# *CHANGING TREND IN MANAGEMENT OF MYASTHENIA GRAVIS*

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**29 JUNE 2025**

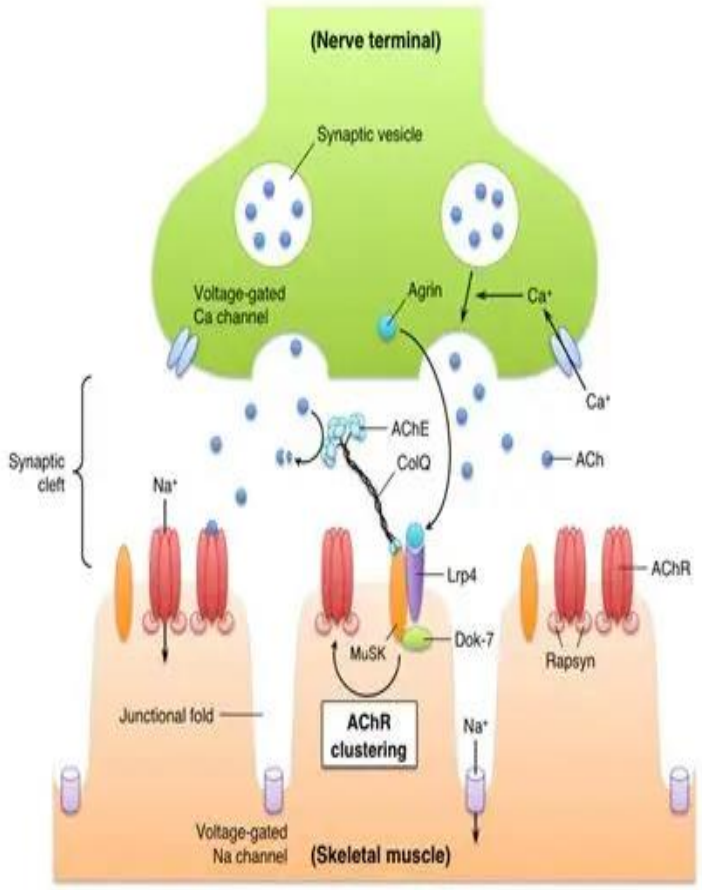
# TOPIC OUTLINE

- Pathophysiology of MG overview
- Subtypes of MG
- Immunopathogenesis of MG
- Role of Thymus & thymus pathology
- Changing trend in management of MG

Myasthenia gravis (MG) is a chronic autoimmune disorder of the neuromuscular junction.

The clinical hallmark of MG is  fatigable weakness of muscle.

It can lead to potentially life-threatening exacerbations, such as myasthenic crisis characterized by respiratory failure necessitating intubation.



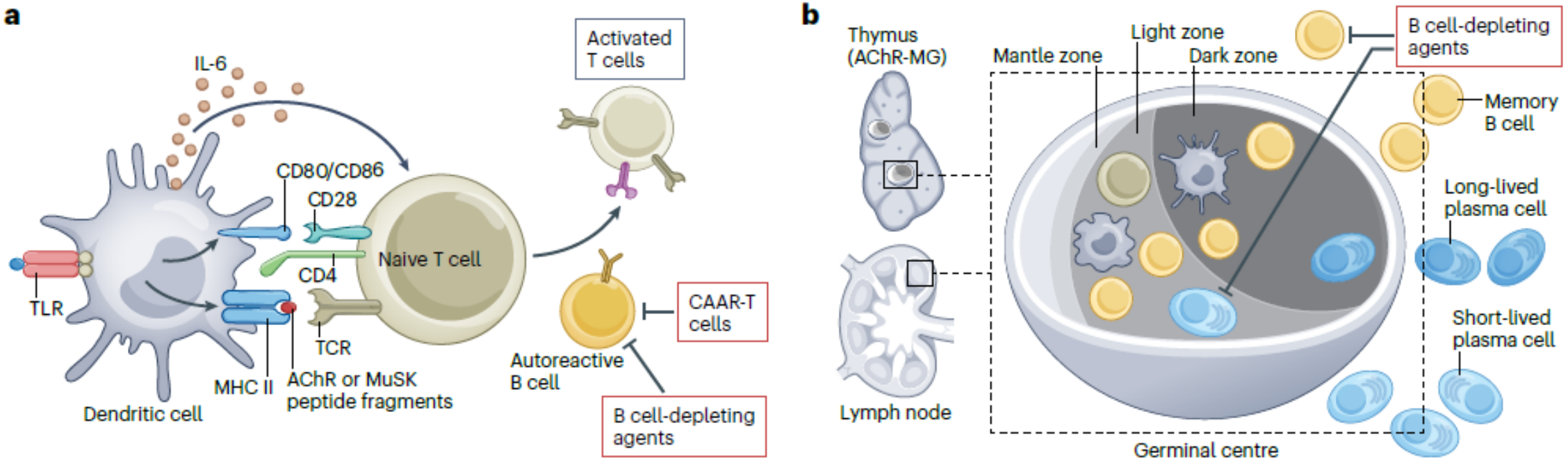

MG is caused by IgG antibodies binding to the extracellular domains of antigens that are expressed on the motor endplate of the neuromuscular junction.

# Pathophysiology of MG

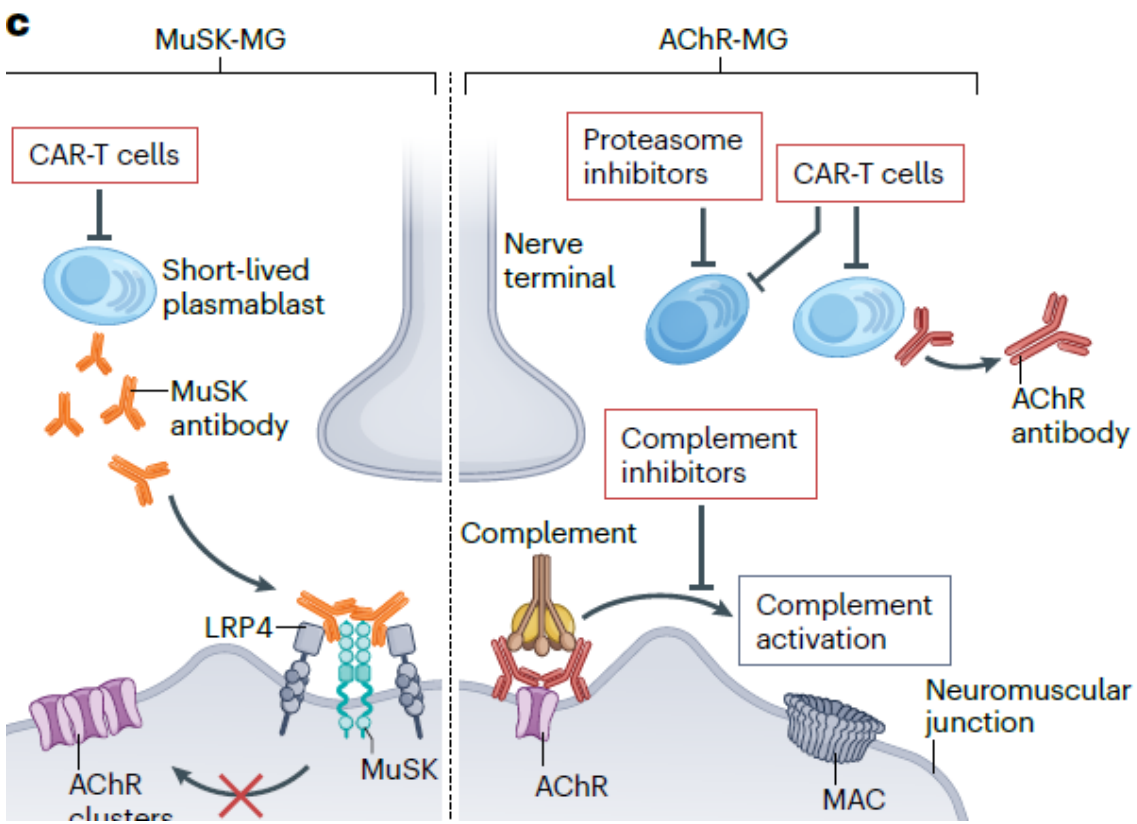
Heterogeneous disease which encompasses various subtypes characterized by distinct antibodies and immunopathogenic mechanisms.

