Introduction to Myasthenia Gravis

Yuebing Li, MD, PhD
Professor of Neurology
Director of Neuromuscular Research
Neuromuscular Center
Cleveland Clinic

Disclosures:

- Served as a consultant for Advisory Board Meeting by Alexion, Amgen, Argenx, Johnson & Johnson, Kyverna, Vertex.

What is myasthenia gravis?

- Name: Latin and Greek in origin
  - Myasthenia: muscle weakness
  - Gravis: grave
- A name of being both true and false
  - True: muscle weakness being the hallmark
  - False: no longer a grave disease if treated appropriately.
    - Most patients have a normal life span.
    - Most live with a relatively normal life style.
    - Most have symptoms well controlled.
    - Very low mortality rate. In most MG patients, the cause of death is not related to MG.

Historical description of myasthenia gravis

Thomas Willis described in "The London Practice of Physick" in 1672:

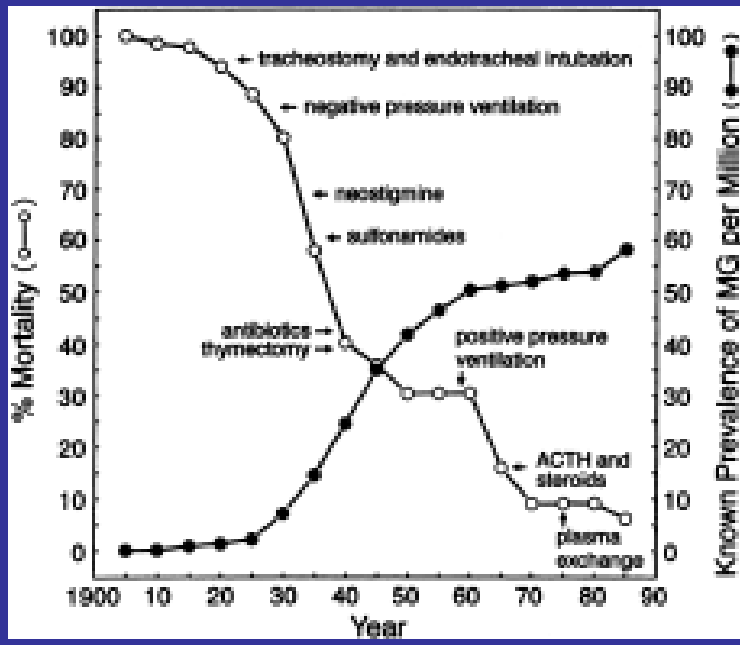
"There is another kind of this disease…in which motion fails wholly. Those who being troubled…are able to first rising in the morning to walk, move their arms…, or to lift up a weight with strength, but before noon…they are scarce to move hand or foot. I have now a prudent and honest woman…this kind of bastard palsy, not only in the limb but likewise in her tongue; this person for some time speaks freely and readily enough, but after long, hasty, or laborious speaking presently she became mute as a fish… and does not recover the use of her voice until after an hour or two."

Milestones in MG Diagnosis

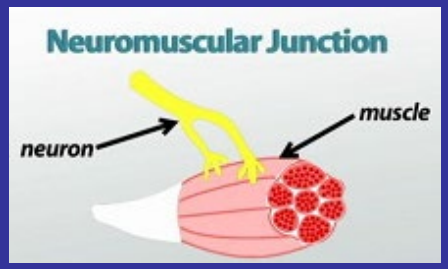
- 1895: Friedrich Jolly, “myasthenia gravis pseudoparalytica”
- 1950s: Repetitive nerve stimulation (EMG)
- 1960s: Recognition of MG as an autoimmune disease
- 1970s: Singer fiber electromyography (SFEMG)
- 1973: Patrick and Lindstrom, blood test for AChR-Ab
- 2001: Blood test for MuSK antibody
- 2012: Blood test for LRP4 antibody

