustering of the AChRs via rapsyn on the post- synaptic membrane of the NMJ.**
- **Autoantibodies are of the IgG4 subtype that does not activate the complement cascade.**





Morren et al, 2018; Wang and Rich, 2018

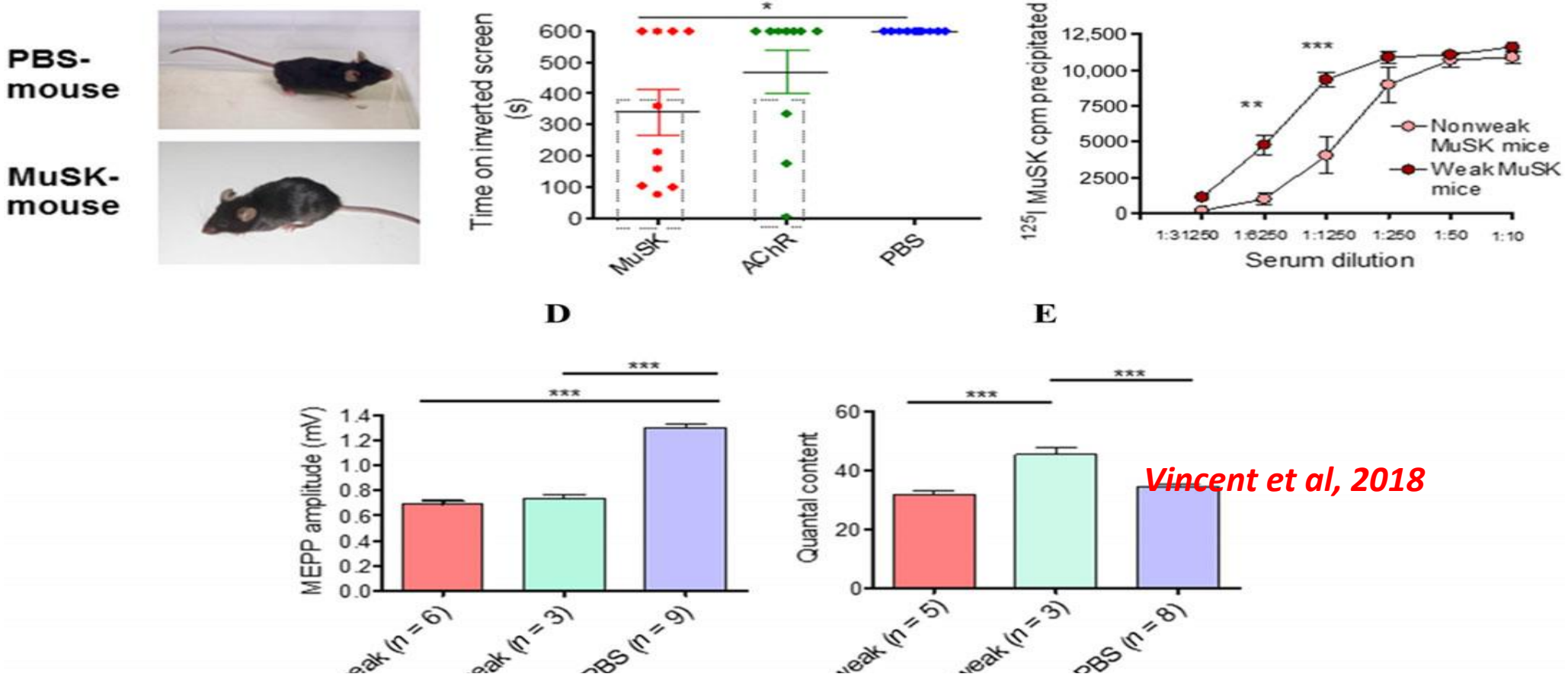


Morren et al, 2018

- Motor terminals were retracted, and dim AChR clusters were dispersed in the NMJs of MuSK-MG mice

- Marked loss of synaptic folds beneath motor terminals was observed in mice with MuSK-MG

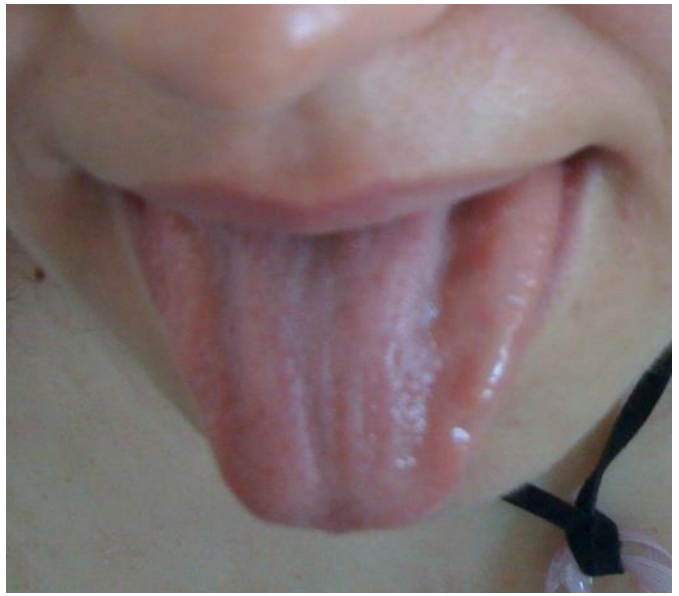
1. Reduction of AChR Clustering on the Postsynaptic Membrane.
2. Blocking of MuSK Interaction With Other Molecules.
3. Lack of Complement Activation.
4. Presence of both presynaptic and postsynaptic dysfunction in MuSK-MG.

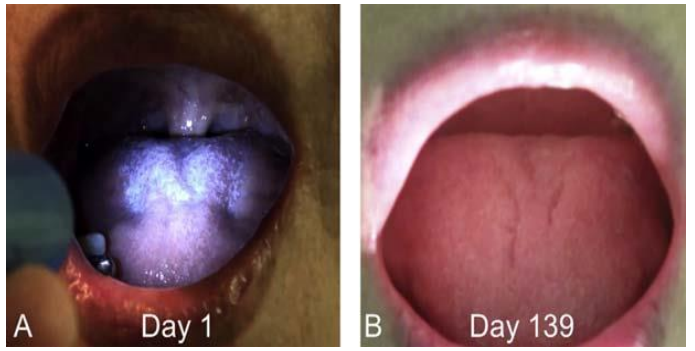


- **The results of passive and active transfer experiments for MuSK MG are consistent in showing a loss of AChRs but without the compensatory increase in acetylcholine release that occurs at MG endplates, and in mice immunized against AChRs.**
- **The lack of compensatory mechanisms in MuSK MG is now believed to be due to interference with an LRP4 presynaptic mechanism.**

MG with anti- MuSK antibodies

- 5 to 7% of the MG patients.
- > 70% are female, early onset (36-38y)
- early involvement of bulbar muscles, neck extensor muscles, and respiratory muscles.
- Ocular symptoms are less prominent than in AChR-MG.
- Tends to have a more severe phenotype when compared with anti-AChR MG
- About 30% of anti-MuSK MG patients will experience MG crisis.
- Muscle atrophy can be observed, especially in the tongue
- Thymic pathology is uncommon in anti-MuSK MG
- Thymectomy does not appear to be associated with improved clinical outcomes in anti-MuSK MG.
- Do not typically improve with acetylcholinesterase inhibitor treatment; sometimes may worsen weakness
- Generally more refractory to treatment.

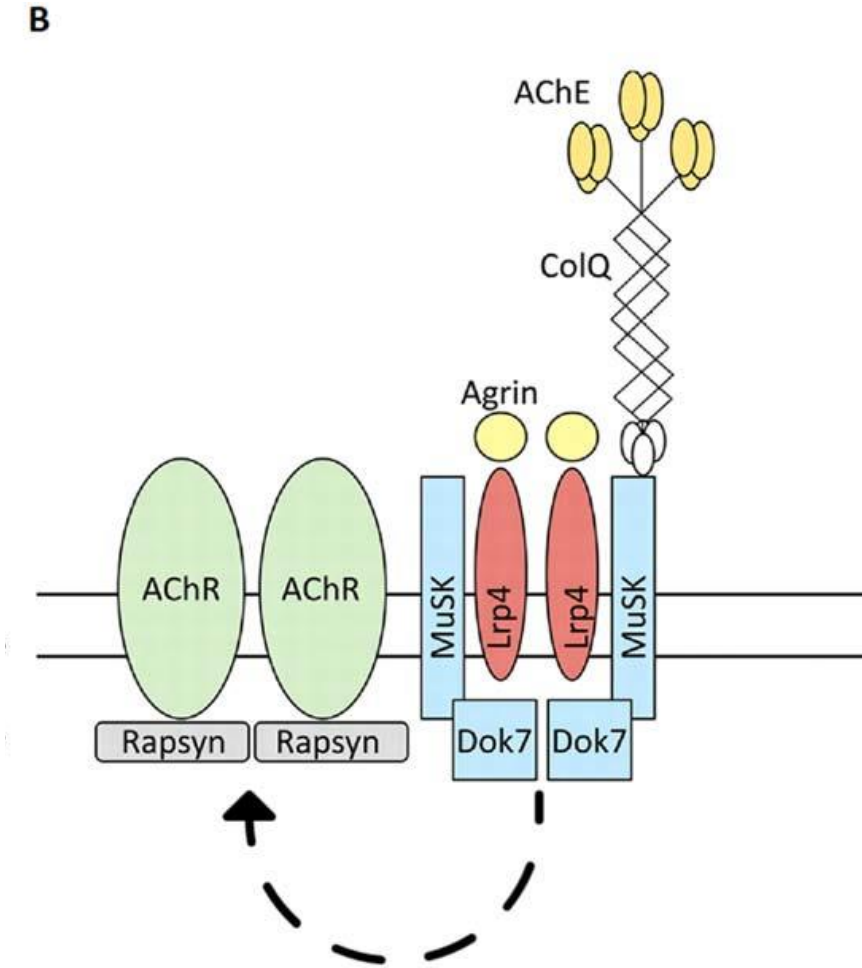




Morren et al, 2018, Evoli, 2017

MG with anti-LRP4 antibodies

- **The LRP4 protein belongs to a family of proteins identified as the receptor for the neural agrin that can activate MuSK.**
- **Patients with anti-LRP4 antibodies were only described in 2011.**
- **discovered in 2% to 27% of MG patients without antibodies to AChR or MuSK**
- **Cases of concurrent AChR/LRP4 and MuSK/LRP4 are also described.**
- **in this case, it resembles the clinical presentation of AChR or MuSK MG respectively**



Zhang et al, 2012; Zisimopoulou et al, 2014;

MG with anti-LRP4 antibodies

- Most of patients: *ocular or generalized mild MG*
- ***About 20%*** of patients: ocular weakness, *Respiratory insufficiency*: very rarely (except in a subgroup with additional MUSK Abds
- Similar response to treatment as anti-AChR MG patients
- Young female predominance.
- Some identified thymic changes (**32%** with follicular hyperplasia, none with thymoma, ***2/3*** of patients: thymus is atrophic and normal for age).
- These patients are predominantly of the IgG1 and IgG2 subtypes that can activate the complement cascade
- The response of LRP4-MG patients to treatment seems more similar to that of AChR-MG than of MuSK-MG patients.
- No routine lab tests to detect efficiently anti-LRP4 antibodies.