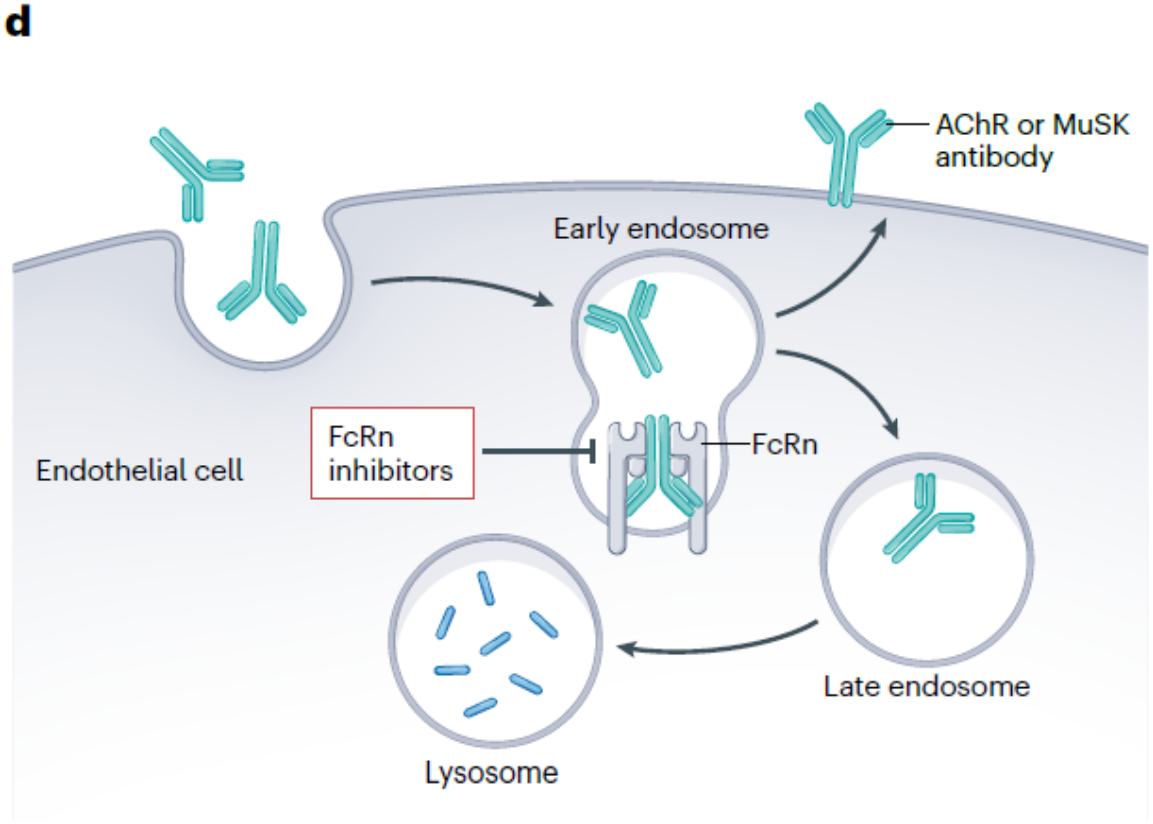
It involves  T cell-dependent , B cell-mediated autoimmune response.

# Immunopathogenesis of AChR-MG and MuSK-MG, and therapeutic targets.



# Immunopathogenesis of AChR-MG and MuSK-MG, and therapeutic targets



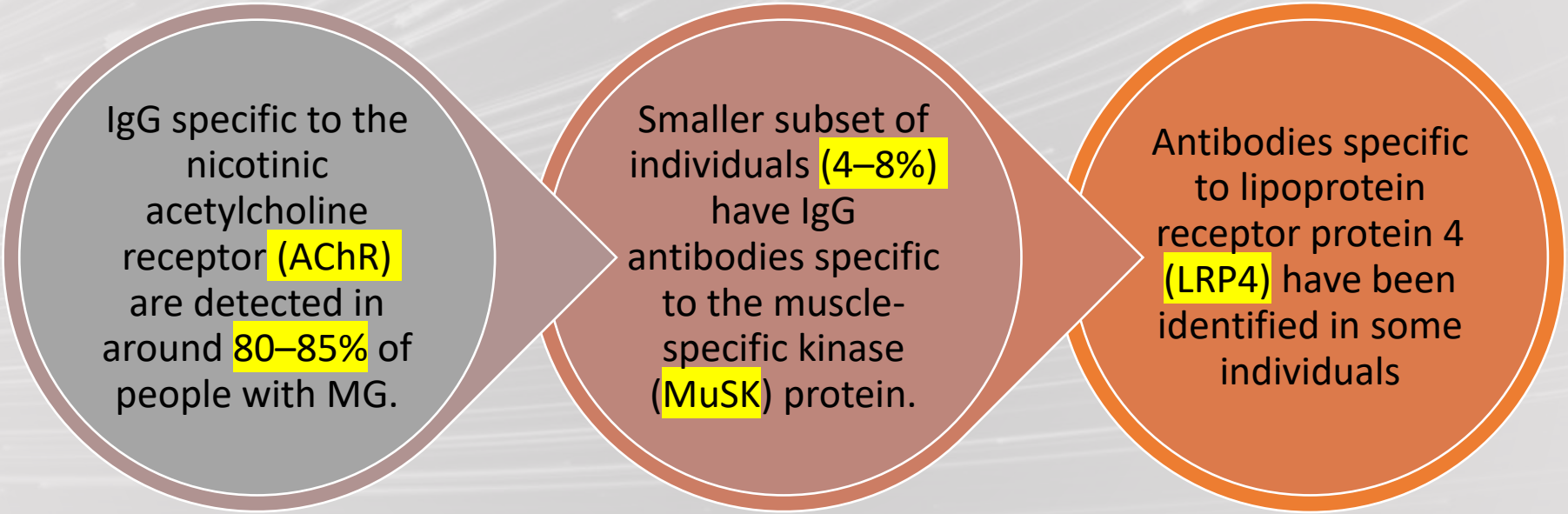
# Autoantibodies Associated with MG

- Anti-AChR antibodies are detectable in the serum of ~85% of all myasthenic patients but in only ~50% of patients with ocular myasthenia.
- The presence of anti-AChR antibodies is virtually diagnostic of MG, but a negative test does not exclude the disease.
- in ~40% of AChR antibody-negative patients with generalized MG, Antibodies to MuSK are present.

MuSK antibodies are rarely present in AChR antibody-positive patients or in patients with MG limited to ocular muscles.

These antibodies may interfere with clustering of AChRs at NMJ.

A small proportion of MG patients without antibodies to AChR or MuSK have antibodies to LRP4.


IgG specific to the nicotinic acetylcholine receptor (AChR) are detected in around 80–85% of people with MG.
Smaller subset of individuals (4–8%) have IgG antibodies specific to the muscle-specific kinase (MuSK) protein.
Antibodies specific to lipoprotein receptor protein 4 (LRP4) have been identified in some individuals

# Seronegative MG

- Approximately 10% of people diagnosed with MG lack detectable antibodies specific to AChR, MuSK or LRP4 — categorized as ‘seronegative’ MG (SNMG).

# Clinical and pathological characteristics of the different subtypes of myasthenia gravis

| Subgroup | Antibody | Age at onset | Thymus | Clinical manifestations | IgG subclass | Complement activation | Antibody-secreting cell subsets |
|---|---|---|---|---|---|---|---|
| Early onset | AChR | <50 years | Hyperplasia common | Ocular and limb weakness | IgG1, IgG3 | Yes | Short-lived plasmablasts, long-lived plasma cells |
| Late onset | AChR | >50 years | Atrophy common | Frequent bulbar symptoms | IgG1, IgG3 | Yes | Short-lived plasmablasts, long-lived plasma cells |
| Thymoma | AChR | Any age (most frequent at 40–60 years) | Cortical thymoma (type B) common | Frequent bulbar symptoms | IgG1, IgG3 | Yes | Short-lived plasmablasts, long-lived plasma cells |
| MuSK | MuSK | Any age | Normal | Frequent bulbar symptoms and myasthenic crisis | IgG4 | None | Short-lived plasmablasts |
| LRP4 | LRP4 | Any age | Normal | Similar to AChR-MG | IgG1 | Unknown | Unknown |
| Seronegative | None detected | Any age | Unknown | Frequent ocular MG | Unknown | Unknown | Unknown |

# Clinical features

- MG has a prevalence as high as 200 in 100,000.
- It affects individuals in all age groups, but peak incidences occur in women in their twenties and thirties and in men in their fifties and sixties.
- Women are affected more frequently than men, in a ratio of ~3:2.

- The course of MG is often variable.
- Exacerbations and remissions may occur, particularly during the first few years after the onset of the disease.
- Unrelated infections or systemic disorders can lead to increased myasthenic weakness and may precipitate “crisis”

- The cardinal features are fatiguable weakness of muscles. The weakness increases during repeated use (fatigue) or late in the day and may improve following rest or sleep.