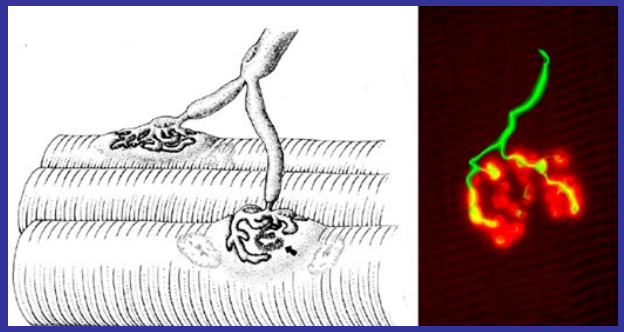
Milestones in MG Treatment

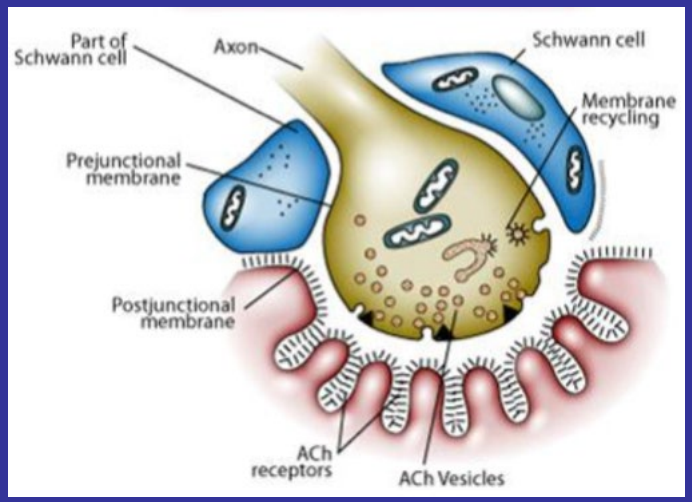
- 1911, Ferdinard Sauerbruch, thymectomy (transcervical)
- 1934, Mary Walker, cholinesterase inhibitor
- 1939, Blalock, thymectomy (thansthoracic)
- 1955, FDA approval of pyridostigmine
- 1965, use of corticosteroid (prednisone in 1971)
- 1967, use of azathioprine
- 1968, use of cyclophosphamide
- 1976, use of plasmapheresis
- 1984, use of IVIG
- 1987, use of cyclosporine
- 1998, use of mycophenolate mofoetil
- 1999, use of rituximab
- 2002, use of tacrolimus
- 2016, MGTX trial result published
- 2017, FDA approval of eculizumab: AChR (+) GMG
- 2021, FDA approval of efgartigimod: AChR (+) GMG
- 2022, FDA approval of ravulizumab: AChR (+) GMG
- 2023, FDA approval of efgartigimod and hyaluronidase: AChR (+) GMG
- 2023, FDA approval of rozanolixizumab: AChR (+) and MuSK (+) GMG
- 2023, FDA approval of zilucoplan: AChR (+) GMG
- 2025, FDA approval of nipocalimab: AChR (+) and MuSK (+) GMG
- 2025, FDA approval of inebilizumab: AChR (+) and MuSK (+) GMG
- 2026, FDA approval of efgartigimod for all GMG, including seronegative GMG.



What causes myasthenia gravis?



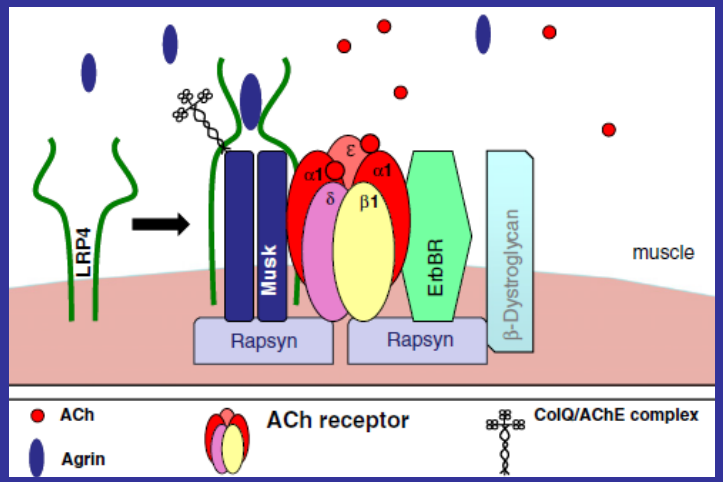




- The basic abnormality in MG is a reduction in the number or the function of acetylcholine receptors (AChRs) at the postsynaptic membrane.
- A (functional>structural) disconnection between nerve and muscle
  - Mostly repairable/reversible, especially at early stage
  - A lot still repairable/reversible at a later stage

What causes myasthenia gravis?