Zisimopoulou et al, 2014

Other autoantibodies

- **Anti-agrin ab**
  - **have been demonstrated in patients with generalized MG and concurrent antibodies to AChR or MuSK.**
  - **phenotype of typical ocular and generalized MG.**
- **Anti-cortactin antibodies**
  - **measured in a subset of primarily seronegative female MG patients <50y with a clinical phenotype similar to AChR MG.**
  - **clinical utility of these antibodies currently under investigation.**
- **Anti-titin and ryanodine receptor antibodies**
  - **discovered in some patients with AChR-positive MG**
  - **pathogenicity of these antibodies has been debated**
  - **merely disease markers with a high prevalence in patients with concurrent thymoma.**

Skeie et al, 2003; Romi et al, 2007; Gasperi et al, 2014; Gallardo et al, 2014;

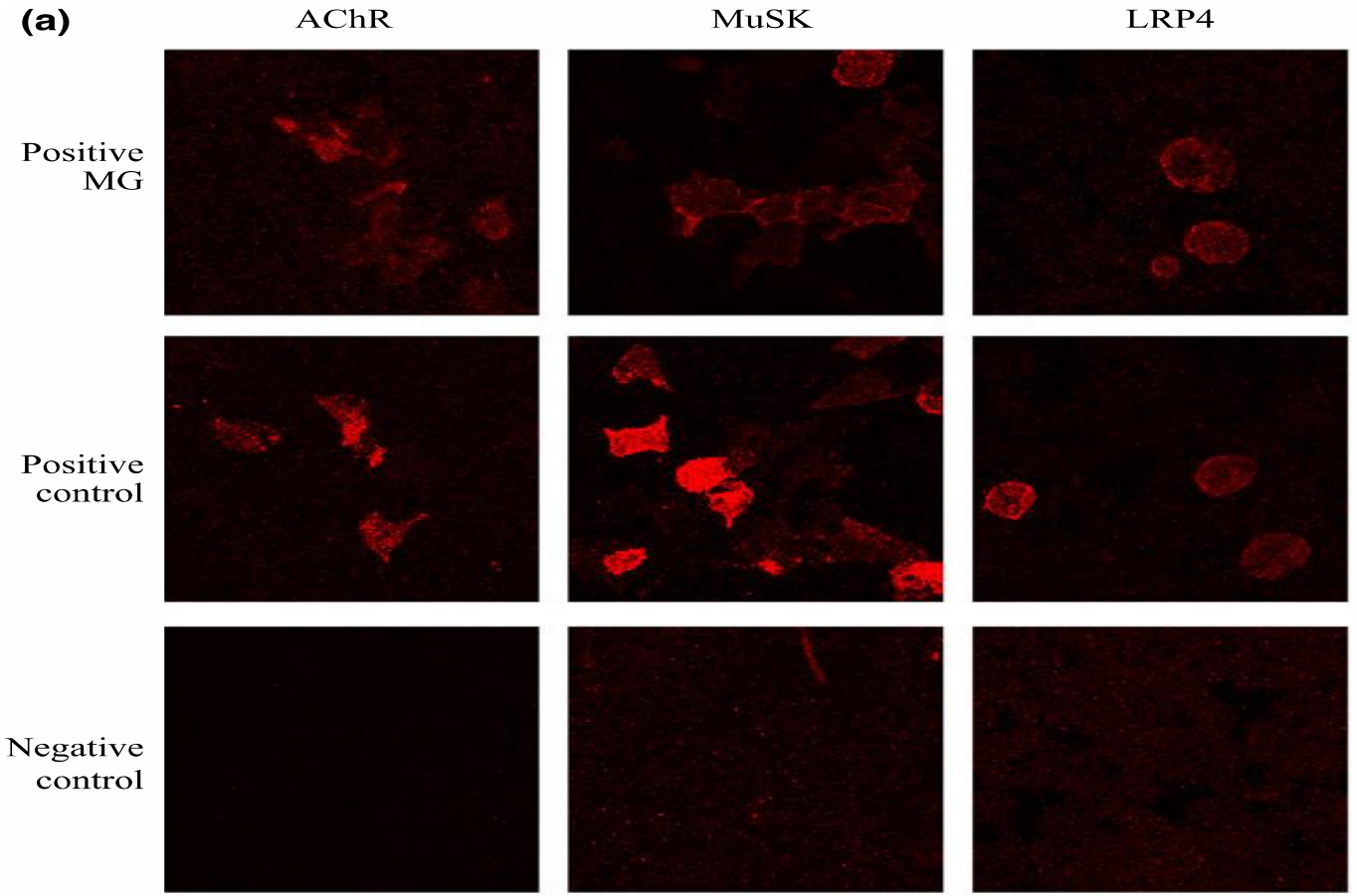
« Seronegative » MG

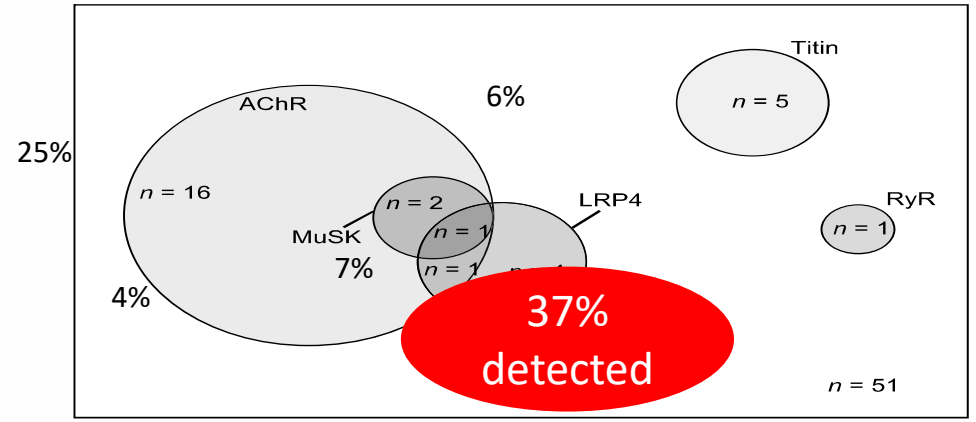
- **When none of the aforementioned antibodies are detected, patients are diagnosed with MG by clinical or electrodiagnostic means**
- **Are termed « seronegative ».**
- **About 7% of generalized MG patients are seronegative compared with between 50% and 70% of ocular MG patients.**
- **Usually have an identical phenotype to AChR-ab+ MG patients.**
- **CBA used to detect clustered AChR antibodies have been found to be useful in making a diagnosis of MG when conventional testing with radio- immunoprecipitation assay has been negative.**
- **Further discovery of pathogenic antibodies and improvements in antibody detection are likely to decrease the percentage of patients with seronegative** MG.

Gilhus, 2016; Hehir et al, 2018

Multiple antibody detection in 'seronegative' myasthenia gravis patients

Hong et al, 2017





- AChR ab+ patients had more severe disease than AChR ab- patients.
- 4 patients with double positive had more severe disease.
- Seronegative patients had milder MG

- Chinese seronegative patients (n=81)
- Samples screened by (i) a novel, highly sensitive radioimmunoassay for AChR antibodies; (ii) cell-based assays for clustered AChR, MuSK and lipoprotein receptor-related protein 4 (LRP4) antibodies; (iii) a radioimmunoassay for titin antibodies.

« Seronegative » MG

- A ***heterogeneous group*** pathogenically
- ***20-50%: low-affinity Abds or low concentration*** of Abds to AChR, MUSK, or LRP4 antigen targets (identified by cell-based methods)
- Abds to ***agrin and cortactin*** often occur in combination with other autoAbds
- Some pathogenic Abds yet undefined
- The DX is ***more challenging*** in patients in whom no specific autoantibodies are detected
- ***Non-MG myasthenic syndromes and other muscle and non-muscle disorders*** should also be considered

Ocular myasthenia gravis

- Weakness is ***restricted to the ocular muscles***
- Patients with purely ocular weakness: ***at risk of developing generalized MG*** (especially early in the disease)
- ***90%*** of those who have had the ocular form for >2 years will remain in this subgroup
- ***Half of*** patients have AChR Abds ***(MUSK Abds very rarely)***

MG subgroups	Age at onset	sex	Thymic histology	Additional auto-antibodies	Clinical presentation
AChR-MG					
Early-onset	<50	F>M	hyperplasia	rare	Ocular frequently to generalized
Late-onset	>50	M>F	Atrophy	Common (anti-titin, anti-RyR)	generalized
Thymoma-associated	Any, but more frequently>50	M>F	Thymoma	Common (anti-titin, anti-RyR, anti-actin)	generalized Severe disease
MuSK-MG	Usually <50	F>M	normal	Rare	generalized Severe disease
LRP4-MG	any	F>M	Normal, no thymoma	Rare (anti RACh, anti MuSK)	Ocular or generalized; mild symptoms; severe if double positive

Mantegazza et al, 2018

Juvenile MG

Gunawan et al, 2007

- **11% to 24% of all MG patients have disease onset in childhood or adolescence.**
- **Usually after 10 years of age (before puberty in half of cases).**
- **Higher incidence of ocular MG in prepubertal patients and generalized MG in postpubertal patients.**

- **Female predominance only after the age of 10y**
- **The occurrence of thymoma is rare.**
- **Spontaneous remission rate in juvenile cases is higher than in adults from 15% to 35%.**

Evoli et al,1998; Castro et al, 2013

Transient neonatal MG

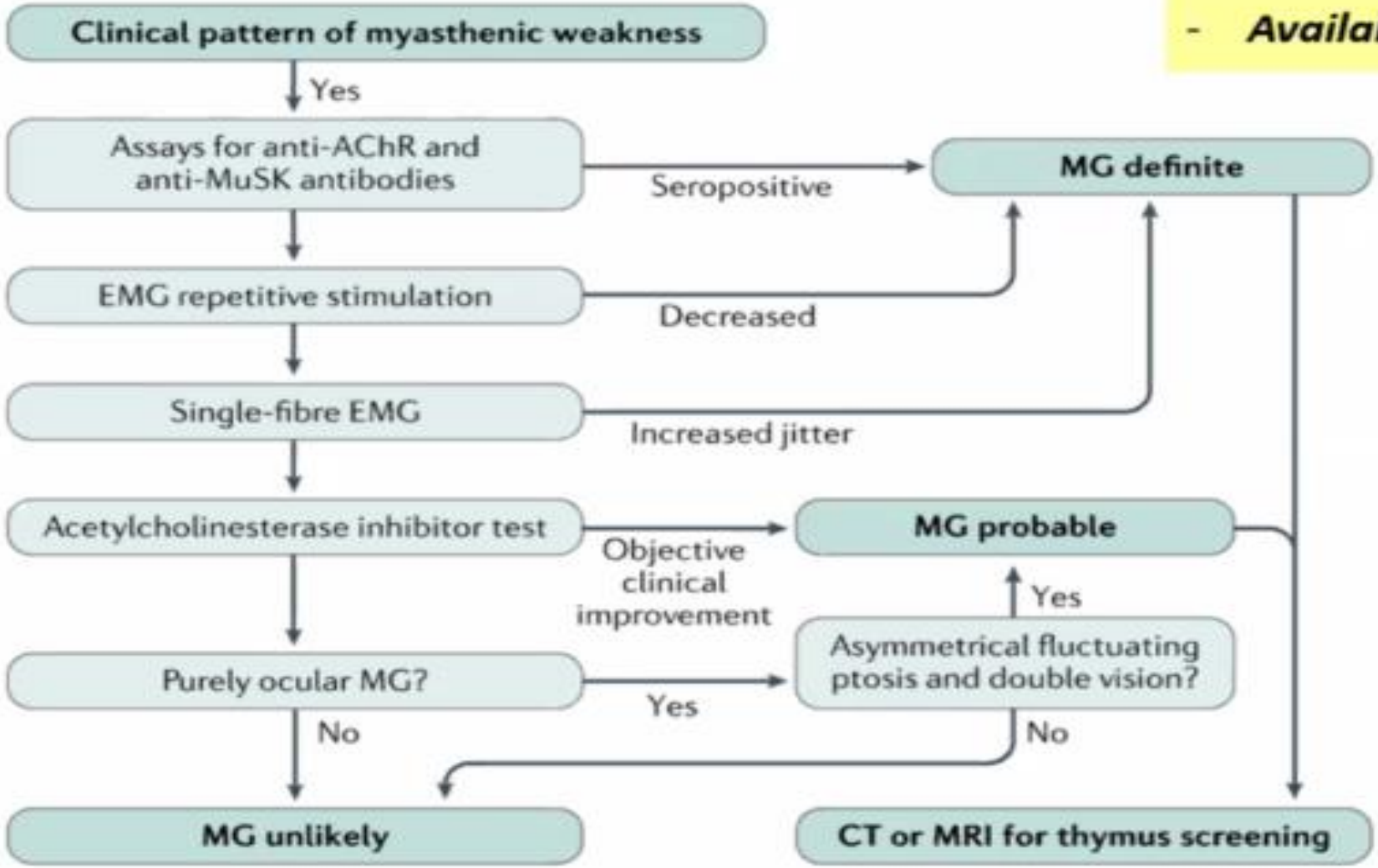
- in 10% to 15% of children born to mothers with the disease
- Is caused by transfer of antibodies across the placenta
- The weakness can lead to weak cry, weak suck, poor feeding, or respiratory difficulties, generalized hypotonia
- rarely arthrogryposis.
- The symptoms last days to a few weeks
- treatable with acetylcholinesterase inhibitors.
- No correlation with the incidence of transient neonatal MG and mother's disease severity or AChR antibody titer