# MG associated with AChR antibodies

**limb weakness is symmetrical and predominantly affects proximal muscles more than distal ones**

People with AChR-MG can exhibit varying degrees of weakness in the extraocular, bulbar, limb and axial muscles.

**Weakness in the external eye muscles is most often asymmetrical.**

Around 60% of individuals experience symptoms such as ptosis or diplopia, or a combination of both.

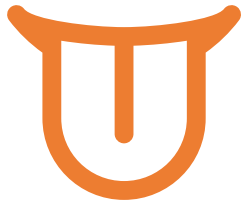
Although the disease is confined to the extraocular muscles in approximately 20% of people.

- The diversity in symptom presentation can be attributed to a complex interplay of factors influencing *neuromuscular transmission*, the *affinity and avidity of antibodies* and the *regenerative capacity of the motor endplate*.

Facial weakness produces a “snarling” expression when the patient attempts to smile.

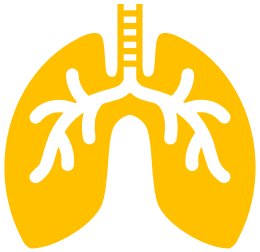
Weakness in chewing is most noticeable after prolonged effort, as in chewing meat.

Speech may have a nasal timbre caused by weakness of the palate or a dysarthric “mushy” quality due to tongue weakness.



Difficulty in swallowing may occur as a result of weakness of the palate, tongue, or pharynx, giving rise to nasal regurgitation or aspiration of liquids or food.

Despite muscle weakness, deep tendon reflexes are preserved.



If ventilatory weakness requires respiratory assistance, the patient is said to be in *crisis*.

# Role of Thymus in Myaesthenia Gravis

Immunological tolerance is a physiological state in which the immune system is unresponsive to self antigen, this state largely established in the thymus where T cells are programmed to self-tolerance.

Break down of self tolerance and subsequent production of AChR Ab and aberration in memory T h cells subsets mainly related to thymus and substantial improvement of clinical symptoms occurred after thymectomy in patients with thymic hyperplasia.

# Relation with thymus pathology

- late-onset AChR-MG subgroup mostly have a normal or atrophic thymus;
- It is more common in men and an association with HLA-DRB1.
- Thymoma occurs in about 20% of individuals with AChR-MG, equally in men and women.
- Thymoma risk is greatest in individuals whose myasthenic symptoms begin in the $4^{th}$ to $6^{th}$ decade of life and is low when symptoms begin before 20 years or after 70 years of age.

# Ancillary Tests

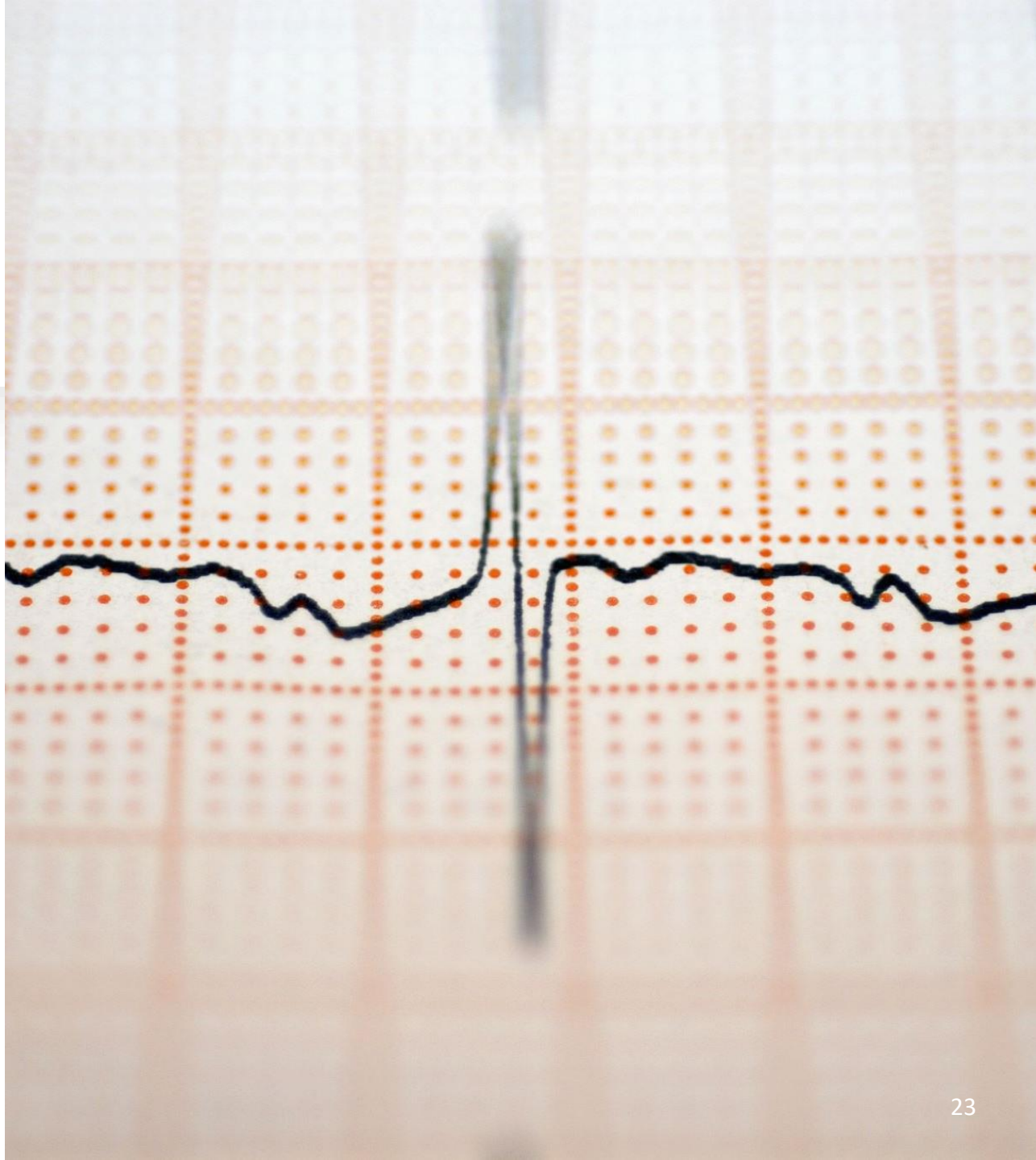
Antibody Testing

Repeatative nerve stimulation

Single fibre EMG

## Electrodiagnostic Testing

- Repetitive nerve stimulation may provide helpful diagnostic evidence of MG.
- Anti-AChE medication should be stopped 6–12 h before testing.
- It is best to test weak muscles or proximal muscle groups.
- In myasthenic patients, there is a rapid reduction of >10% in the amplitude of the evoked responses.



# Disorders associated with myasthenia gravis and recommended laboratory tests

Associated disorders

- *Disorders of the thymus*: thymoma, hyperplasia
- *Other autoimmune neurologic disorders:* chronic inflammatory demyelinating polyneuropathy, neuromyelitis optica
- *Other autoimmune disorders*: Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis, systemic lupus erythematosus, skin disorders, family history of autoimmune disorder
- *Disorders or circumstances that may exacerbate myasthenia gravis*: hyperthyroidism or hypothyroidism, occult infection, medical treatment for other conditions (see Table 448-4)
- *Disorders that may interfere with therapy*: tuberculosis, diabetes, peptic ulcer, gastrointestinal bleeding, renal disease, hypertension, asthma, osteoporosis, obesity

Recommended laboratory tests or procedures

- CT or MRI of chest
- Tests for antinuclear antibodies, rheumatoid factor
- Thyroid function tests
- Testing for tuberculosis
- Fasting blood glucose, hemoglobin $A_{1c}$
- Pulmonary function tests
- Bone densitometry

## Drugs That May Exacerbate MG

**Antibiotics**

Aminoglycosides: e.g., streptomycin, tobramycin, kanamycin

Quinolones: e.g., ciprofloxacin, levofloxacin, ofloxacin, gatifloxacin

Macrolides: e.g., erythromycin, azithromycin

**Nondepolarizing muscle relaxants for surgery**

D-Tubocurarine (curare), pancuronium, vecuronium, atracurium

**Beta-blocking agents**

Propranolol, atenolol, metoprolol

**Local anesthetics and related agents**

Procaine, Xylocaine in large amounts

Procainamide (for arrhythmias)

**Botulinum toxin**

Botox exacerbates weakness

**Quinine derivatives**

Quinine, quinidine, chloroquine, mefloquine (Lariam)

**Magnesium**

Decreases acetylcholine release

**Penicillamine**

May cause MG

**Check point inhibitors**

May cause MG and other autoimmune neuromuscular disorders (e.g., myositis, inflammatory neuropathy)

# Differential Diagnosis

- nonautoimmune congenital myasthenia
- drug-induced myasthenia
- Lambert-Eaton myasthenic syndrome (LEMS)
- neurasthenia
- hyperthyroidism (Graves' disease)

# Differential Diagnosis

- botulism
- intracranial mass lesions
- oculopharyngeal dystrophy
- mitochondrial myopathy (Kearns-Sayre syndrome, progressive external ophthalmoplegia)

The management of MG has predominantly relied on

- acetylcholinesterase inhibitors (AChE-I),
- steroids and
- immunosuppressants.

