Accelerating myasthenia gravis diagnosis and treatment: Practical strategies and therapeutic advances

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A conversation between:

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Learning objectives

1. Describe the characteristic clinical and laboratory findings of myasthenia gravis, and the confirmatory diagnostic tests
2. Explain the serological subgroups of myasthenia gravis and their implications for treatment selection
3. Interpret the latest data for newly available therapies in the treatment of generalized myasthenia gravis and their implications for clinical practice

Agenda

How can we overcome diagnostic delay in myasthenia gravis?

How important is serological diagnosis in myasthenia gravis?

How can we integrate new and emerging agents for the treatment of generalized myasthenia gravis into clinical practice?

How can we overcome the diagnostic delay in myasthenia gravis?

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Clinical manifestations of myasthenia gravis

MG is characterized by fatigable muscle weakness, which improves with rest[1]

Most frequent presenting symptoms include[1,2]

Extraocular muscle weakness: Ptosis, double vision

Bulbar muscle weakness: Difficulty chewing, choking, dysphagia

Limb weakness: Upper limbs usually more impacted than lower limbs

If untreated, MG can lead to progressive weakness due to neuromuscular junction degradation, affecting quality of life, independence and employment[3]

MG, myasthenia gravis.

1. Dresser L, et al. *J Clin Med*. 2021;10:2235; 2. Beloor Suresh A, Asuncion RMD. Myasthenia Gravis. 2023. In: StatPearls [Internet]. Available at: www.ncbi.nlm.nih.gov/books/NBK559331/ (accessed 14 April 2025); 3. Nguyen M, et al. *Neurol Clin Pract*. 2024;14:e200244.

Delay in diagnosis of myasthenia gravis

In a recent study of European patients with MG (N=387):

Average diagnosis delay was ~1 year

Over 25% of patients experienced >1-year delay in diagnosis

MG, myasthenia gravis.

Cortés-Vicente E, et al. *Ann Clin Transl Neurol*. 2024;11:2254–67.

Question 1

What factors contribute to the delay in diagnosis of myasthenia gravis?

Question 2

What impact does diagnostic delay have on patient outcomes?

Question 3

Are there key signs and symptoms that primary care physicians and non-neuromuscular specialists should be aware of to prompt investigation of myasthenia gravis?

Question 4

What are the key diagnostic tools to confirm diagnosis or facilitate rapid diagnosis?

How important is serological diagnosis in myasthenia gravis?

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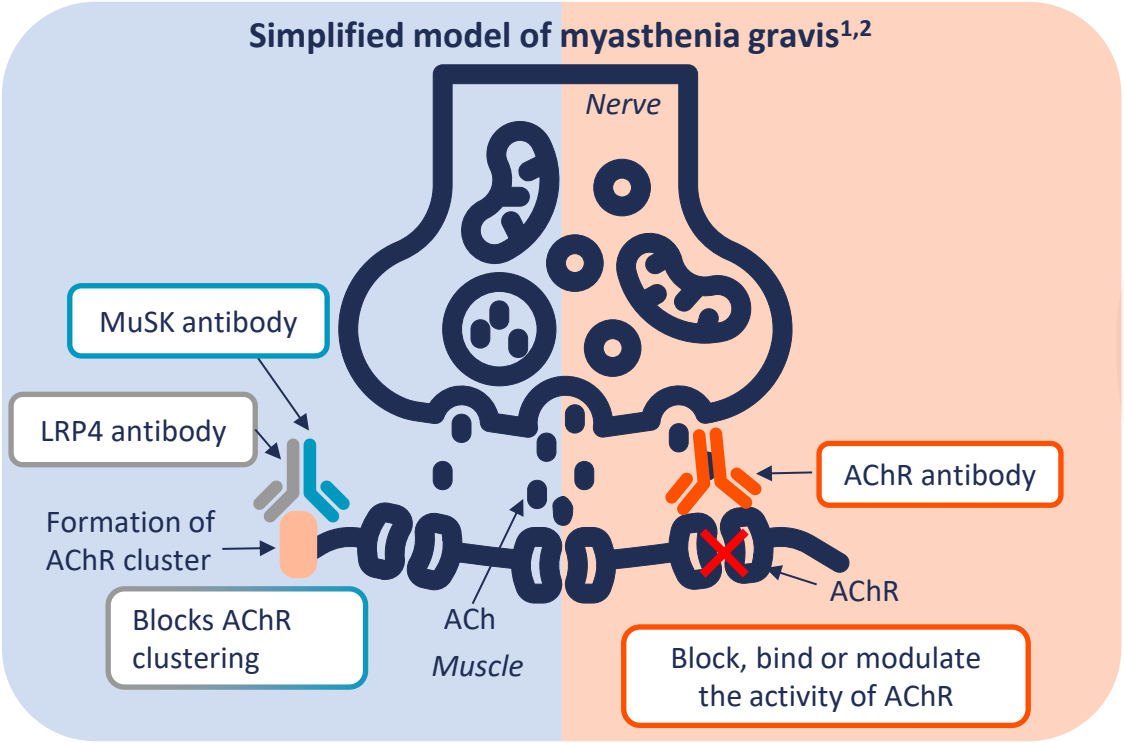
Myasthenia gravis pathology: Importance of serology