Hassoun et al, 2010

Hehir et Silvestri, 2018

A simplified diagnostic algorithm for MG

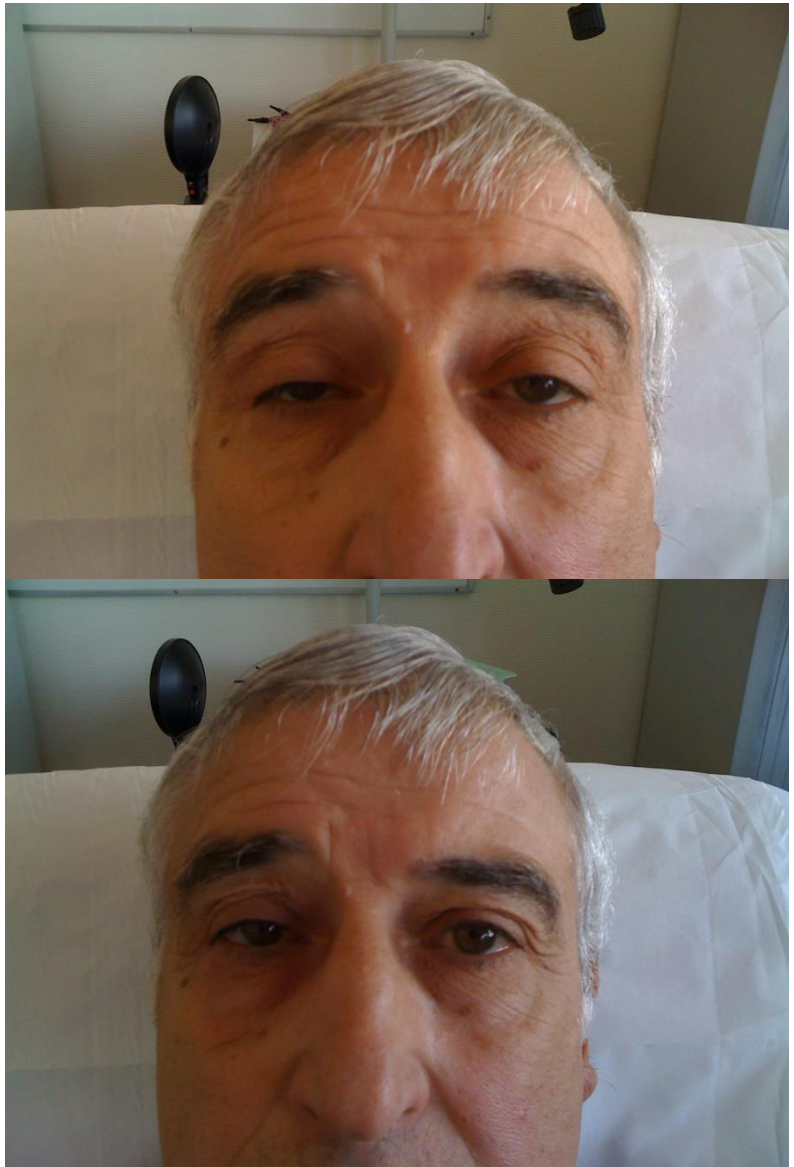
- *Specificity*
- *Sensitivity*
- *Availability*



Gilhus et al. 2019 *Nature Rev. Dis. Primers*

ICE PACK TEST

- **Good sensitivity and specificity**
- **More subject to false-positive and false-negative results than the edrophonium chloride test.**
- **A cold ice pack, disposable glove, or specimen filled with ice is applied to the ptotic eyes for 1 to 2 minutes.**

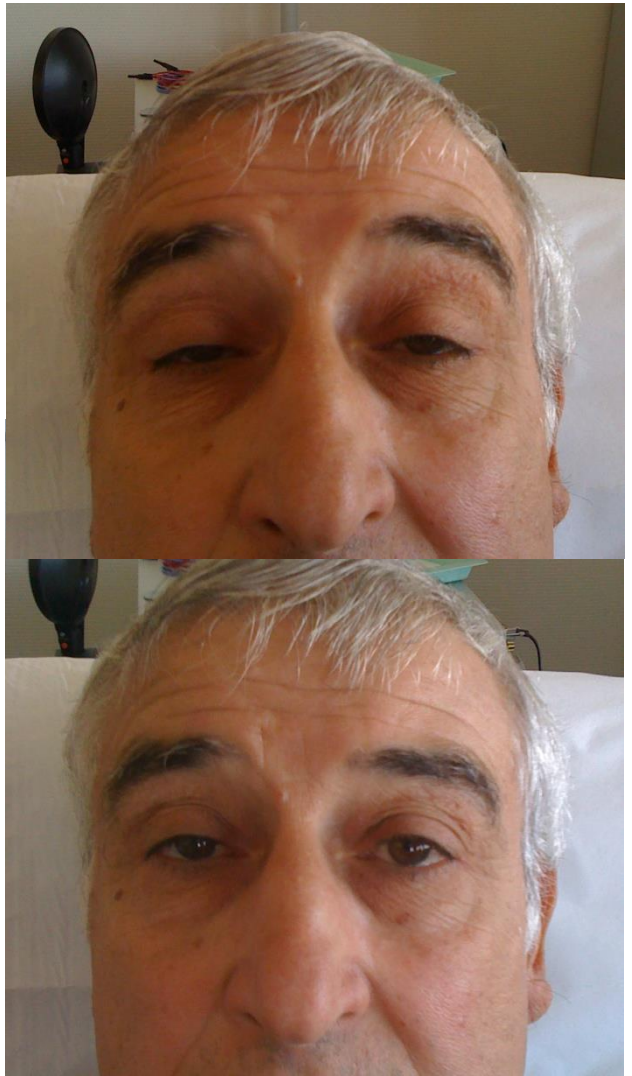


EDROPHONIUM CHLORIDE (TENSILON) TEST

Edrophonium testing: method

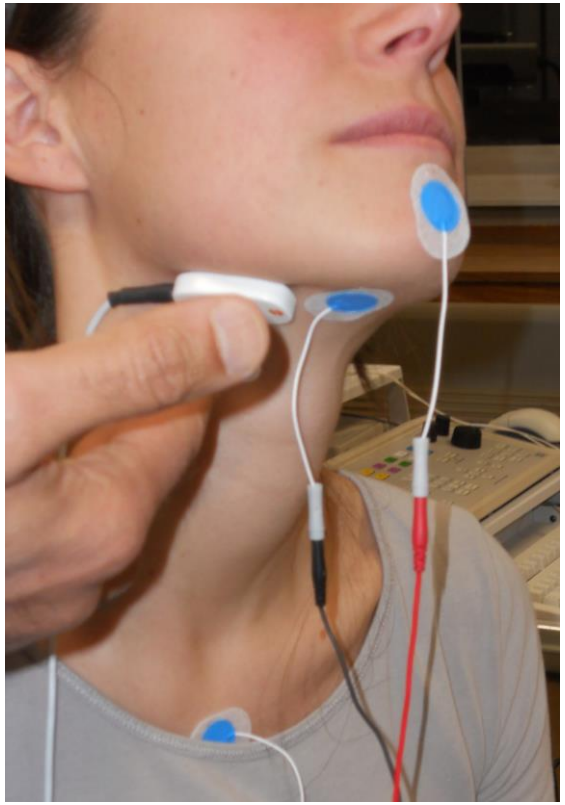
1. Patients are instructed not to take certain medications including pyridostigmine bromide for at least 12 hours before the testing.
2. Identify the objective parameter that you can test, for example, ptosis.
3. Baseline measurements of the objective parameter are obtained; for example, for ptosis, measure the palpebral fissure length between the two eyelids in the center with patients looking straight ahead.
4. An IV needle is placed in the arm.
5. Edrophonium (10 mg/mL) is taken into a 1-mL tuberculin syringe, and 0.2 mL is injected initially. Wait for 30 to 60 seconds; if there are no side effects (fasciculations, sweating, nausea), the rest of the 0.8 mL is injected. Another method used by some physicians includes injecting 0.2 mL, wait for 5 minutes, and then give 0.3 mL; after 5 minutes, if there are no side effects, give the rest of the 0.5 mL.
6. Blood pressure and heart rate have to be monitored closely every 2 minutes during and for 10 minutes after the procedure.
7. Measurements of the objective parameter identified and measured at the baseline are repeated immediately after the injection.

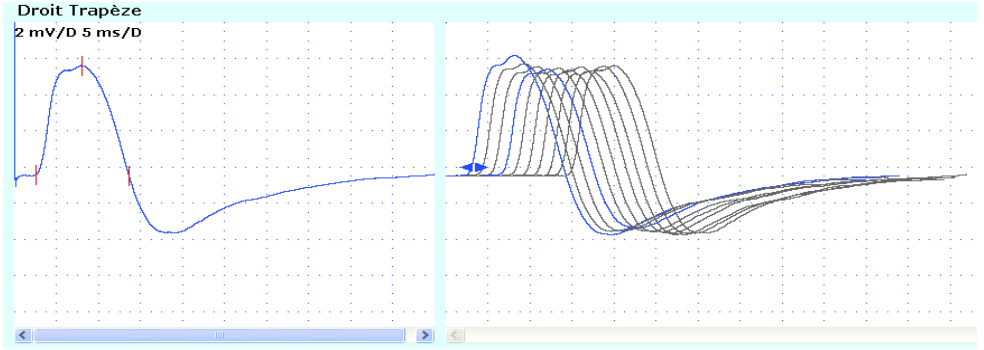
- **Good sensitivity**
- **Be aware of side effects**



Repetitive nerve stimulation

- Decremental response of the compound muscle action potential (CMAP) to slow (2–3 Hz) motor repetitive nerve stimulation (RNS)
- A decrement of greater than 10% is considered a positive RNS study.
- A decrement is more often observed in clinically weak muscles.
- A decremental response is more likely present in a proximal muscle than in a distal muscle.
- No guidelines concerning the number or the choice of muscles needed for the diagnosis of MG.





A new strategy for improving the diagnostic sensitivity of repetitive nerve stimulation in myasthenia gravis

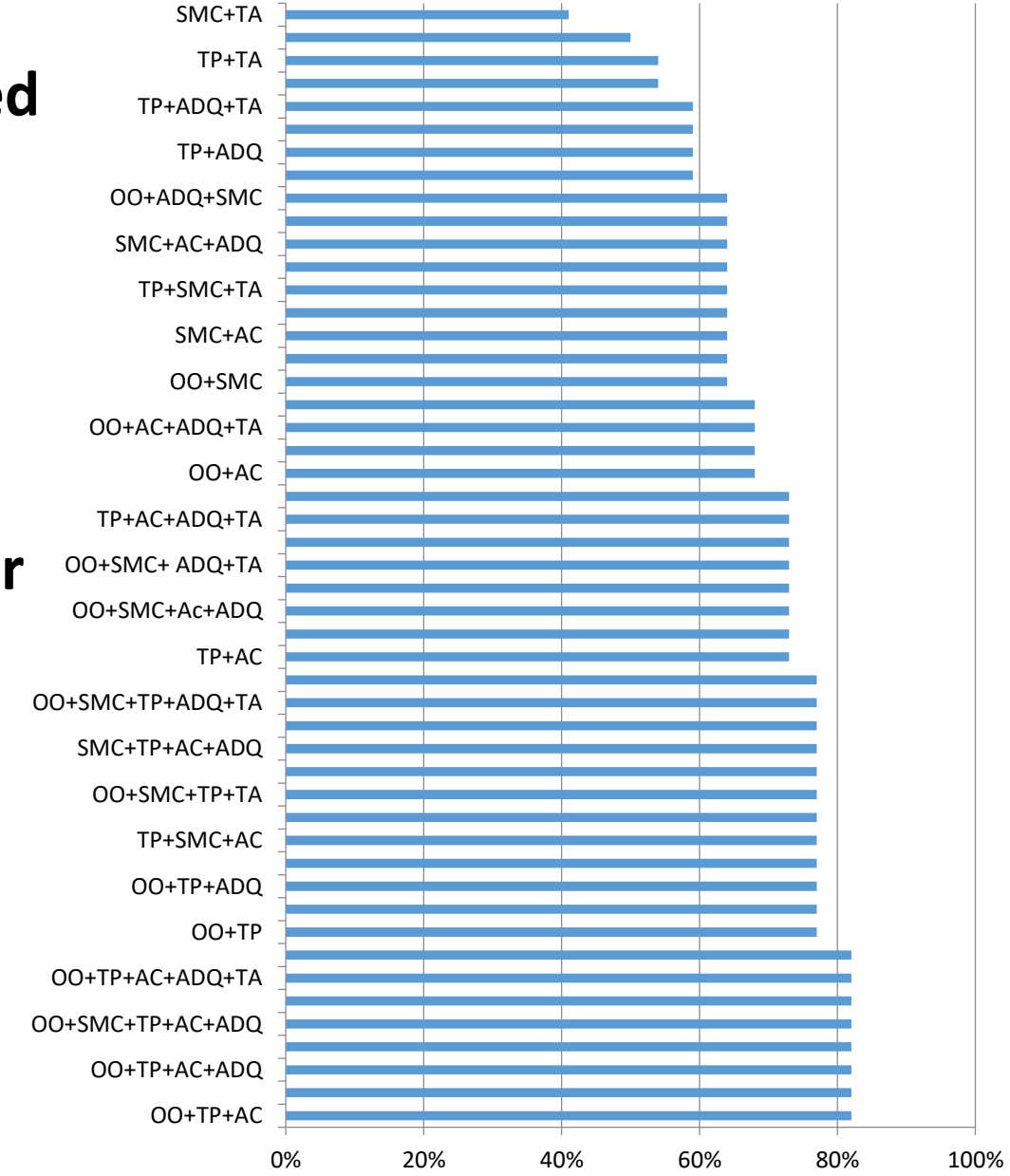
2017

Bou Ali H, Salort-Campana E, Grapperon AM, Gallard J, Franques J, Sevy A, Delmont E, Verschueren A, Pouget J, Attarian S.