Existing standard of care in the management of MG typically involves the use of AChE-I as first-line treatment .

If the symptoms are not adequately controlled with AChE-I alone, corticosteroids are often added to the treatment regimen.

When tapering of corticosteroids proves unsuccessful, non-steroidal immunosuppressive therapies are frequently used as steroid-sparing agents.

- Azathioprine, cyclosporine, mycophenolate mofetil or tacrolimus, can help to modulate the immune response and decrease the reliance on high doses of steroids.

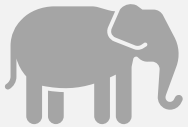
- Thymectomy is a standard procedure routinely performed in individuals diagnosed with generalized AChR-MG who are under 50 years of age or have thymoma-associated MG.

- Plasma exchange and intravenous immunoglobulin are traditionally used as rescue therapies in people experiencing myasthenic crisis;

however, in those who are refractory to standard treatment, these interventions can occasionally be employed as long-term therapies.

# Management of MuSK -MG

intravenous immunoglobulin and AChE-I, have limited effectiveness in people with MuSK-MG.



AChE-I do not improve muscle strength in most people with MuSK-MG.

These individuals often exhibit cholinergic hypersensitivity upon administration of AChE-I.

AChE-I can sometimes precipitate a paradoxical exacerbation of weakness, potentially leading to a cholinergic crisis in some individuals.

Symptom management of MuSK-MG often requires prolonged and high-dose steroid administration, which can pose challenges during the tapering process.

# Standard Therapy

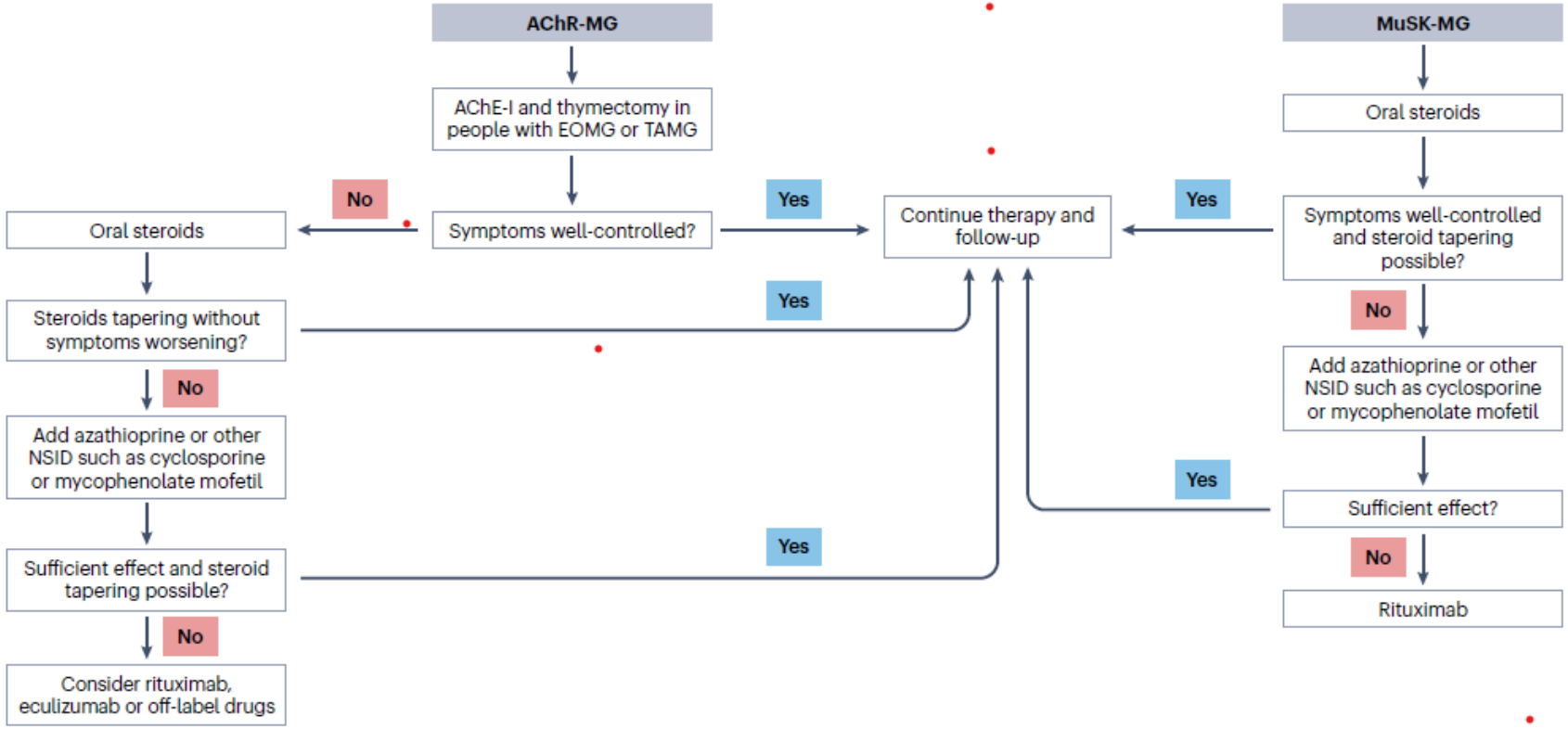



**Fig. 2 | Standard therapy algorithm for the management of AChR-MG and MuSK-MG.** The algorithm details traditional decision-making for the management of myasthenia gravis (MG) associated with acetylcholine receptor (AChR) antibodies (AChR-MG) or muscle-specific kinase (MuSK) antibodies (MuSK-MG) with standard therapies. AChE-I, AChE inhibitor; EOMG, early-onset MG; NSID, non-steroidal immunosuppressive drugs; TAMG, thymoma-associated MG.

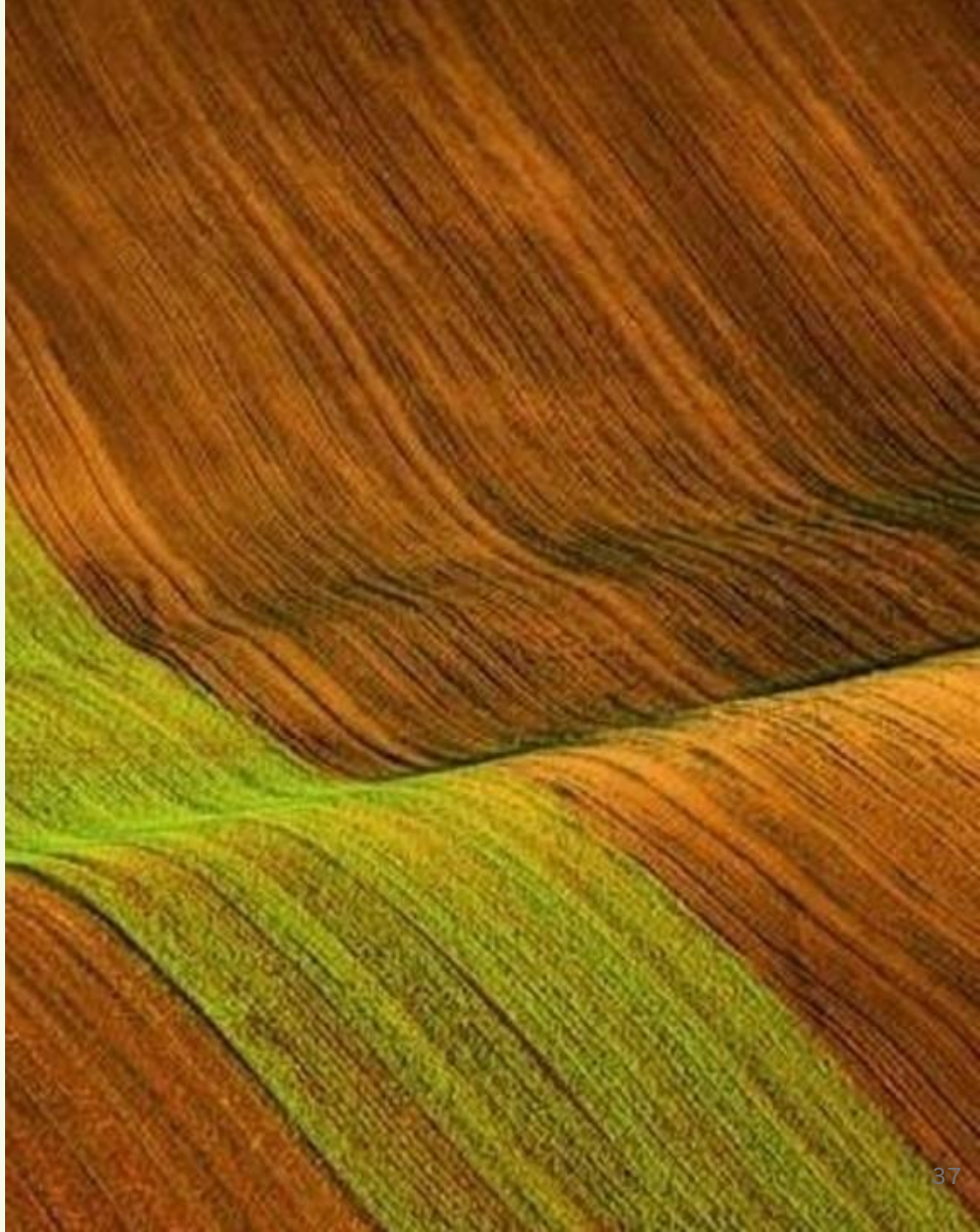
- 10–15% of people with MG fail to respond to conventional immunotherapy and are considered to have refractory disease.