Leads to reduced muscle contraction

ACh, acetylcholine; AChR, ACh receptor; LRP4, low-density lipoprotein receptor-related protein 4; MuSK, muscle specific kinase.

1. DeHart-McCoyle M, et al. *BMJ Med*. 2023;2:e000241; 2. Dresser L, et al. *J Clin Med*. 2021;10:2235.

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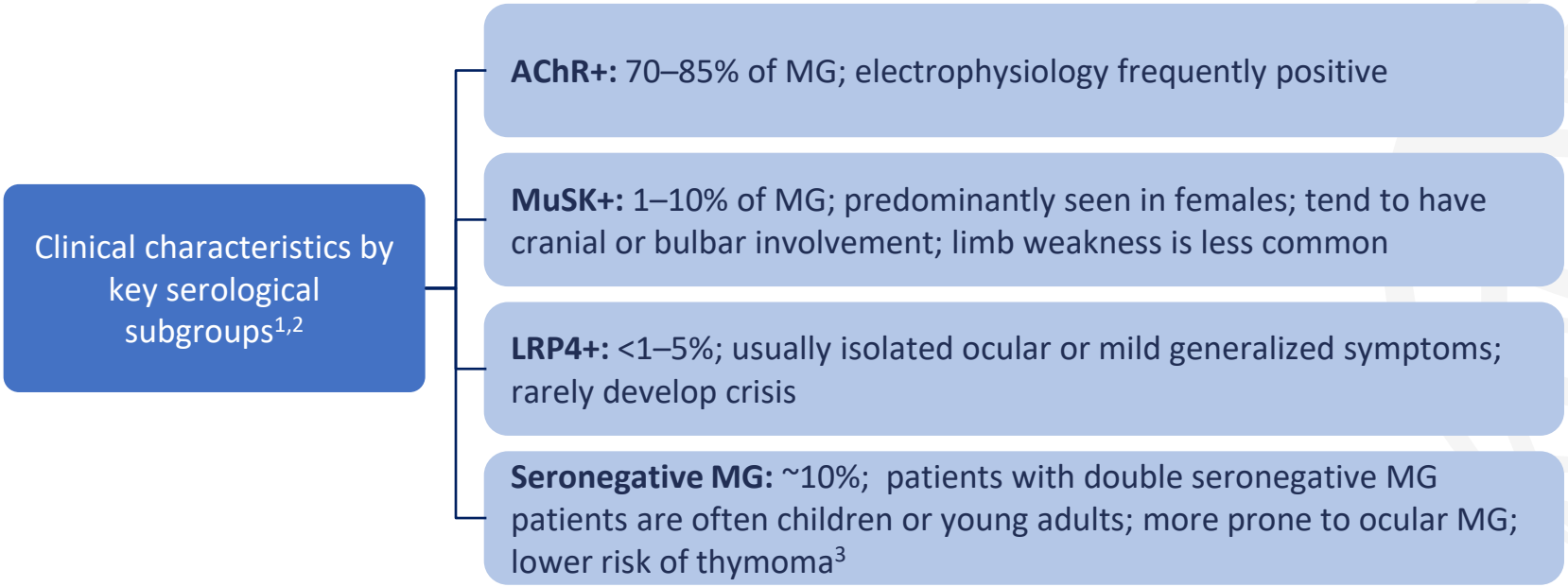
Question 1

How do serological subgroups affect clinical characteristics of myasthenia gravis?