- ***To determine the diagnostic sensitivity and specificity of repetitive nerve stimulation (RNS) of 12 muscles in patients with myasthenia gravis (MG).***
- **45 patients suspected for MG were enrolled consecutively:**
  - **22 patients had clinical signs and laboratory test results consistent with MG (MG group).**
  - **23 patients =pathological control group.**
- **6 nerve-muscle systems were studied on both sides of all subjects using RNS.**
- **In MG group, 33% of the decrements were unilateral.**
- **The global sensitivity of RNS was 82% and specificity was 100%.**
- **The sensitivity in the MG subgroups was as follows:**
  - **group Ocular = 67%**
  - **group Oculobulbar = 86%,**
  - **group Generalized = 89%.**

- **The diagnostic sensitivity of RNS was improved by *increasing the number of muscles tested and by assessing the muscles bilaterally*.**
- **RNS sensitivity was low in the ocular form**
- **Improved by exploring more sensitive muscles, such as a facial muscle, the anconeus or the submental complex.**

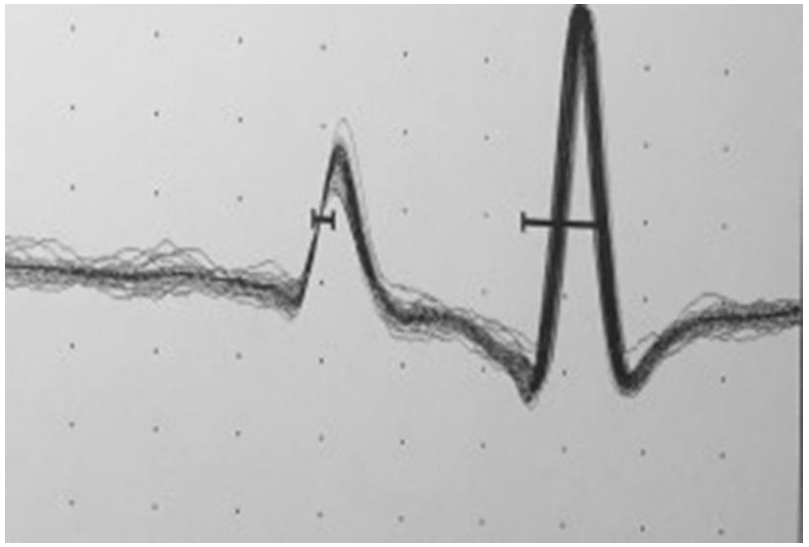
- **We recommend systematic, bilateral exploration of at least six muscles: a facial muscle (orbicularis oculi or nasalis), the trapezius, and the anconeus.**



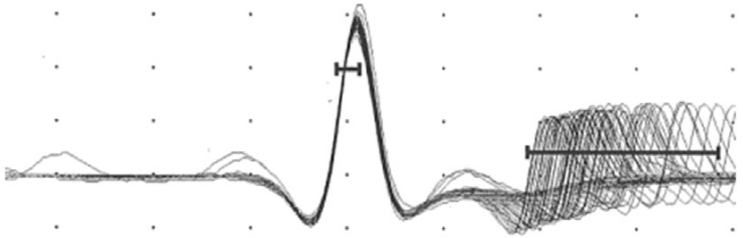
Global diagnostic sensitivity of different muscles combinations explored bilaterally.

SINGLE-FIBER ELECTROMYOGRAPHY

- **Observator-dependant**
- **Need an experienced electrophysiologist**



- **A fascicle of motor nerve is stimulated by using a monopolar needle electrode, and recording is made by SFEMG or a concentric needle electrode and recording is made by SFEMG or a concentric needle electrode.**
- **Stimulation is delivered at 2 to 10 Hz, and the stimulus intensity is adjusted accordingly.**
- **The jitter value is the measurement of the variation of the interpotential interval be- tween the triggered potential and the time-locked, second single muscle fiber potential**
- **Myasthenic patients have increased jitter values.**



- **Has the highest sensitivity in both generalized and ocular MG, particularly in weak muscles.**

Ef cacy of Gaze Photographs in Diagnosing Ocular Myasthenia Gravis

Ahn et al, 2018

- The various tests routinely used to diagnose generalized myasthenia gravis, have lower diagnostic sensitivity in ocular myasthenia gravis (OMG).
- Records of gaze photographs were available for 25 of 31 consecutive patients diagnosed with OMG.
- The margin reflex distance 1 (MRD1) was measured on each of the gaze photographs, with MRD1 <2 mm or an interlid MRD1 difference of ≥2 mm on any of the gaze photographs defined as a positive sign of OMG.

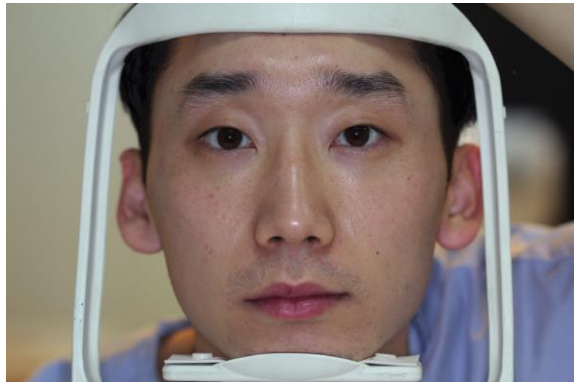


Fig. 1. A fixation support for use when taking gaze photographs. The

The diagnostic sensitivities:

- RNS test: 56%
- AChR-Ab test: 64%,
- gaze photographs:80%
- ice test :73%

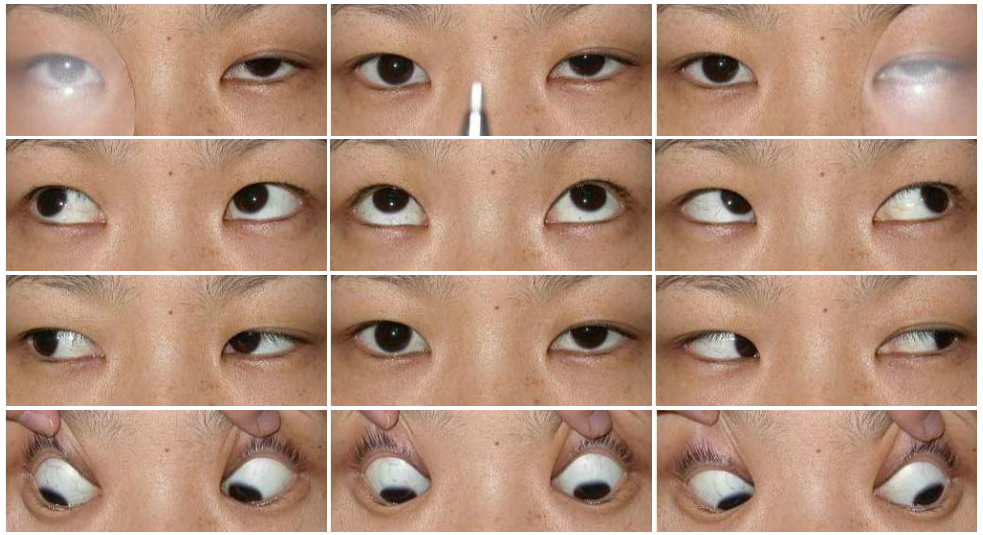


Fig. 2. Gaze photographs of a patient who showed negative results in anti-acetylcholine-receptor antibody and repetitive nerve stimulation tests, but showed a variable degree of ptosis of the left eye.

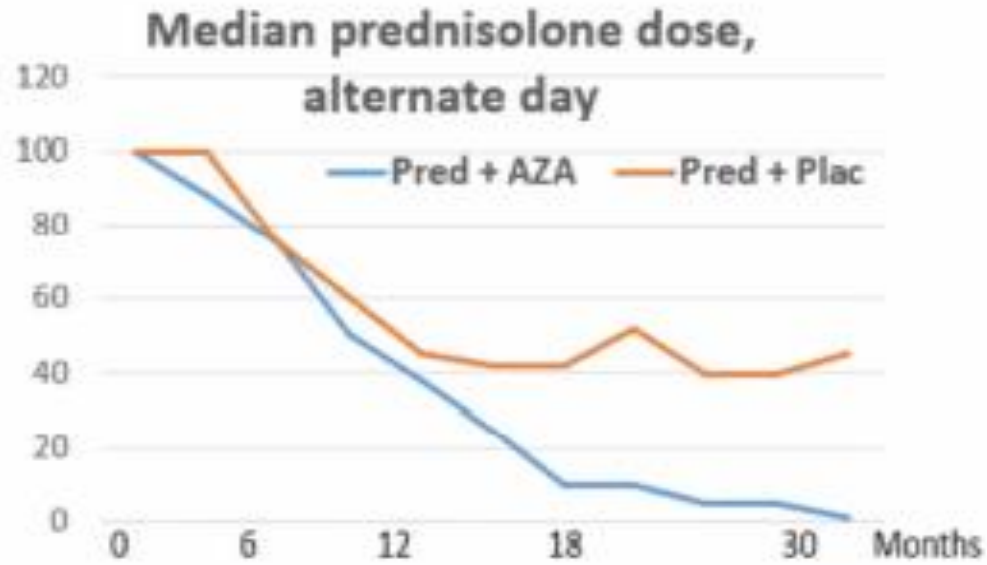
Myasthenia Gravis Treatment

Myasthenia gravis treatment

- Anticholinesterase drugs
- Thymectomy
- Immunosuppressive drugs; corticosteroids, azathioprine, rituximab, mycophenolate, cyclosporine A, methotrexate, tacrolimus, cyclophosphamide, other
- Emerging drugs
- Ivlg
- Plasma exchange
- Supportive therapy

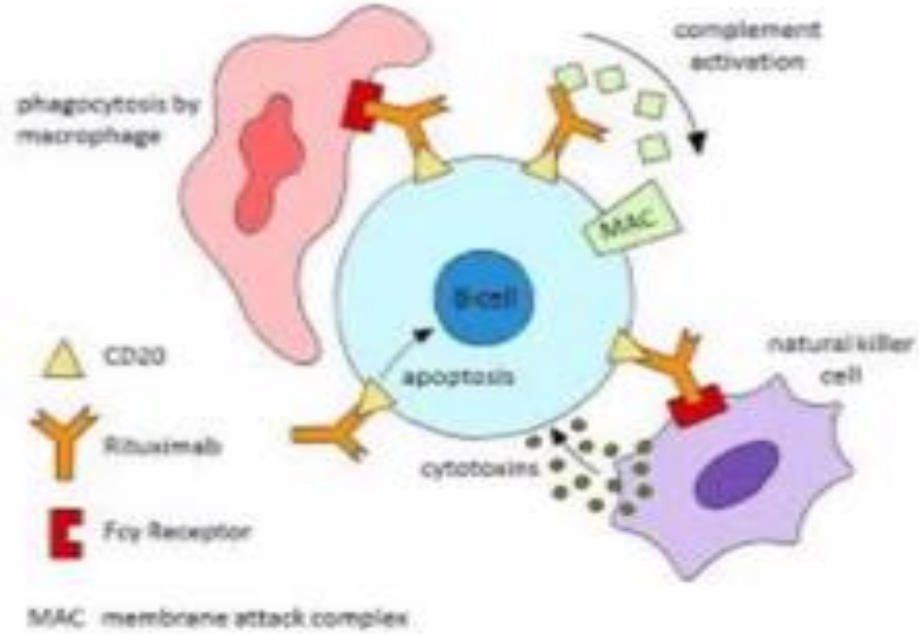
Prednisolone vs. prednisolone + azathioprine

- Prednisolone dose reduced at 2 - 3 years
- Relapses more frequent in prednisolone alone
- Remit failures more frequent in prednisolone
- Treatment failures more frequent in prednisolone
- Side-effects more common in prednisolone
- Very few patients (34, 18 at end)