Although immunosuppressive therapies are considered as established treatments, considerable limitations in terms of safety and long-term risks are---

- a heightened vulnerability to severe infections with potentially life-threatening consequences,
- adverse systemic effects,
- a delayed onset of action,
- significant long-term risk of developing malignancies and drug-related toxicity .

# *CHANGING TREATMENT LANDSCAPE IN MYAESTHCENIA GRAVIS*

The advent of molecular therapies has transformed the treatment landscape of MG.

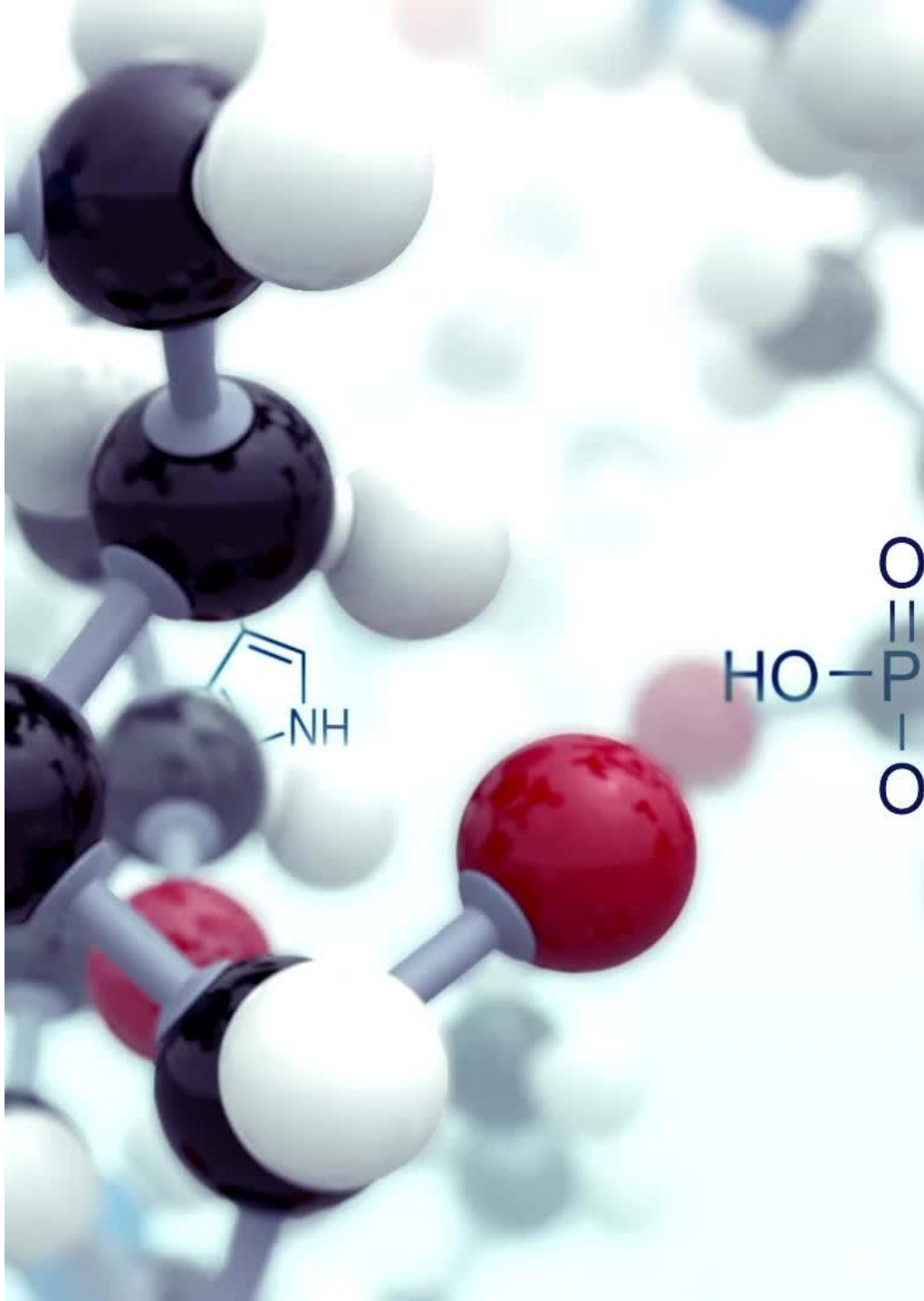


# Biologics and new molecular therapies

These treatments are designed

- to selectively target components of the immune system implicated in MG pathophysiology.

- This approach aims to achieve efficacy in symptom management alongside potentially reducing the side effects commonly associated with broader immunosuppressive therapies