Clinical characteristics by serological subgroup



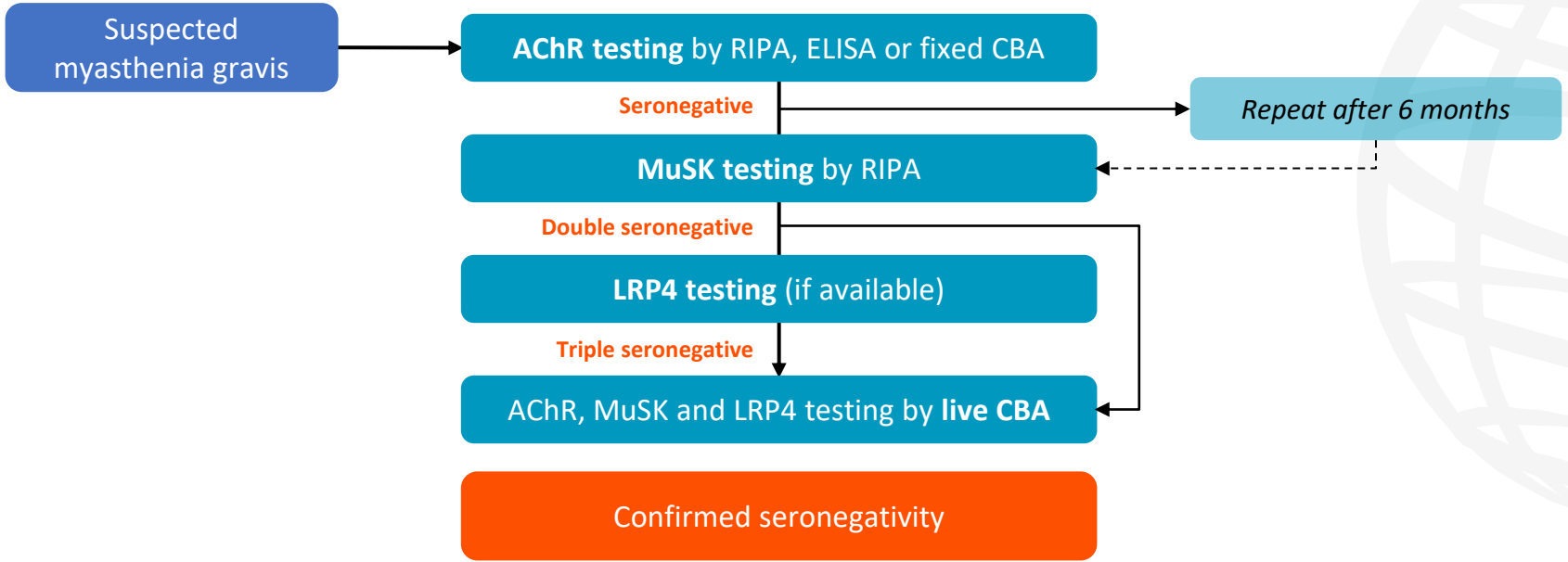
AChR, acetylcholine receptor; LRP4, low-density lipoprotein receptor-related protein 4; MG, myasthenia gravis; MuSK, muscle-specific kinase.

1. Li Y, et al. *Ann Transl Med*. 2023;11:290; 2. Tannemaat MR, et al. *Handb Clin Neurol*. 2024;200:283–305; 3. Vinciguerra C, et al. *Brain Sci*. 2023;13:1286.

Question 2

What are the latest recommendations for serological testing in patients with myasthenia gravis?