Autoimmune: antibody mediated
- – Acetylcholine receptor antibody (80-85%)
- – MUSK antibody (6%)
- – LRP4 antibody (1%, ?)
- – Cortactin antibody (?)
- – Agrin, ColQ antibody (rare) (?)
- – Other unrecognized antibodies

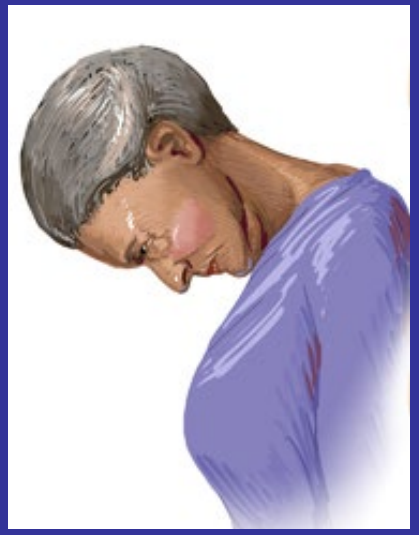


• Seronegative MG (<5%): No detectable antibody towards known or unknown components of the neuromuscular junction.
- This portion of patients accounts for a gradually smaller group.
- There is often a need to further verify the diagnosis in this group of patients.

• Misfire: Antibody produced by patients' own immune system affecting own neuromuscular junction.

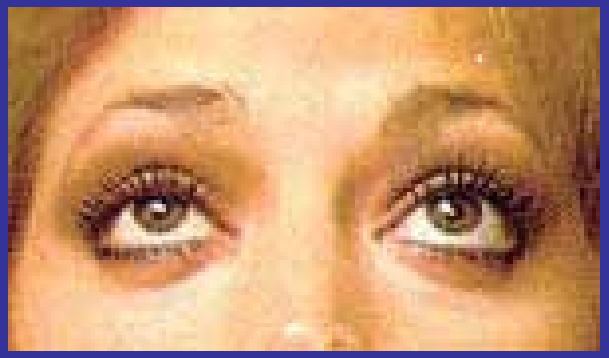
What muscles are weak?

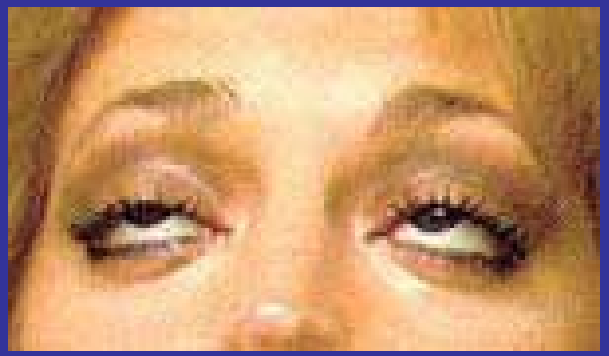
- Muscles involved
  - – Ocular: Eye movement and eyelid opening
  - – Facial expression (no smile or vertical smile)
    - –Mouth corners not drawn up and out due to buccinators weakness
    - –Mouth open in vertical direction
    - –Failure of eye closure upon smiling
  - – Oropharyngeal: shewing/swallowing/speaking
  - – Arms and legs (proximal, muscle groups close to the spine)
  - – Respiratory: chest wall muscles/diaphragm
  - – Abdominal wall muscles (breathing, posture, labor)
  - – Muscles along the spine: keeping spine straight



Ocular Symptoms and Signs: Ptosis

- Usually asymmetric and bilateral but can be unilateral especially at the onset
- Alternative eyelid droop is diagnostic.
- Evident on prolonged upgazing for 1 to 2 minutes
- Ice test: improved droopy eyelid upon ice-pack application of two minutes. However, it can be positive in other conditions.





Other symptoms of myasthenia gravis

- Double vision and drooping eyelid (Seen in 95% of MG patients at least once)
  - Double, not triple or more
  - Disappears (improved vision) when closing one eye (either eye)
- Lack of facial expression or forced smiling (usually ignored by patients/doctors
- Difficulty in chewing, jaw drop after chewing, jaw ache
- Soft voice with nasal speech, infrequent hoarseness
- Choking, more often with liquid, food coming out of nose
- Shortness of breath, difficult to lie down
- Difficulty holding arms up (shaving, hair-dressing, working overhead)
- Difficulty getting up from sitting/squatting position
- Head drop or head lag
- Fatigue and lack of energy

- Worse with repetition or in the second half of day. Usually better in the AM.
- Worse in hot temperature/weather.