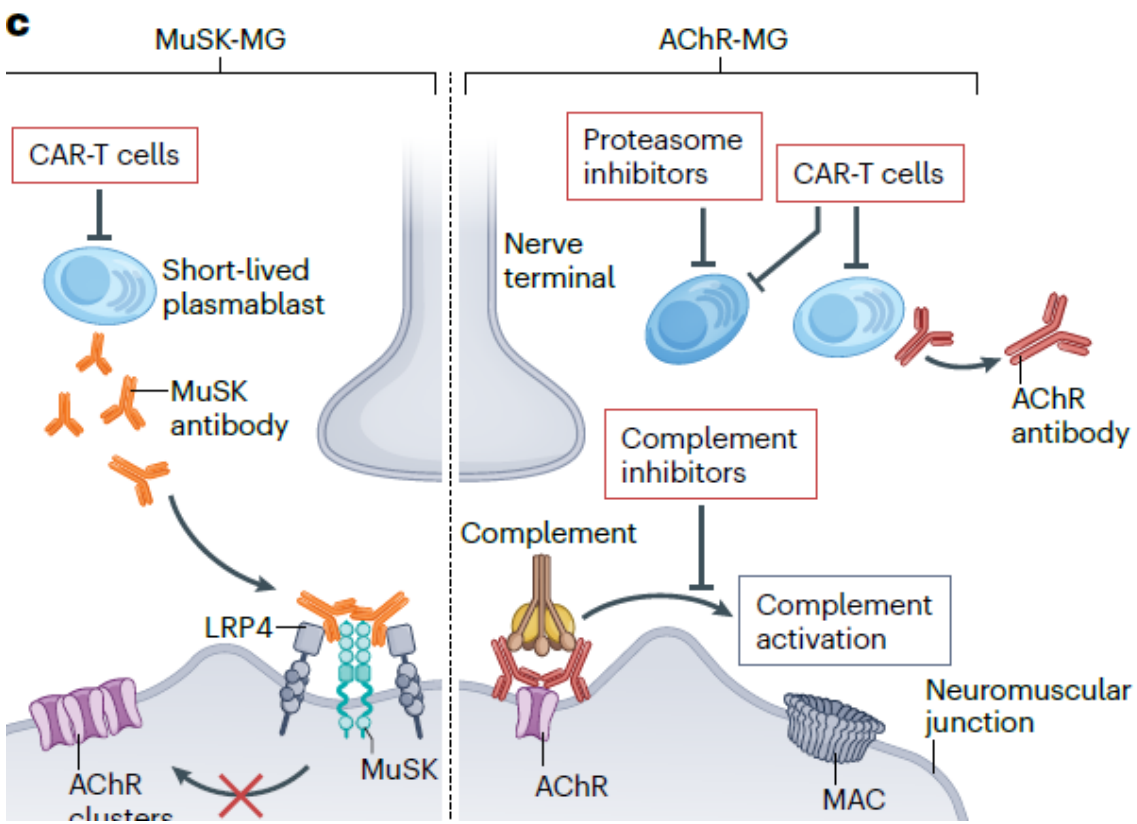


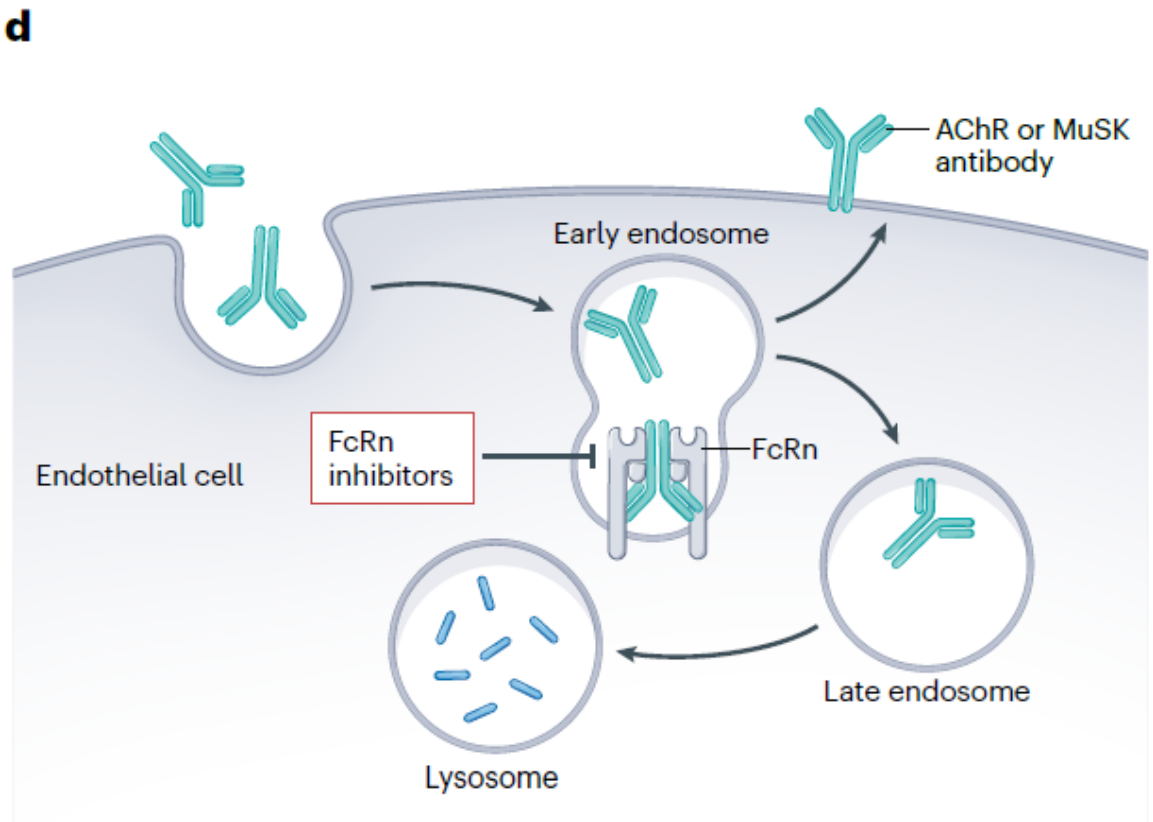
# Molecular therapies for myasthenia gravis

| Anti-CD20 | | | |
|---|---|---|---|
| Rituximab | BEAT-MG[94] | Depletes CD20 expressing B lymphocytes | One cycle every 6 months; 375 mg/m$^2$ IV weekly for 4 weeks |
| Rituximab | RINOMAX[95] | Depletes CD20 expressing B lymphocytes | 500 mg IV single infusion at baseline |

# Molecular therapies for myasthenia gravis

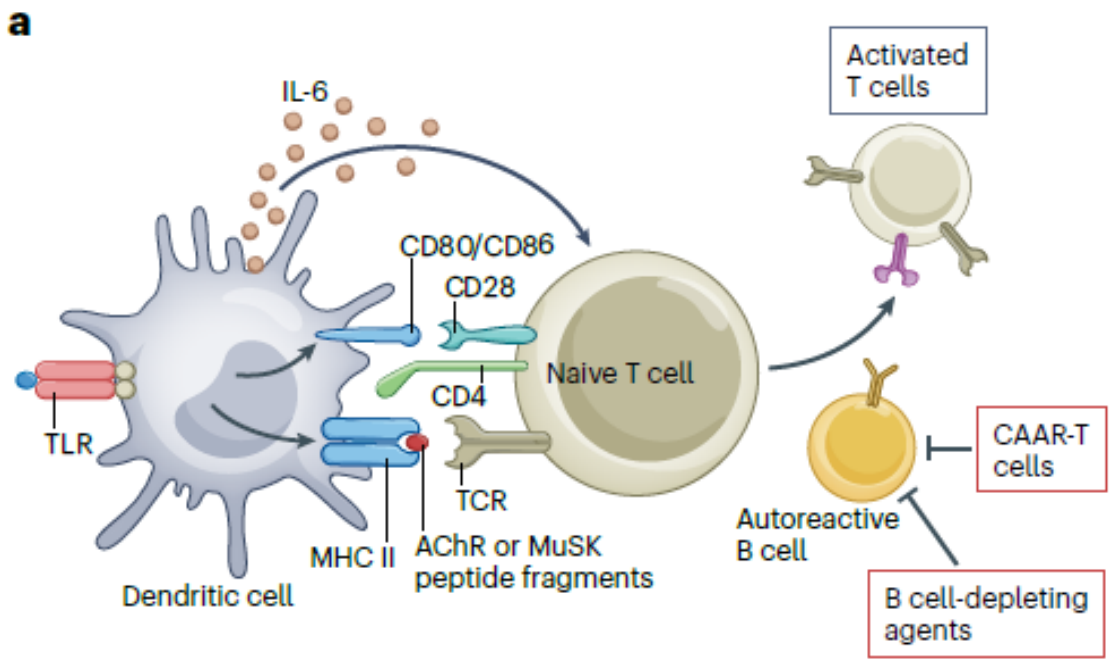
| Drug name | Clinical trial | Mechanism | Dosing schedule |
|---|---|---|---|
| **Complement inhibitors** | | | |
| Eculizumab | REGAIN[111] | Inhibits C5 activation and terminal complement/MAC formation | Loading 900 mg IV weekly for 4 weeks; maintenance 1,200 mg IV every 2 weeks |
| Ravulizumab | CHAMPION MG[121] | Inhibits C5 activation and terminal complement/MAC formation | Variable dosing based on weight |
| Zilucoplan | RAISE[125] | Short 35 kDa macrocyclic peptide targeting C5/C5b; inhibits terminal complement/MAC formation | 0.3 mg/kg BW daily SC injections |