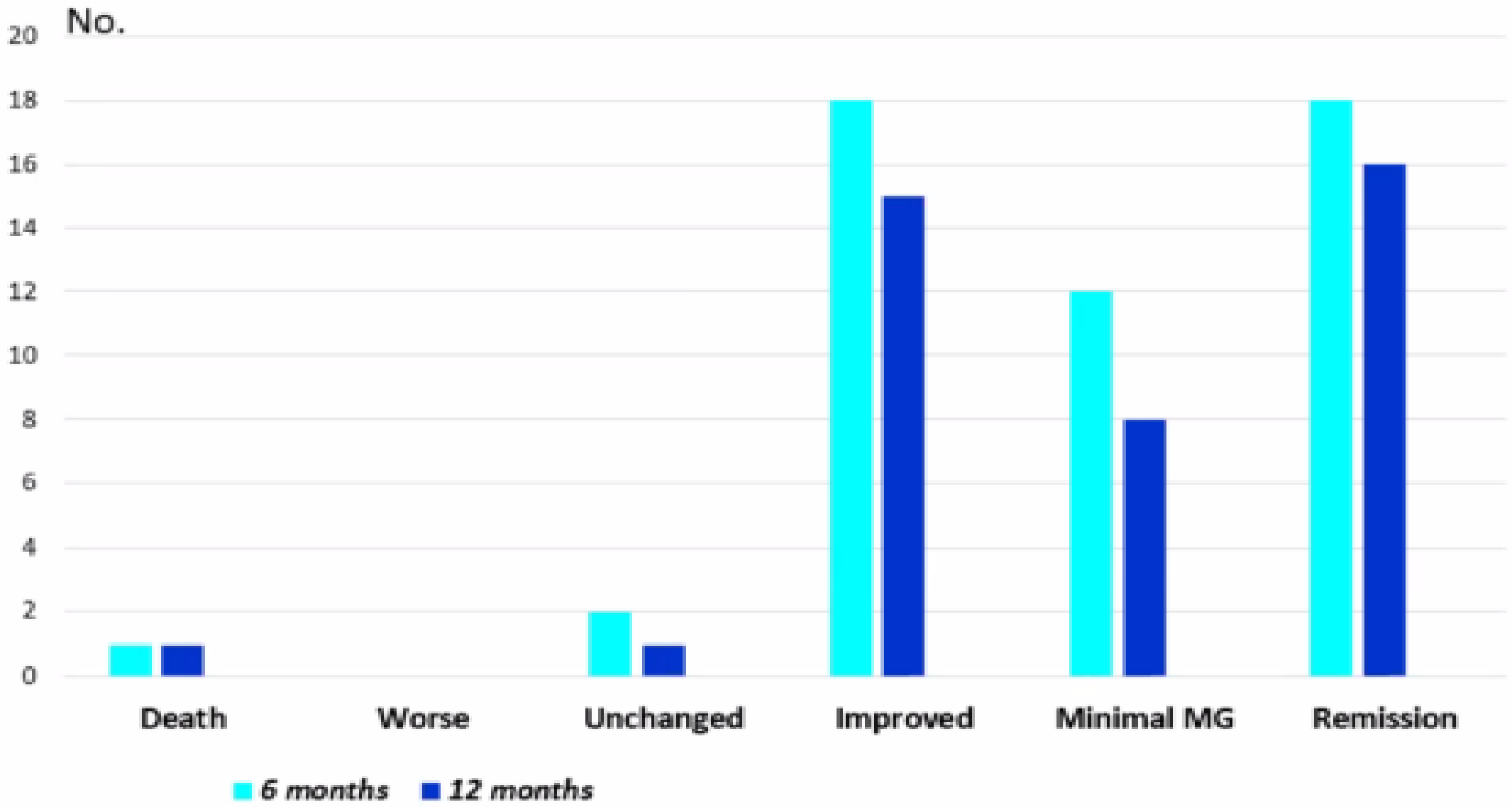
Palace et al Neurology1998

Rituximab in MG



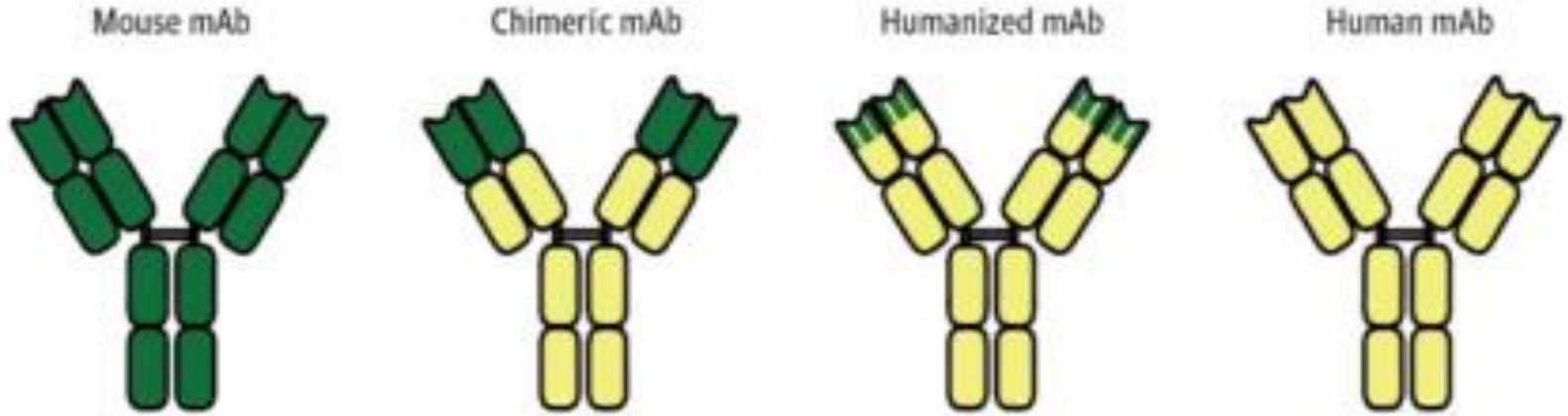
- Generalized and severe MG
- First-choice drugs not effective
- IgG1 monoclonal antibody
- Depletes B-cells
- Two-thirds with a positive response in open studies
- Anti-MuSK MG
- Treatment regime
- PML and other opportunistic infections ?
- Controlled trial
- Use in MS

Rituximab for MG in Austria; a retrospective study



Topakian et al 2019, J Neurol

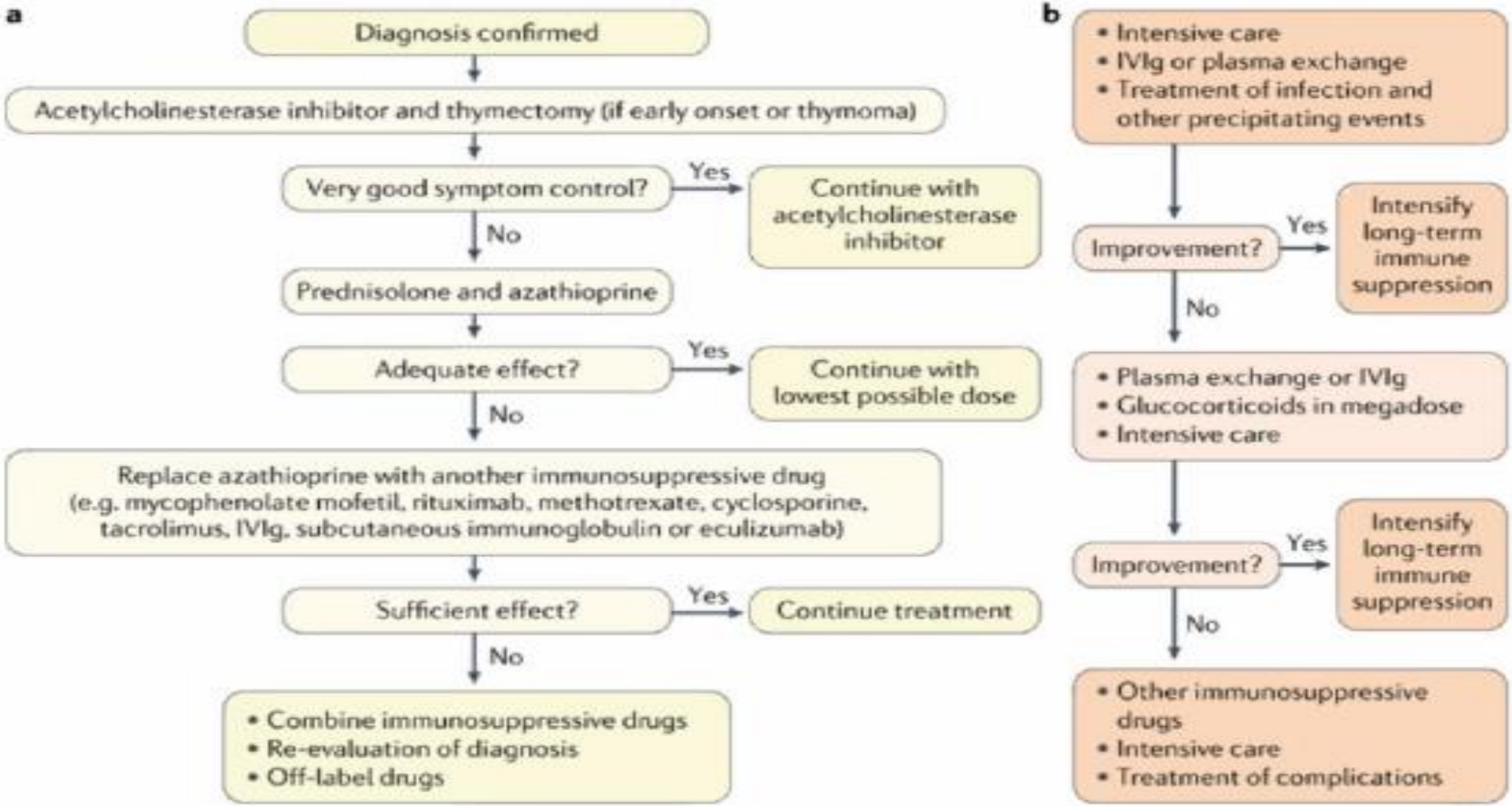
Rituximab vs ocrelizumab



-momab	-ximab	-zumab	-mumab
Not evaluated in MS	Rituximab	Alemtuzumab Daclizumab Natalizumab Ocrelizumab	Ofatumumab
Infusion reactions very frequent (>50%)	Infusion reactions frequent (approximately 30%)	Infusion reactions occasional (5%-10%)	Infusion reactions rare (<1%)

Bruck et al., JAMA Neurology 2013

Treatment algorithms for chronic MG and acute MG exacerbations



Gilhus, N. E. et al. 2019 *Nature Rev Dis Primers*

Subcutaneous immunoglobulin in MG

- *Beecher et al 2017:* **23 patients. Open. Safe and effective in mild to moderate exacerbations. QMG-, MMT-, MGC-scores**

- *North American open label:* **Abstract only. 23 patients. 12 weeks. Ivlg as part of routine clinical care. «Success» in 17 patients.**

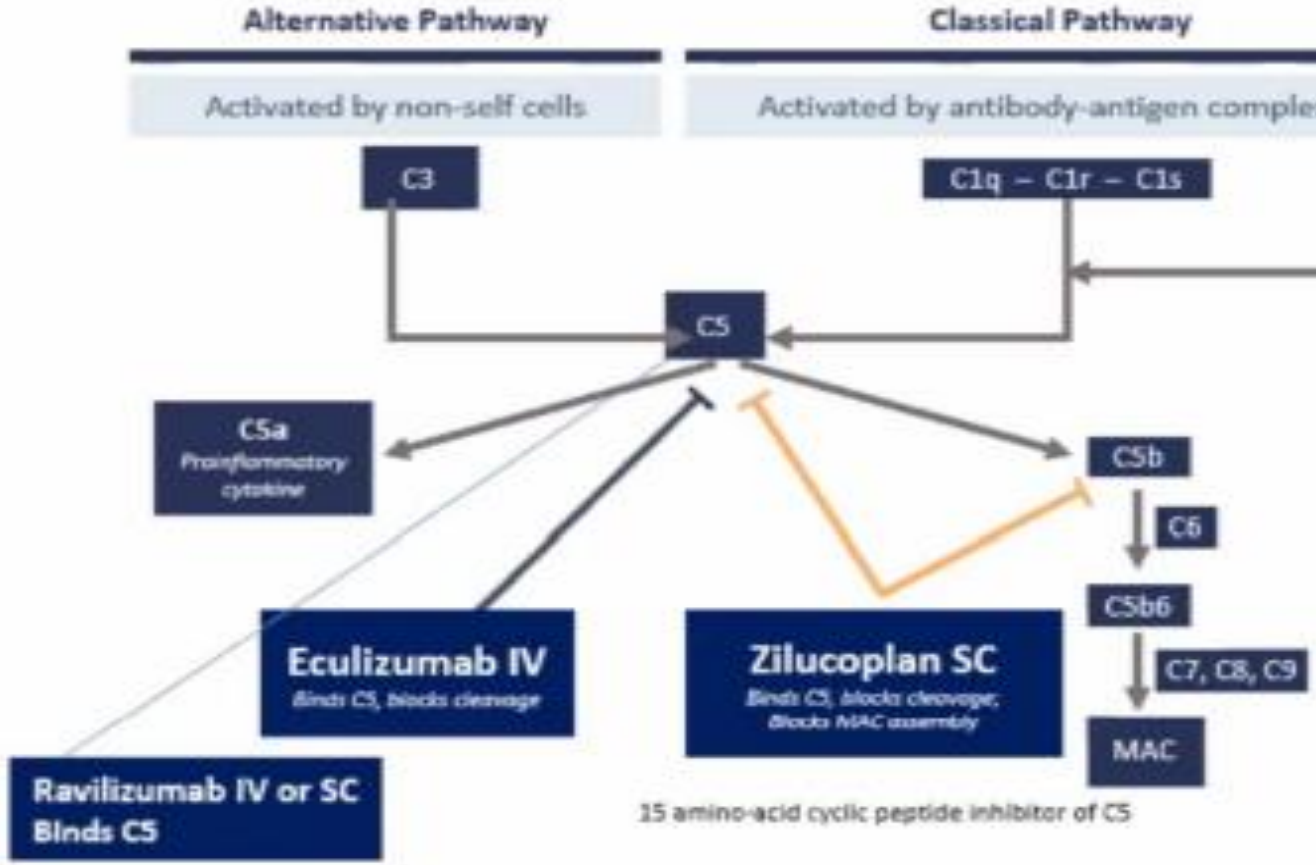
- ✓ **Effectiveness**
- ✓ **Tolerability**
- ✓ **Costs**
- ✓ **Practical aspects**