MG and Associated Conditions

- Other autoimmune diseases commonly seen in patients and family members
  - Second autoimmune disease found in at least 15% of MG patients.
  - Rarely MG in family members (father/son, father/daughter, husband/wife)

- Vaknin-Dembinsky (2011): 164 patients
  - 25 autoimmune thyroiditis
  - 6 SLE (lupus) or antiphospholipid antibody syndrome
  - 3 immune thrombocytopenic purpura
  - 2 inflammatory bowel diseases (Crohn's, ulcerative colitis)
  - 1 each of rheumatoid arthritis, insulin DM, polymyositis, CIDP, psoriasis, scleroderma, Sjogren syndrome

Associated Symptoms in MG

- Fatigue (Tran et al Muscle Nerve 2018)
  - Correlation with disease severity, also related to female sex, generalized subtype and anxiety/depression.
  - Could be due to mental fatigue, autonomic dysfunction, insomnia etc.
  - Can occur even when MG is well controlled.
  - Can improve with treatment in some patients, but not all.
    - It is hard to improve fatigue with immunotherapy.
- Depression and anxiety
  - Conflicting report regarding whether this is increased in MG.
  - MG patients may not be more depressed but have a physical disease mimicking typical symptoms of depression.
  - Possible association between depression and high dose steroid
- Sleep related disorder
  - Sleep apnea, disordered sleep pattern, poor sleep quality, insomnia

Who Gets Myasthenia Gravis?

- All ethnic groups, both gender
- Not inherited although there is a genetic predisposition.
- Non-contagious.
- Prevalence of 100 to 200 cases per million and annual incidence of 2.5 to 20 per million
  - Prevalence of 5 times higher in older (>65) patients
  - Approximately 2 to 3 times less common than multiple sclerosis (MS)
  - Approximately 8 to 10 times more common than amyotrophic lateral sclerosis (ALS, Lou Gehrig disease).

Grading the severity of myasthenia gravis: MGFA classification

- 0 - remission
- 1 - ocular
- 2 - mild generalized
- 3 - moderate generalized
- 4 - severe generalized
- 5 - crisis (intubated for MG)

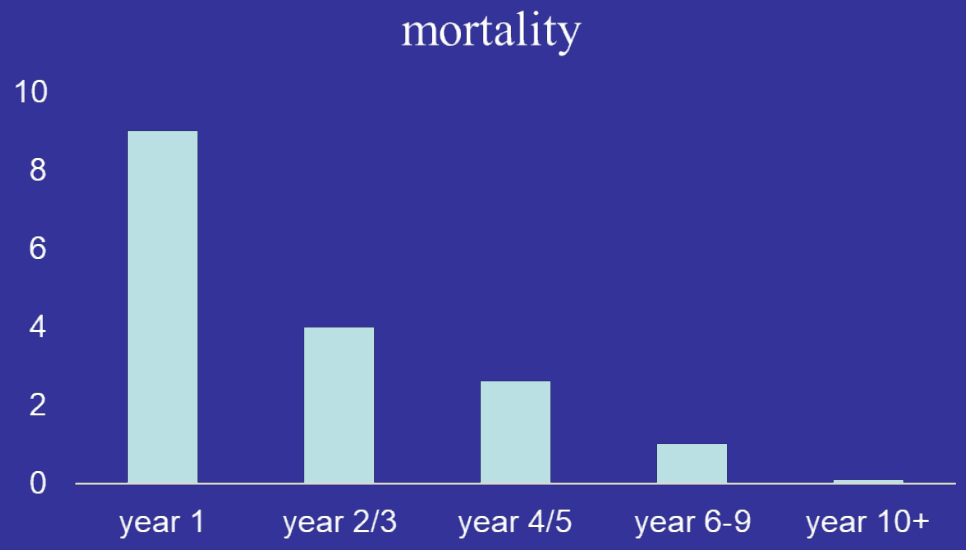
- Impending crisis: rapid clinical worsening of MG that could lead to crisis in days to weeks.