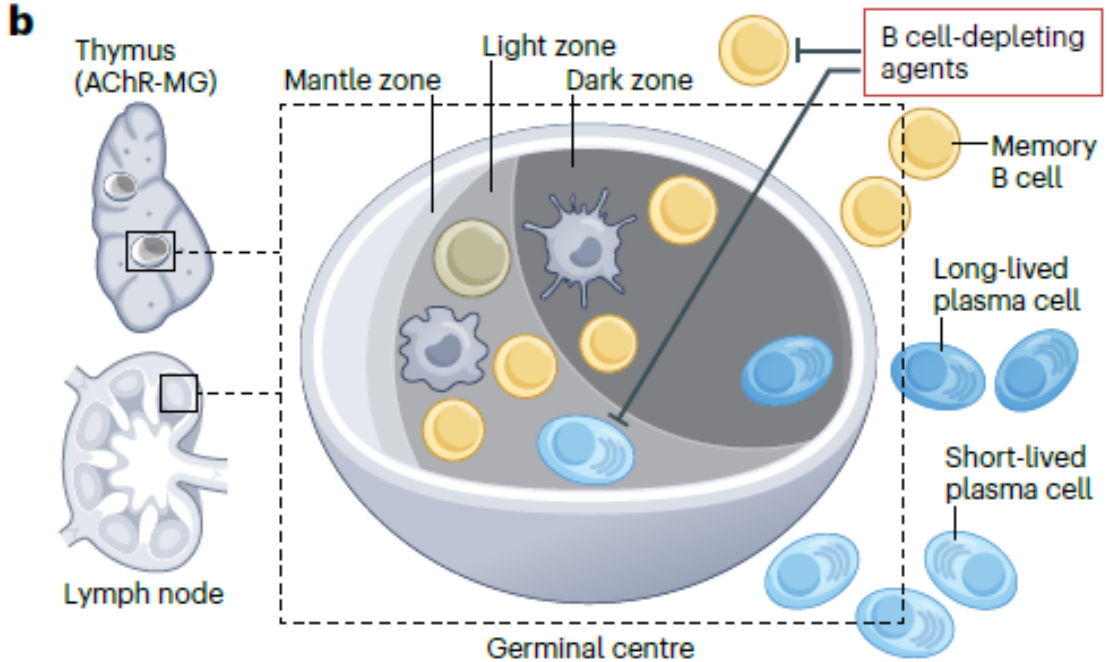

c
MuSK-MG
AChR-MG
CAR-T cells
Short-lived plasmablast
MuSK antibody
LRP4
AChR clusters
MuSK
Proteasome inhibitors
CAR-T cells
Nerve terminal
AChR antibody
Complement inhibitors
Complement
Complement activation
Neuromuscular junction
AChR
MAC


d
AChR or MuSK antibody
Early endosome
Endothelial cell
FcRn inhibitors
FcRn
Late endosome
Lysosome

# Molecular therapies for myasthenia gravis

| | | | |
|---|---|---|---|
| **FcRn Antagonists** | | | |
| Efgartigimod | ADAPT[132] | Reduces autoantibody levels | 10 mg/kg BW IV once weekly for 4 weeks |
| Rozanolixizumab | MycarinG[134] | Reduces autoantibody levels | 7 or 10 mg/kg BW SC weekly for 7 weeks |
| **Anti-CD20** | | | |
| Rituximab | BEAT-MG[94] | Depletes CD20 expressing B lymphocytes | One cycle every 6 months; 375 $mg/m^2$ IV weekly for 4 weeks |
| Rituximab | RINOMAX[95] | Depletes CD20 expressing B lymphocytes | 500 mg IV single infusion at baseline |

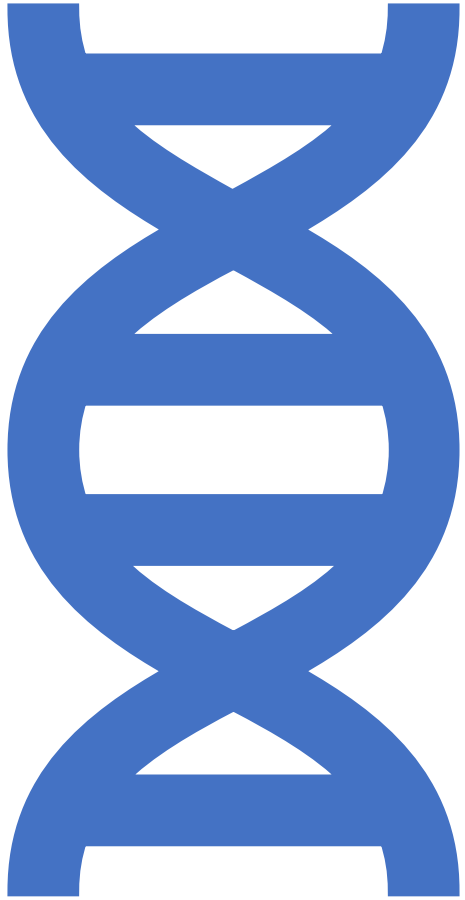

a
IL-6
CD80/CD86
CD28
CD4
TCR
TLR
MHC II
AChR or MuSK
peptide fragments
Dendritic cell
Naive T cell
Activated
T cells
Autoreactive
B cell
CAAR-T
cells
B cell-depleting
agents

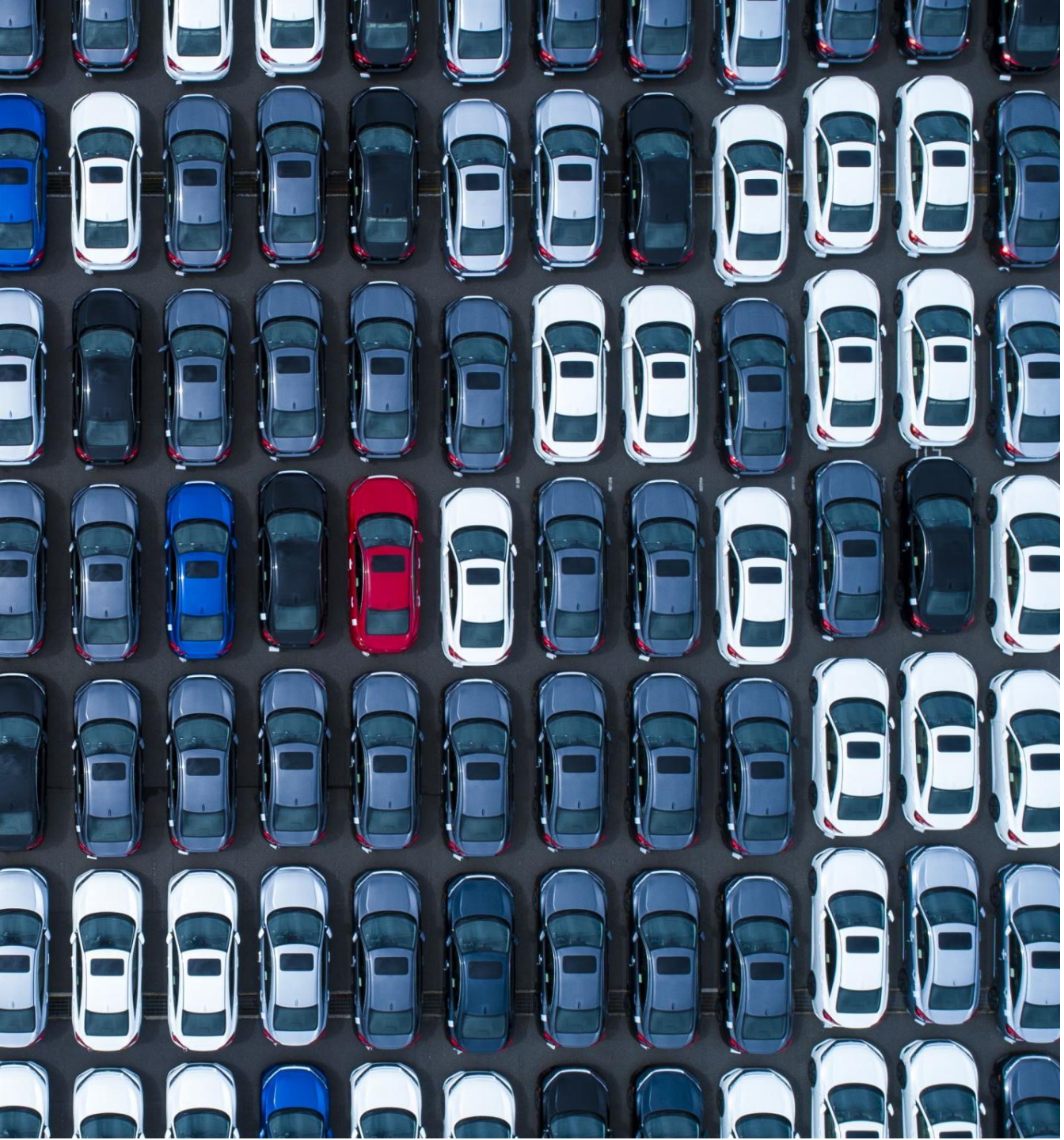

b
Thymus
(AChR-MG)
Lymph node
Mantle zone
Light zone
Dark zone
Germinal centre
B cell-depleting
agents
Memory
B cell
Long-lived
plasma cell
Short-lived
plasma cell

CAR-T (Chimeric Antigen Receptor T cell therapy)& CAAR-T(Chimeric Autoantibody Receptor T cell therapy)

- Adoptive cellular therapy (ACT) is an advanced form of immunotherapy that involves harvesting T cells from either the patient or a donor.

- The T cells are then cultivated in a laboratory where they can be genetically modified.