New treatments

- Complement inhibition
- IgG FcRn blocking
- B cell inhibition *CD19, CD20, CD21, CD22, CD79, CD179, etc*

  rituximab, ocrelizumab, iscalimab, inebilizumab
- BAFF inhibition *belimumab*
- Proteasome inhibitor *bortezomib*
- T cell inhibition
- IFN and cytokine inhibition *tocilizumab, atlizumab, etanercept, rontalizumab, anifrolumab*
- Stem cell transplantation
- Strengthening the neuromuscular synapse
- Antigen-specific therapies *acting on antibodies, B cells, T cells*

Complement inhibitors



Antibodies or peptides

Various C-elements

Safety

Long-term effect

Cost-benefit

Binding and activation of complement at the NMJ

- **Predominant pathogenic mechanism of anti-AChR antibodies.**
- **In the MG thymus, the activation of the complement cascade has also been observed on myoid cells and on thymic epithelial cells.**
- **Numerous studies on EAMG models have clearly shown that inhibition of complement pathways effectively and specifically diminish the NMJ destruction induced by anti-AChR antibodies.**

Changes in complement concentration can influence the severity of MG

(1) Experiments in rats showed that blocking or depletion of complement protects animals from developing EAMG

(2) Antibodies that block complement component C6 or soluble complement receptor 1 protect rodents from EAMG

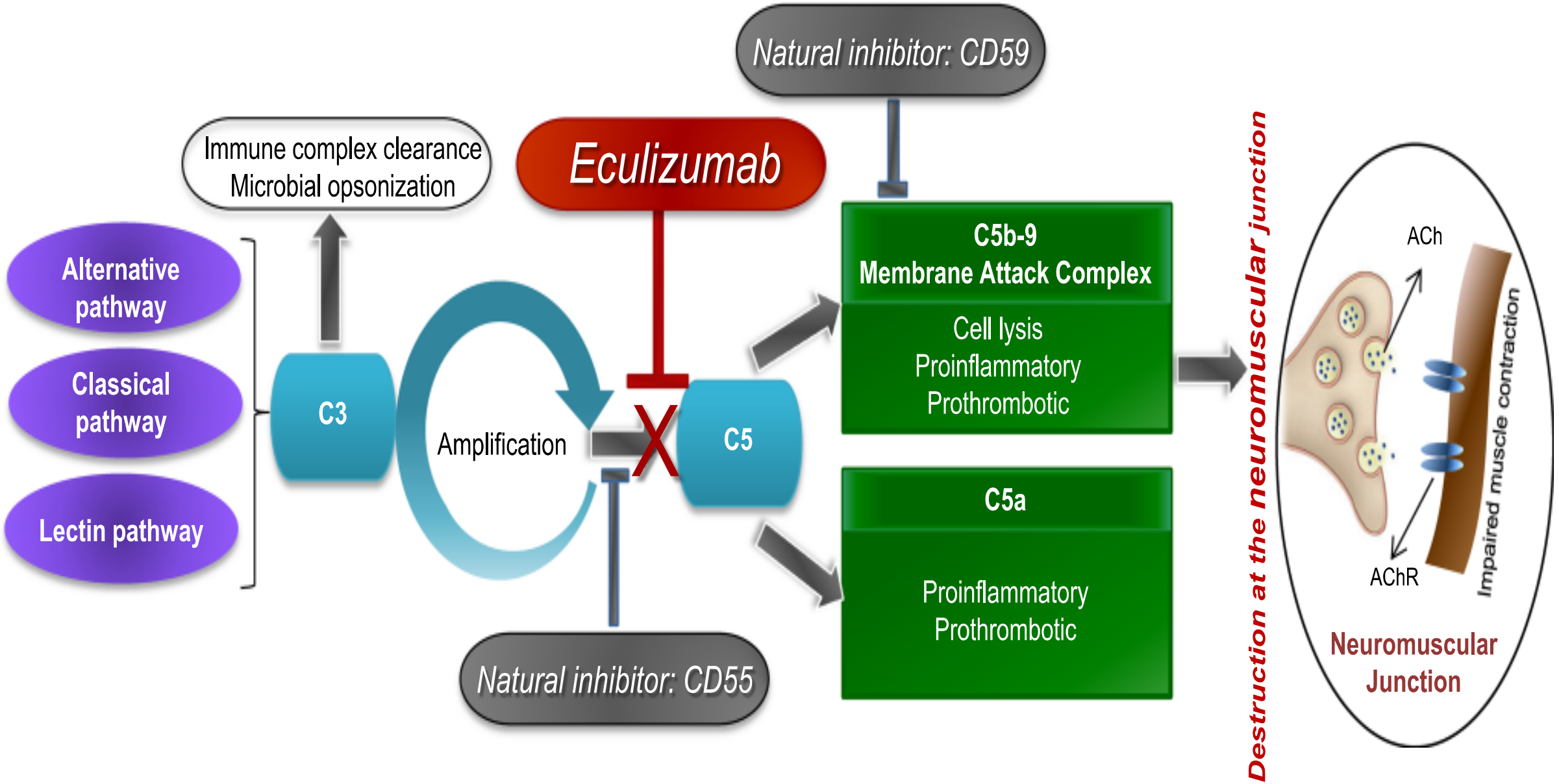
(3) An inhibitor of C5 reduces symptoms in the rat EAMG model

(4) Mice deficient for classical complement pathway factors are resistant to antibody and complement mediated EAMG

(5) Increased complement consumption was detected in MG patients with high AChR antibody concentrations

Eculizimab

- **Molecules aiming at decreasing complement deposition at the NMJ could represent a therapeutic approach of major interest.**
- **Only Eculizimab (SolirisTM, Alexion Pharmaceuticals) has been considered for MG patients.**
- **Humanized monoclonal antibody that inhibits the cleavage of the complement protein C5 acting at the terminal complement activation cascade.**
- **An initial phase II pilot study showed clinically improvements in severe and refractory of AChR- MG patients.**


Natural inhibitor: CD59
Immune complex clearance
Microbial opsonization
Eculizumab
Alternative pathway
Classical pathway
Lectin pathway
C3
Amplification
C5
C5b-9
Membrane Attack Complex
Cell lysis
Proinflammatory
Prothrombotic
C5a
Proinflammatory
Prothrombotic
Natural inhibitor: CD55
Destruction at the neuromuscular junction
ACh
AChR
Impaired muscle contraction
Neuromuscular Junction

Dilhon, 2018

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

2017

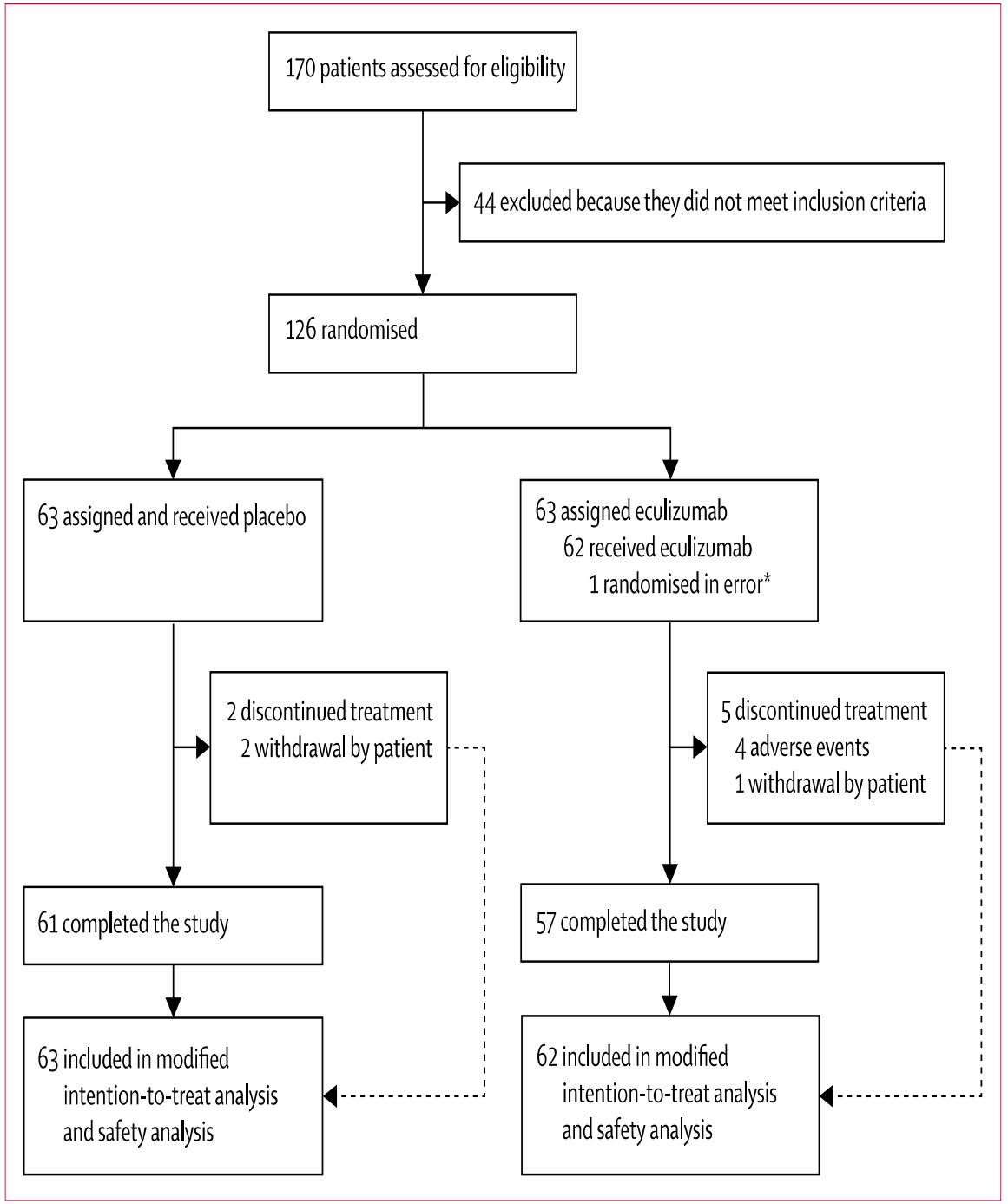
*James F Howard Jr, Kimiaki Utsugisawa, Michael Benatar, Hiroyuki Murai, Richard J Barohn, Isabel Illa, Saiju Jacob, John Vissing, Ted M Burns, John T Kissel, Srikanth Muppidi, Richard J Nowak, Fanny O'Brien, Jing-Jing Wang, Renato Mantegazza, in collaboration with the REGAIN Study Group**

- Phase 3, randomised, double-blind, placebo-controlled, multicentre study (REGAIN)
- 76 centres in 17 countries
- Inclusion criteria:
  - >18 years
  - Myasthenia Gravis-Activities of Daily Living (MG-ADL) score >6 or more
  - MGFA class II–IV
  - vaccination against Neisseria meningitides
  - previous treatment with at least two immunosuppressive therapies or one immunosuppressive therapy and chronic intravenous immunoglobulin or plasma exchange for 12 months without symptom control.
- Exclusion criteria:
  - history of thymoma or thymic neoplasms, thymectomy within 12 months before screening
  - use of intravenous immunoglobulin or plasma exchange within 4 weeks before randomisation
  - rituximab within 6 months before screening

- Participants were randomly assigned to either intravenous eculizumab or intravenous matched placebo for 26 weeks.
- Dosing for eculizumab was 900 mg on day 1 and at weeks 1, 2, and 3; 1200 mg at week 4; and 1200 mg given every second week there after as maintenance dosing.
- Where possible, patients were maintained on their previous therapies
- **Primary efficacy endpoint=**

change from baseline to week 26 in MG-ADL total score measured by worst-rank ANCOVA.