Anxiety about MG crisis

- Crisis does not occur in isolation!
  - Usually following other MG symptoms, especially speech/chewing/swallowing/neck weakness.
  - Usually there is a cause (change in medication, infection, undiagnosed).
- Crisis does not occur suddenly without gradual evolution for a few days to weeks, especially if already on immunotherapy!
- Crisis does not go away without treatment adjustment.
- Crisis does not manifest as episodic shortness of breath with exertion only. Reminder: at least >50% of American adults have dyspnea on exertion.
- Crisis does not manifest as sudden onset of shortness of breath that wake you up in the middle of night, then go away within half an hour.

Natural Course of MG Without Treatment

- Grob D (1987): mortality rate for 406 patients (91 patients with thymectomy, no immunotherapy) with generalized MG (1940-1957)
  - 9% died within first year of onset.
  - 4% during second and third year.
  - 2.6% during fourth and fifth year.
  - <1% per year from sixth through ninth year.
  - <0.2% per year more than 10 years after onset.
  - Our current treatment results are much better!!!



Natural Course of MG: more recent data

- Grob (2008):
  - 1986 patients from USA
  - Maximum weakness reached within first two years in 82% patients.
- Mantegazza (1990):
  - 1152 patients from Italy
  - Maximum severity seen within first three years in 77% patients.
- If a MG patient can be kept alive for the first three years, the course of the disease is usually a gradual improvement or steady state, with fluctuation/exacerbation seen in the minority.

Fluctuating Course of MG

- Remission:
  - Without treatment, spontaneous remission could occur and last longer than one year in 15-20% patients. But recurrence is seen in most cases.
  - Treatment induced remission is more common.
  - Minimal manifestation (MM) status: no symptoms or functional limitations from MG but has some weakness is seen on exam.
  - Approximately 20% patients can discontinue all medications.

- Exacerbation (flare-ups)
  - Mostly triggered by infection, hot weather, surgery, child birth, medications or reduction of treatment
  - Usually more frequent within first three years but can occur later in a portion of patients

- Refractory MG (10-15% of MG patients): MG with thymoma, MuSK MG, early onset MG.

How to diagnose myasthenia gravis?

- There is unfortunately a common delay in the diagnosis, mostly due to unfamiliarity of the condition.
- Careful neurological and ophthalmological examination.
- Most patients end up with MRI of brain.
- In suspected patients:
  - Blood tests for antibodies (everybody)
  - Chest CT scan (everybody)
  - Tensilon (edrophonium) test (mostly unnecessary, and no longer available in USA)

Four essential components to diagnose myasthenia gravis (at least 2 is required)

- Classical symptoms and signs
  - Task specific, location appropriate weakness that are fatigable upon repeated usage
  - Not just overall fatigue without specifics

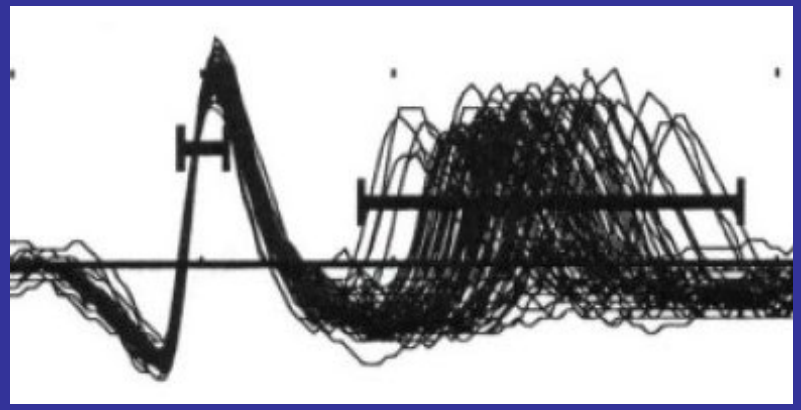
- Meaningful positive blood tests
  - Not just borderline testing results
  - Abnormal AChR antibody results can be seen in other diseases.
  - LRP4 antibody testing in USA is problematic.

- Abnormal electrophysiology study (EMG)
  - Not just borderline, non-reproducible changes.
  - SFEMG is NOT the golden standard in diagnosing MG.

- Positive treatment response to pyridostigmine and immunotherapy
  - Treatment responses need to be reliable, and specific, not just “I feel better”.
  - Treatment responses follow specific time course.