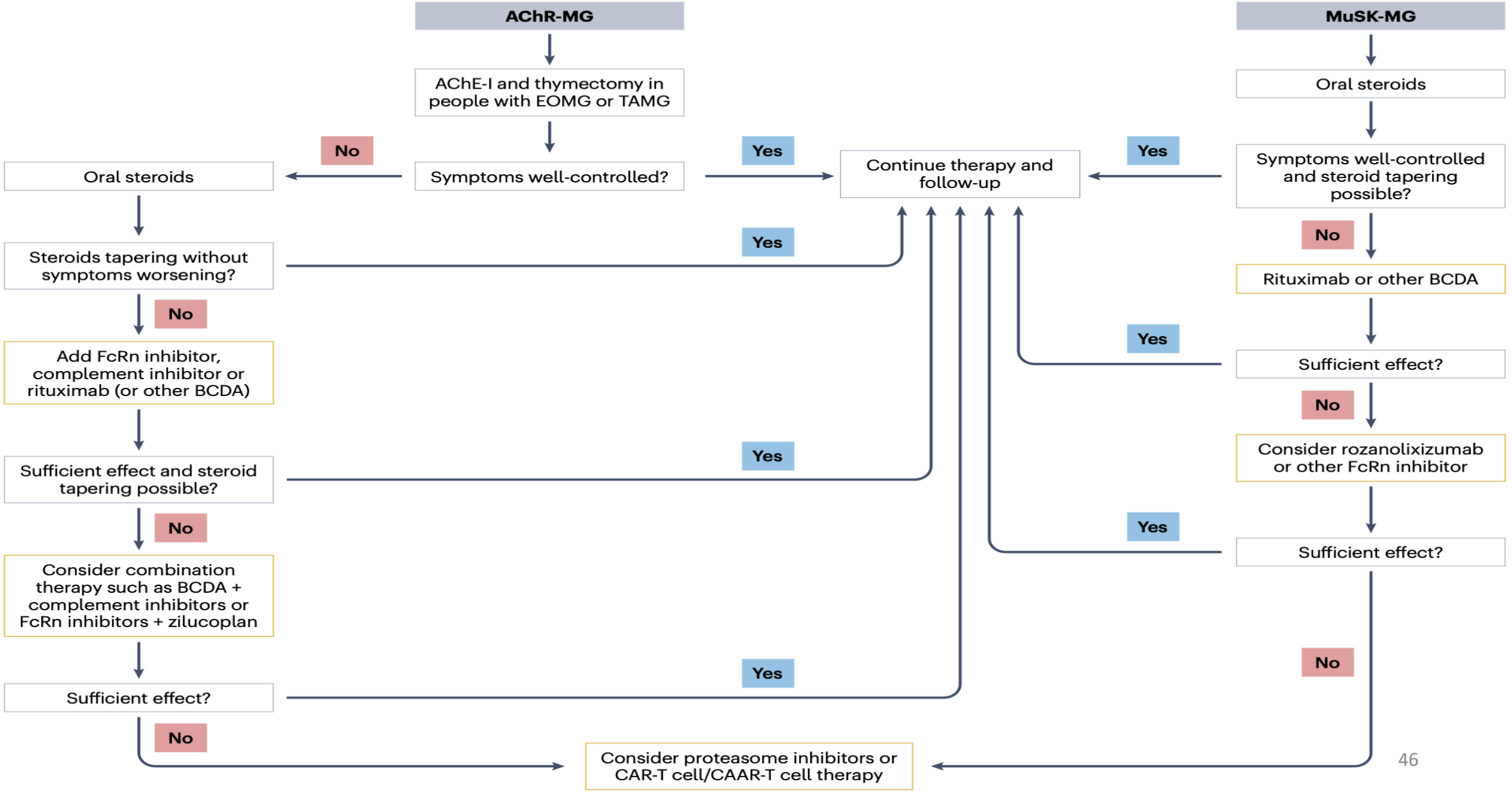


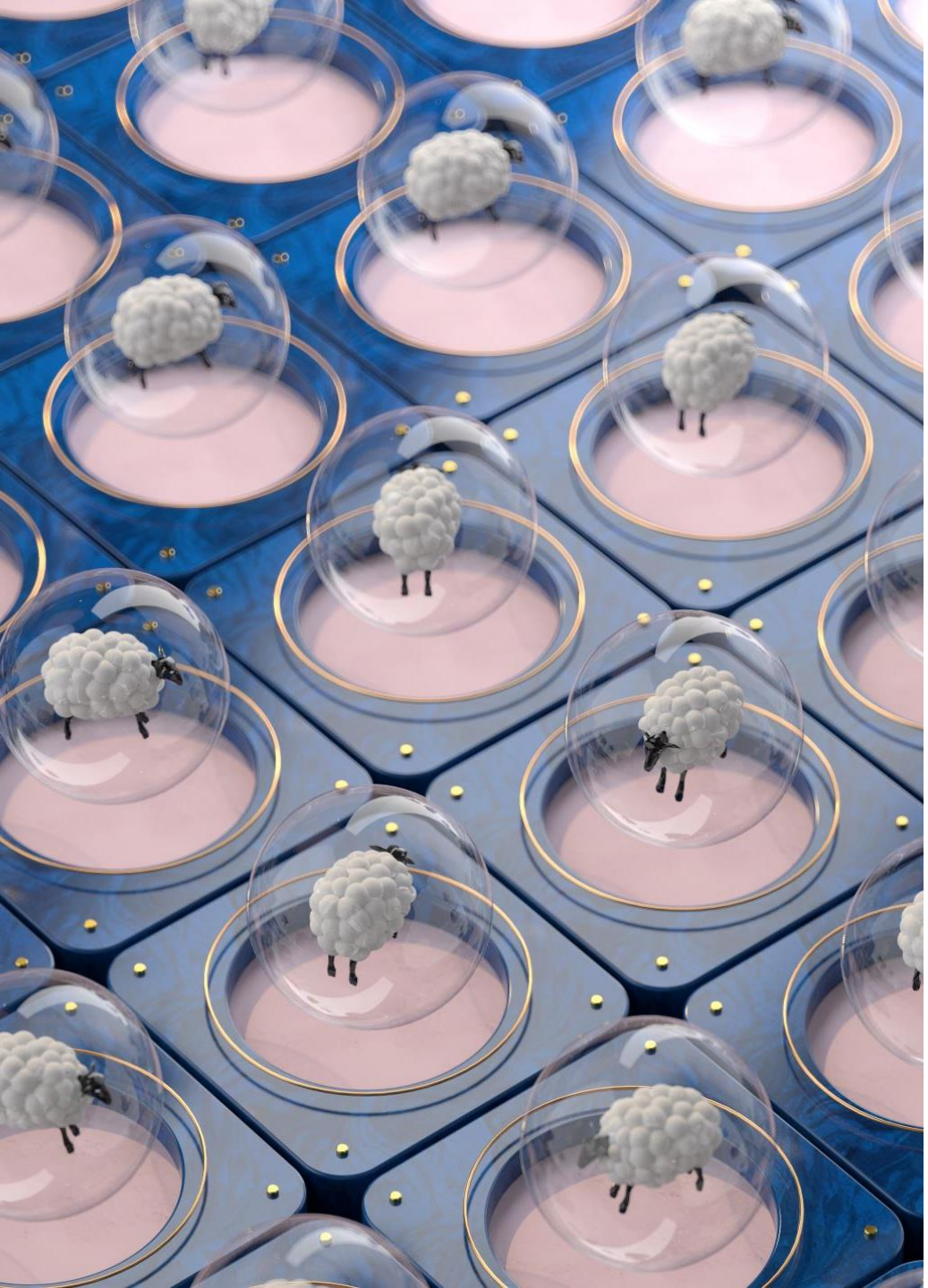
# CAR-T and CAAR-T cell therapies

- The primary side effect associated with CAR-T cell therapy is cytokine release syndrome (CRS), which can manifest as mild constitutional symptoms or progress to severe CRS, potentially resulting in multiorgan dysfunction.

- Well-designed and highly specific CAAR-T cells should potentially lower the risk of CRS and off-target toxicity.

# An algorithm for the management of AChR-MG and MuSK-MG incorporating new molecular therapies





# Final tips & Takeaways

- Up to 15% of individuals with MG exhibit limited or no response to these standard therapies.
- The emergence of molecular therapies, including monoclonal antibodies, B cell-depleting agents and CAR-T cell therapy, has the potential to revolutionize the MG treatment landscape.
- They explores the potential for personalized medicine approaches.

- Davidson,s Textbook of Medicine 24 th edition
- Review article,Nature reviews neurology
  http://doi.org/10.1038/s41582-023-00916-w


THANK YOU