- **Secondary efficacy endpoints**
  - change from baseline in QMG total score,
  - responder analysis of the MG-ADL score (≥3-point improvement)
  - responder analysis of the QMG score (≥5-point improvement)
  - change from baseline in MGC total score
  - change from baseline in MG-QOL15

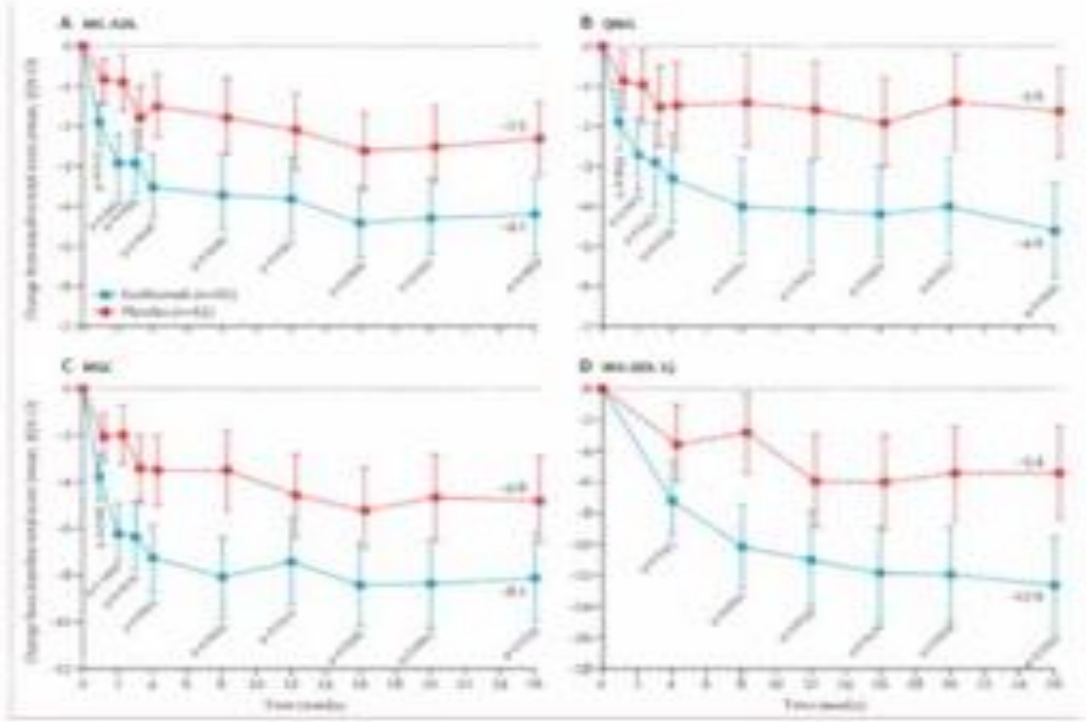


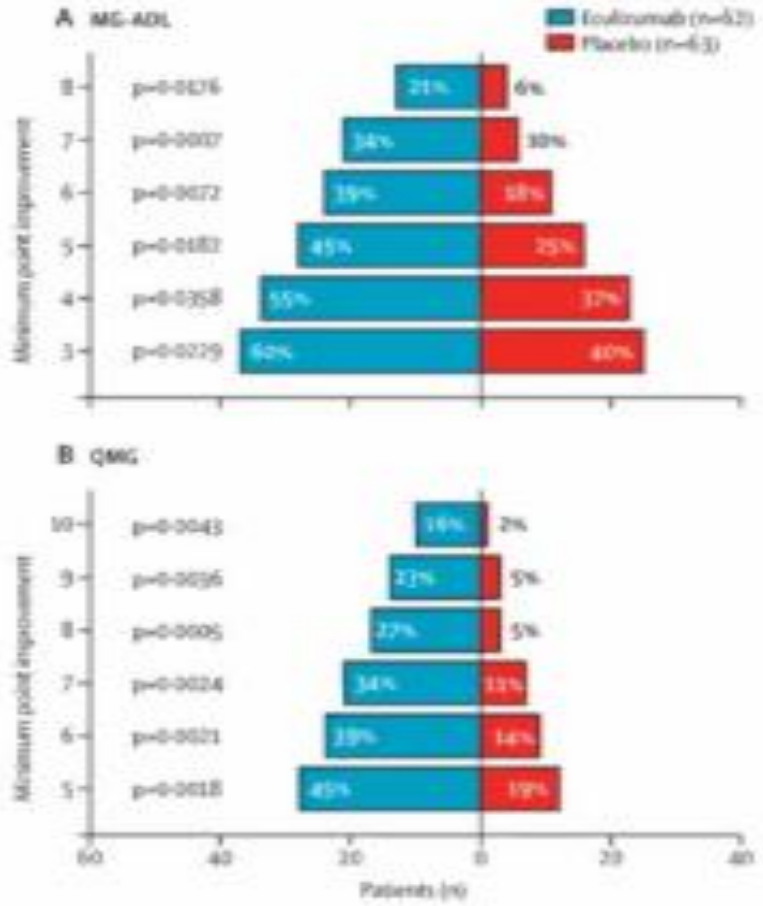
The difference between the groups in change in MG-ADL total score from baseline to week 26 for the eculizumab and placebo groups did not achieve significance

	Eculizumab (n=62)	Placebo (n=63)	Difference (95% CI)	p value*
Prespecified worst-rank ANCOVA score†				
MG-ADL‡	56·6 (4·5)	68·3 (4·5)	−11·7 (−24·3 to 0·96)	0·0698
QMG	54·7 (4·5)	70·7 (4·5)	−16·0 (−28·5 to −3·4)	0·0129
MGC	57·3 (4·5)	67·7 (4·5)	−10·5 (−23·1 to 2·1)	0·1026
MG-QOL15	55·5 (4·6)	69·7 (4·5)	−14·3 (−27·0 to −1·6)	0·0281
Prespecified sensitivity repeated-measures model analysis with immunosuppressive treatments as covariate§				
MG-ADL	−4·1 (0·5)	−2·3 (0·5)	−1·8 (−3·2 to −0·5)	0·0077
QMG	−4·6 (0·6)	−1·7 (0·6)	−2·9 (−4·6 to −1·2)	0·0007
MGC	−7·9 (1·0)	−4·6 (1·0)	−3·3 (−5·9 to −0·6)	0·0168
MG-QOL15	−13·8 (1·6)	−6·7 (1·6)	−7·1 (−11·3 to −3·0)	0·0009
Post-hoc sensitivity worst-rank ANCOVA score¶				
MG-ADL	54·8 (4·5)	70·2 (4·4)	−15·4 (−27·8 to −2·9)	0·0160
QMG	53·9 (4·5)	71·6 (4·4)	−17·7 (−30·1 to −5·3)	0·0055
MGC	56·1 (4·5)	69·0 (4·4)	−12·9 (−25·4 to −0·5)	0·0414
MG-QOL15	54·6 (4·5)	70·6 (4·5)	−16·0 (−28·6 to −3·4)	0·0134

Eculizumab in MG

REGAIN study



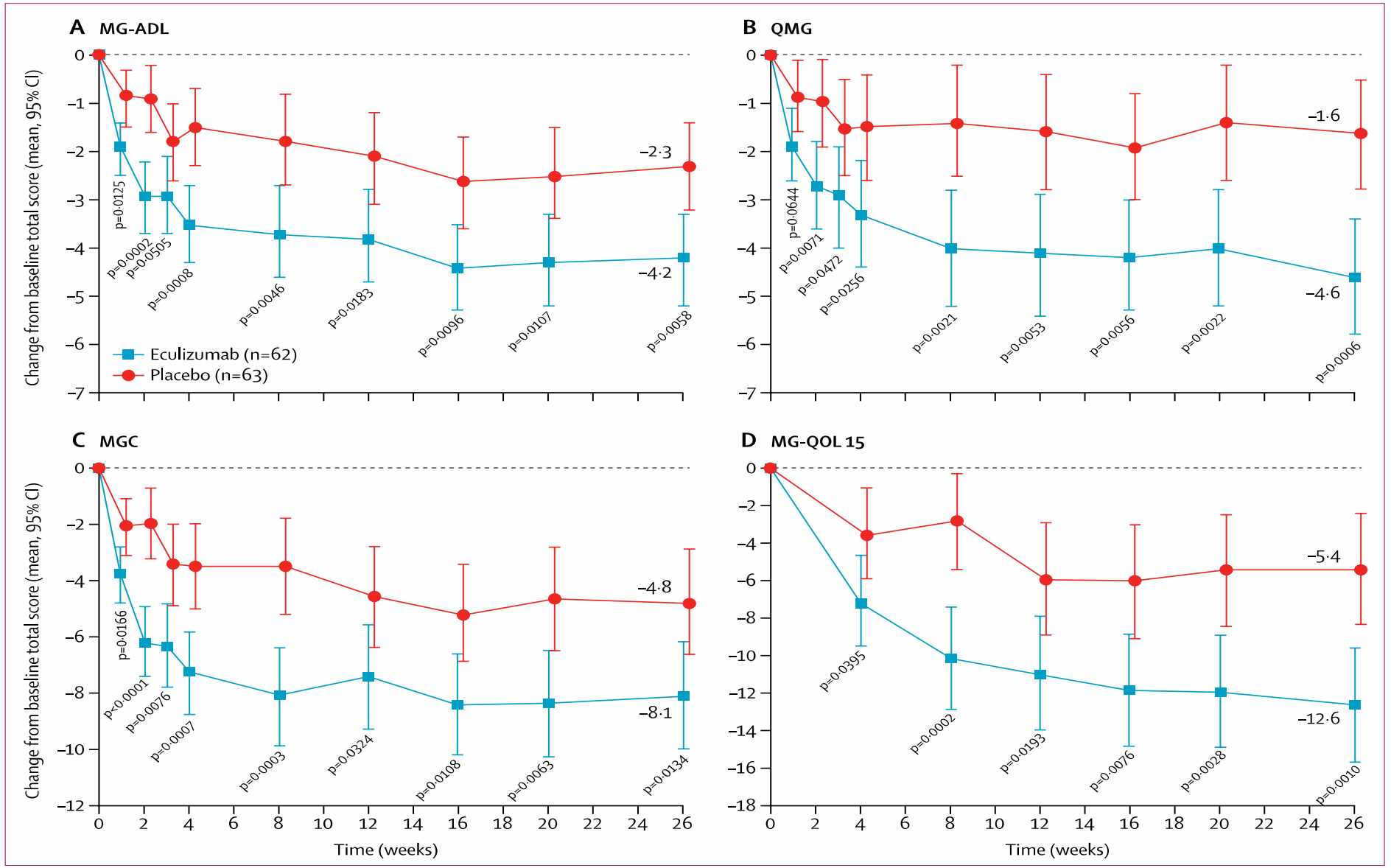


Moab inhibiting C5 cleavage

- Phase 3 study positive, but not for primary end-point
- Fast action
- Safe(?)
- Cost-benefit?