Role of EMG in diagnosing myasthenia gravis

- EMG is unnecessary in patients who have typical symptoms and positive antibodies.
- Single fiber electromyography (mostly unnecessary)
  - Should probably be reserved for patients with mild/regional symptoms.
  - Sensitive but not specific
  - Mostly useful in two scenarios:
    - ❖ High suspicion for MG but other tests all negative
    - ❖ Excluding MG diagnosis completely.



Myasthenia gravis: treatment strategy

- Induce a remission first and quickly
  - Patients with mild symptoms: mestinon or low dose steroid
  - Urgent treatment for patients in crisis: IVIG, plasmapheresis, and perhaps newer therapies
  - Rapid improvement for patients with disabling features: prednisone , intravenous steroid, IVIG, plasmapheresis, complement inhibitors, FcRN antagonist

- Maintain the remission with least cost/benefit ratio
  - Combination treatment to minimize side effects (prednisone and "steroid-sparing agents", thymectomy)
  - Gradual tapering to find minimal required dosage: Goal of prednisone less than 5 to 7.5mg per day on average. Use of Imuran or cellcept.
  - Complement inhibitors, FcRN antagonist, B cell depletion therapy

A partial list of newer-generation immunotherapies

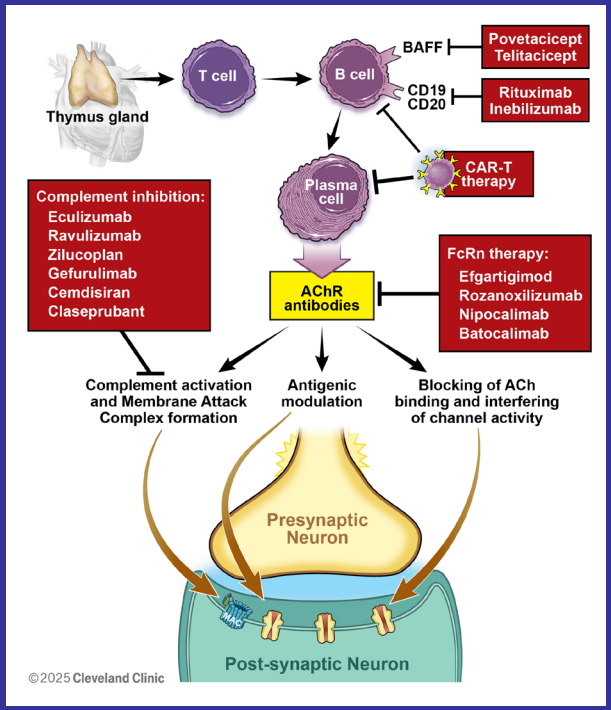
B cell depletion therapy:
- Inebilizumab
- Others: rituximab*, telitacicept*, povetacicept

Neonatal Fc receptor (FcRn) therapy
- Efgartigimod
- Rozanolixizumab
- Nipocalimab
- Others: Batoclimab*

Complement inhibition therapy
- Eculizumab
- Ravulizumab
- Zilucoplan
- Others: gefurulimab*, cemdisiran (+/- pozelimab)*, claseprubant

Cellular therapy:
- Stem cell and CAR-T/CAAR-T therapy

Others:
- Remibrutinib, satralizumab etc.



Green color denotes approved therapy; * Positive phase III trial results

What are the advantages of newer-generation therapy?

- Specific mechanisms of action
  - All aim to act on ONW key step of the immune pathway;
  - Action is not MG-specific or MG-exclusive.

- Fast onset of clinical efficacy
  - Clinical efficacy for most: usually evident in 1-2 weeks
  - Inebilizumab: approximately by 2-3 months

- Not affecting parenchymal organ (liver, kidney, lung, heart) functions. No need for CBC/CMP monitoring

- Broad spectrum:
  - Both AChR and MuSK antibody positive MG (AChR-MG for complement inhibitors)
  - GMGs; plus recent positive result of efgartigimod on OMG (OCULUS)
  - Seronegative GMG: efgartigimod.
  - Pediatric: eculizumab (6+ yr, AChR-MG), nipocalimab (12+ years, AChR-MG, MuSK-MG)
  - Myasthenic crisis (case reports/series), especially those who failed IVIG/plasmapheresis

Traditional MG medications

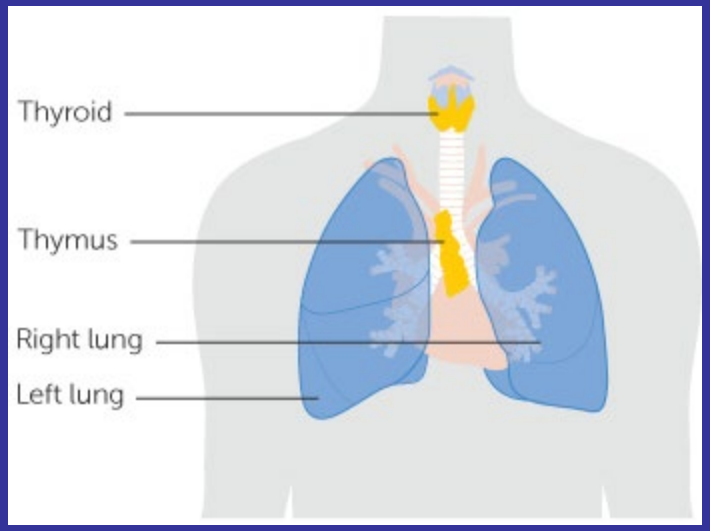
- Mestinon (pyridostigmine)
  - Regular and controlled-release form (Timespan)
  - Mostly useful in patients with mild symptoms or as adjunct treatment of immunotherapy
  - Dosage should not exceed 360 mg per day in general. When one feels a need of more mestinon, it is usually time to start or adjust immunotherapy.
  - When MG is controlled, the need for mestinon is less. Patients may self-adjust the dosage of mestinon within dosage limit.

- Prednisone:
  - Very rapid, easy to use.
  - Side effects: generally absent when dosage<7.5 mg per day.

- Azathioprine (Imuran), mycophenolate (cellcept), tacrolimus (prograf)
  - Easy to use, but onset of action slow

Thymus gland and myasthenia gravis

• Thymus gland is larger and more active in early life, regressed (involution) in adulthood.
• Abnormal thymus gland in MG:
  –Hyperplasia (excessive growth): mostly young patients, AChR-Ab positive)
  – Few (5%) with tumor or cancer, seen on CT or MRI
• More significant role in young patients with AChR-Ab.
• Efficacy of thymectomy seen in 6 to 12 months after surgery
• Benefit clearly seen in <50 years of age, less clear in patients of 50 to 65 years of age



Complement Inhibitor

- Eculizumab (solirius), Ravulizumab (ultomiris), Zilucoplan (zilbrysq)
- Approved by FDA for AChR-Ab positive generalized MG.
- Eculizumab and ravulizumab very similar but frequency different
  - Eculizumab: infusion once every two weeks
  - Ravulizumab once every 8 weeks
  - Zilucoplan: injection daily.
- Side effects: possibility of meningococcal infections including meningitis
  - Every patient should receive vaccination prior to treatment.
    - MenACWY: 2 doses, plus booster doses
    - MENB: 3 doses, plus booster doses
  - Vaccination reduces but does not eliminate infection.
- Not for everybody
  - Effective in approximately 60% of patients in trials.
- Efficacy is sustained but do not lead to disease remission.

FcRN antagonists

- Efgartigimod (vyvgart); rozanolixizumab (rystiggo); nipocalimab (Imaavy)
- All reduce antibody level but do not stop antibody production.
- Efgartigimod and rozanolixizumab: used in cycles
  - Data support using efgartigimod once every two weeks as well.
- Nipocalimab: infusion once every two weeks
- No need for vaccination
- Again: each is only effective in a portion (about 60%) of patients

- May lose its efficacy gradually:
  - Antibody continuously produced, sometimes more
  - Human body getting used to these mAbs by producing anti-drug or neutralizing antibodies