Howard et al 2017

Secondary end points and sensitivity analyses suggested efficacy of Eculizumab leading to a reduction in disease severity

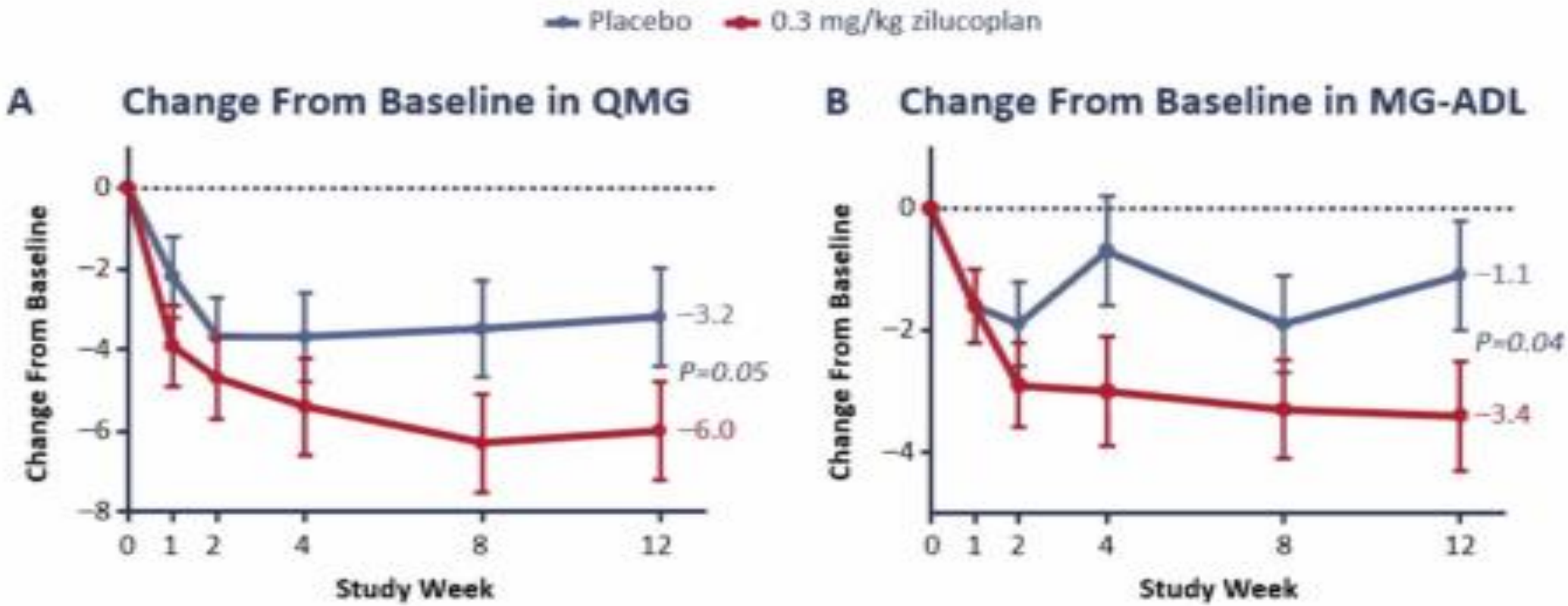


- **No deaths or cases of meningococcal infection occurred during the study**
- **Most common adverse events were headache and upper respiratory tract infection in both groups**
- **MG exacerbations were reported by six (10%) patients in the eculizumab group and 15 (24%) in the placebo group.**
- **Six (10%) patients in the eculizumab group and 12 (19%) in the placebo group required rescue therapy.**
- **Eculizumab was well tolerated.**
- **The use of a worst-rank analytical approach proved to be an important limitation of this study since the secondary and sensitivity analyses results were inconsistent with the primary endpoint result.**
- **In October 2017, the US Food and drug administration has extended the indication for this molecule as a potential treatment for patients with refractory and generalized AChR-MG**

Zilucoplan phase 2 study, 44 patients

JAMA Neurol 2020

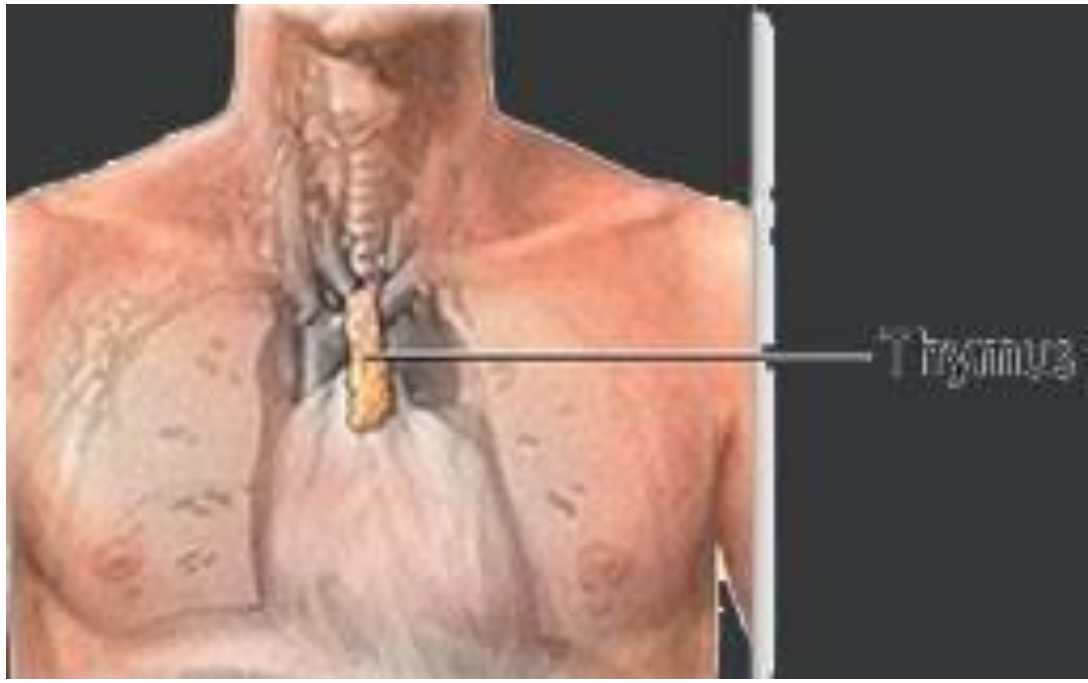
Statistically Significant Reduction in QMG (Primary Endpoint) and MG-ADL



Pre-specified significance testing at 1-sided alpha of 0.1 with LOCF ANCOVA p values shown; error bars denote standard errors of least squares mean; mITT

A peptide C5 inhibitor

Thymectomy



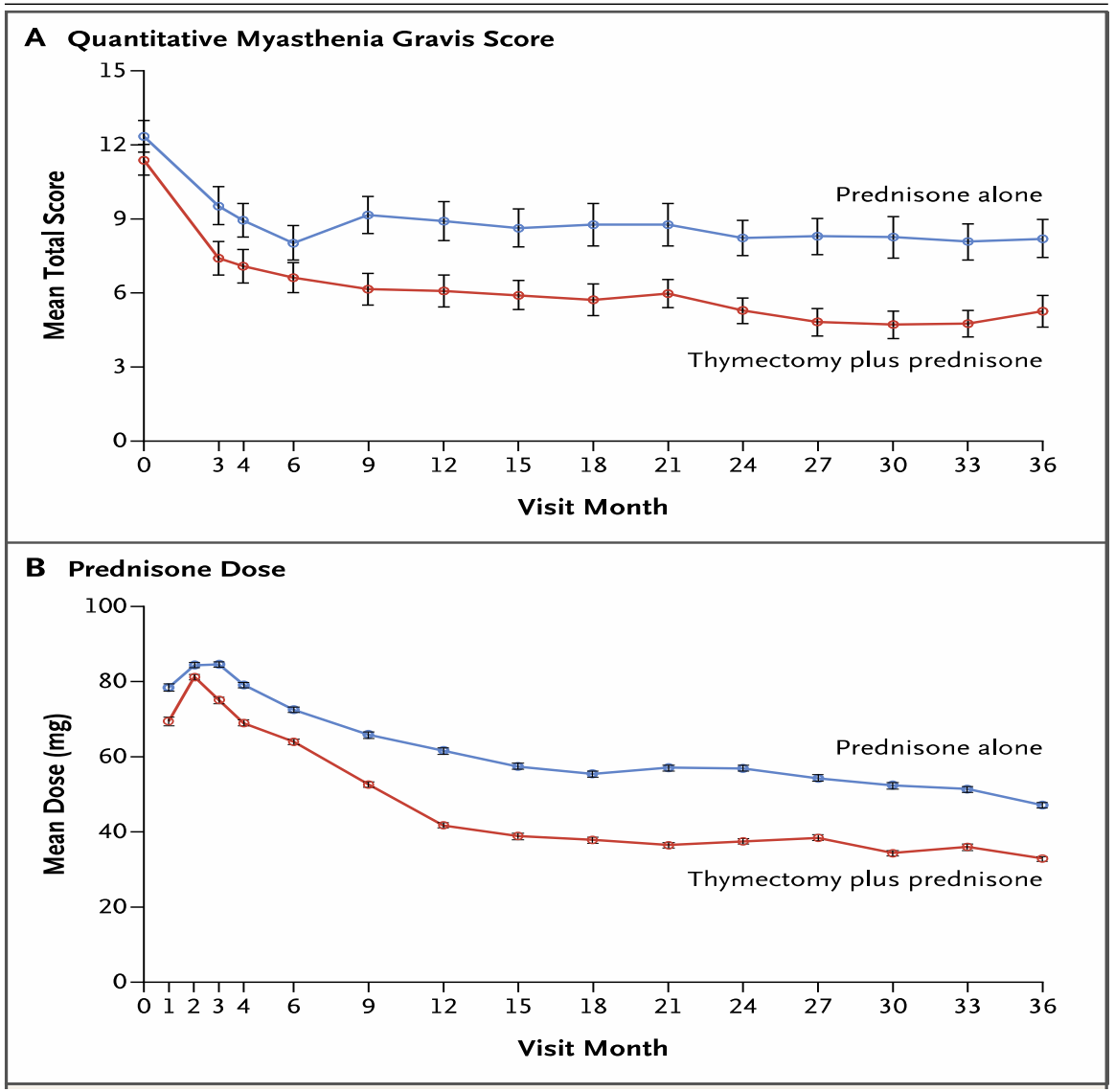
- **In thymomatous MG, the tumor should be removed.**
- **In non thymomatous generalized MG, thymectomy has become the standard despite a lack of evidence from a good prospective clinical trial.**

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*

- Multicenter, randomized trial comparing thymectomy plus prednisone with prednisone alone.
- 126 recently diagnosed patients were randomized to receive either extended transsternal thymectomy plus prednisone versus medical management with prednisone.
- Inclusion criteria
  - patients 18 to 65 years of age who had generalized nonthymomatous myasthenia gravis with a disease duration of less than 5 years were included if they had Myasthenia Gravis Foundation of America clinical class II to IV disease (on a scale from I to V, with higher classes indicating more severe disease) and elevated circulating concentrations of acetylcholine-receptor antibody.
- Exclusion criteria:
  - thymoma on computed tomography or magnetic resonance imaging of the chest, previous thy- mectomy, immunotherapy other than prednisone, pregnancy or lactation, unwillingness to avoid pregnancy, contraindications to glucocorticoids, and substantial medical illness that would pre- clude participation.
- To preserve rater blinding, participants were seen exclusively until month 4, by a neurologist who was aware of the trial-group assignments.

3-year follow-up period



The time- weighted average QMG score was lower in the patients who underwent thymectomy (6.15 vs 8.99; *P*<.001)

The thymectomy group had a lower time-weighted alternate-day prednisone dose requirement (initially 44 mg vs 60 mg; *P*<.001), which was later corrected to 32 mg versus 54 mg (12–32 mg; *P*<.001)

In the thymectomy group, there were fewer patients requiring additional immunosuppression, fewer adverse events, and fewer admissions for myasthenic crises.

Emerging therapies for MG : summary

- **Ravulizumab** (Alexion) Phase 3 starting to evaluate next generation C5 drug Q8 wks
- **Rituximab** - monoclonal Ab to B-cells
  - completed-negative trial
- **Belimumab (GSK)** -monoclonal to BLS
  - completed-negative trial
- **Subcutaneous immune globulin** (Dimachkie)
  - Completed- positive study
- **IVIg** - 2 studies (Grifols)
  - Awaiting results
- **ArgenX** (Efgartigimod) - Fc receptor blockade
  - IV Phase 2 done / Phase 3 done-Any MG; Awaiting results
- **Ra Pharma** (Zilucoplan) -complement inhibitor/ SC subcutaneous
  - Phase 2 study positive
- **TAK-079** - Anti-CD38 depletes plasma cells (Takeda)
- **New Alexion study**
  - Every 2 months IV
- **Argenx** (Efgartigimod) - Fc receptor blockage
  - IV Phase 2 done / Phase 3 starting
- **Momenta** -Fc receptor blockage
  - IV-Phase 2 starting soon
- **UCB** - (rozanolixizumab) Fc receptor blockage
  - SC-Phase 2 done / Phase 3 starting
- **Catalyst**- Firdapse for 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/

- 1st Line: Pyridostigmine
  Corticosteroids
  Thymectomy
- 2nd Line: Azathioprine
  Cyclosporine
  IVIG
  Tacrolimus
- 3rd Line: Plasma exchange
  Eculizumab (immunization
  Mycophenolate Mofetil
  Methotrexate
  ? FcRN Blocker
- 4th Line: Rituximab in MuSK*
  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

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

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

Gajdos et al. Ann Neurol 1997;41:789-796

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

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

THANKS FOR YOUR ATTENTION