B cell depletion therapy

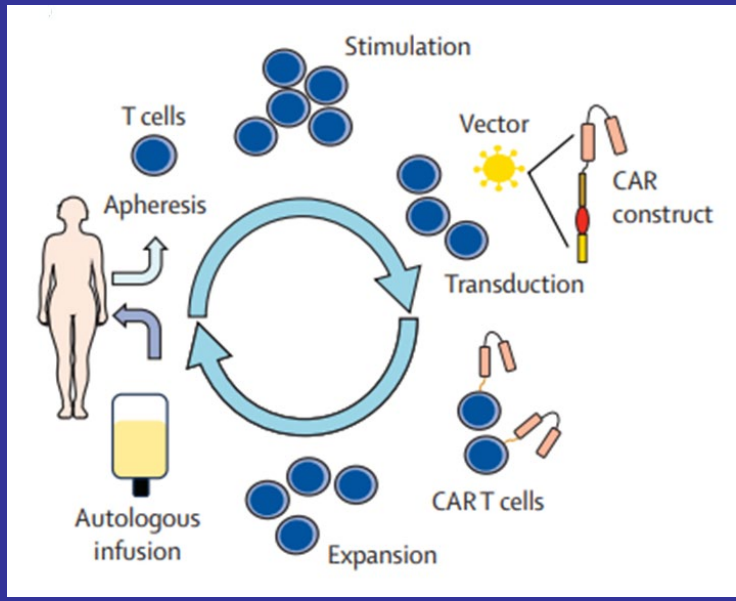
- Uplizna (inebilizumab)
- Infusion twice a year after loading dose
- Reduce antibody level
- Slower onset of action (a couple of months)
- Effective for both AChR and MuSK MG.

Hematopoietic Stem cell and CAR-T therapy

- An updated review on the utility of hematopoietic stem cell transplant in the treatment of refractory myasthenia gravis. RRNMF Neuromuscular Journal. 2025: 22;6(1).
  - 16 patients from 8 publications.
  - All patients demonstrated symptomatic improvement
  - 11 achieving CSR and 14 discontinue all MG medications.

- Chimeric antigen receptor (CAR-T therapy):
  - RNA based/DNA based; CD19/BCMA based, autologous/allogenic
  - CAR T therapy is expected to deplete plasma cells, thereby reducing antibodies. The effect of CAR T cells is sustained long-term by their in vivo multiplication.

- More significant improvement achievable, but short-term and long-term safety remains as a concern. May be reserved for truly refractory patients.



Efficacy of MG treatment

• 75% to 90% of patients reach MMS (minimal manifestation status) at 2 to 3 years of treatment.

• Mortality rate from MG:
- <1% of total patients
- 2.2% of hospitalized patient
- 4.5% in MG crisis (Alshekhlee et al 2009)

Treatment of myasthenic gravis: other

- Good nutrition. Healthy nutrition. Less processed food.
  - Gluten free tide, Mediterranean diet, autoimmune diet
- Regular light exercises
- Sleep well. Treat obstructive sleep apnea.
- Minimize infection risk.
- Check vitamin D level and correct vitamin D deficiency. Low vitamin D may increase the risk of autoimmune disorders.
- Probiotics: microorganism. Some data showed efficacy in dampening immunological responses in MG animal models.

Myasthenia gravis exacerbation by medication

- Drugs with clear effects on myasthenia, only a short list
  - Antibiotics: neomycin; streptomycin; gentamicin, kanamycin, amikacin, tobramycin,
  - Antibiotics: azithromycin (Zithromax), ciprofloxacin (cipro) and levofloxacin (Levaquin): exacerbation in 2% of MG patients.
  - Beta-blockers: propranolol and others (for crisis)
  - Intravenous magnesium
  - Anti-PD-1 chemotherapy for cancer (pembrolizumab, ipilimumab)
  - Other: penicillamine, quinidine; procainamide

- Only a small portion of these drugs are absolutely contra-indicated in myasthenia, and mostly for patients with prominent MG symptoms (rather than stably controlled patients).

How to treat myasthenia gravis? Patient's perspective

- Have a one-to-two-page diary of your MG history including test/treatment and share it with every physician you are seeing.
- Frequent follow-ups but no panic.
- Learn about the common side effects of treatment.
- Stay active but avoid overt exertion.
- Be strong. Cope with stress. Good nutrition. Sleep well.
- Find an experienced physician (neuromuscular specialist or neurologist)
- Work closely with family physicians (mainly for observation and monitoring of side effects).
- Look for "90% of yourself".
  - Very difficult to get rid of feeling of fatigue
  - Be aware the downside of "over-treat".

Where to get more information?

- Myasthenia Gravis Foundation of America, Inc.
  mgfa@myasthenia.org
  http://www.myasthenia.org
  - MG support group
  - MG research trials
- Muscular Dystrophy Association
  mda@mdausa.org
  http://www.mda.org
- MG Ohio Support Group
  https://mgohio.org