Proposed serological testing algorithm in suspected myasthenia gravis



AChR, acetylcholine receptor; CBA, cellular assays; ELISA, enzyme-linked immunosorbent assay; IchE, acetylcholinesterase inhibitor; LRP4, low-density lipoprotein receptor-related protein 4; MuSK, muscle-specific kinase; RIPA, radioimmunoprecipitation assays.
Adapted from: Vinciguerra C, et al. *Brain Sci*. 2023;13:1286.

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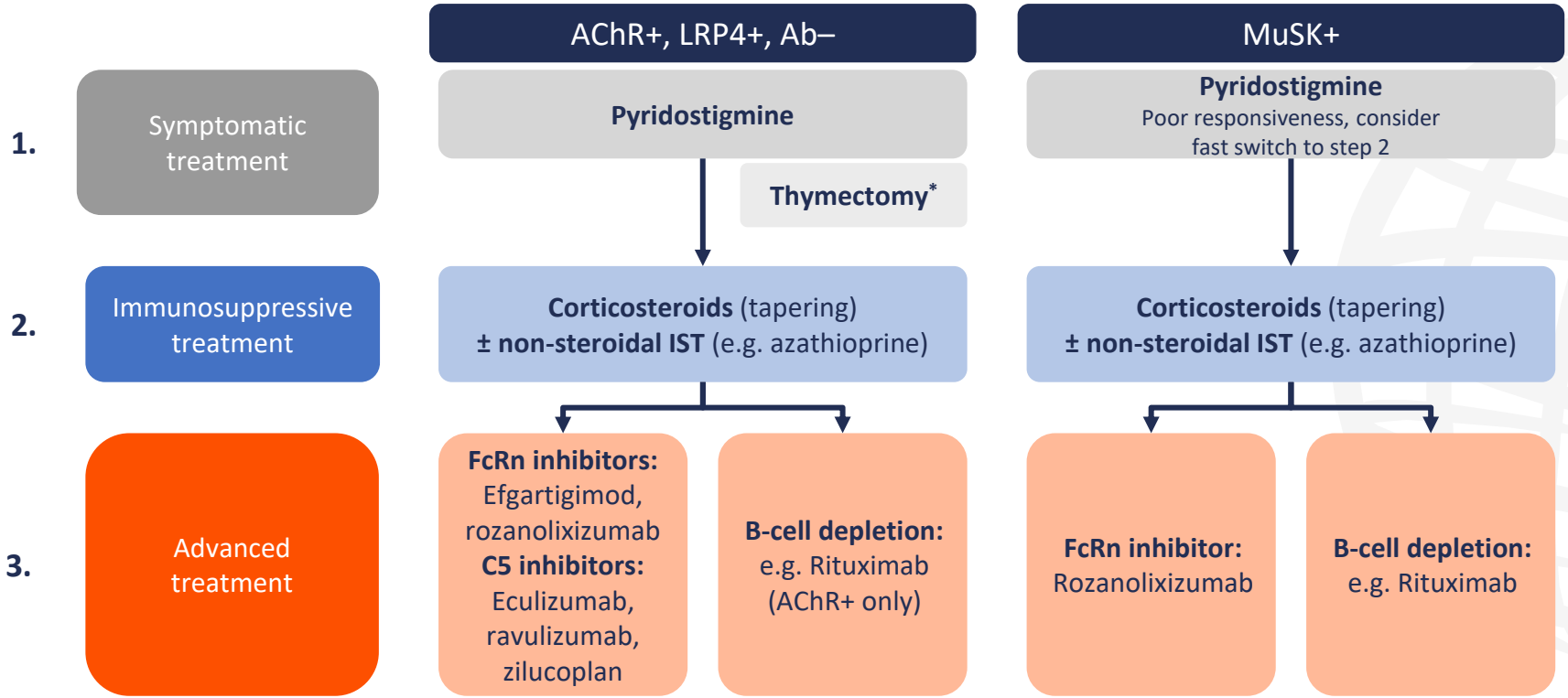
Question 3

How can serological subgroups guide treatment selection?

Treatment algorithm for generalized myasthenia gravis[1]



*Thymectomy is recommended in AChR+ patients who are eligible and should be performed within 2 years after diagnosis.

Ab, antibody; AChR, acetylcholine receptor; FcRn, neonatal Fc receptor; LRP4, low-density lipoprotein receptor-related protein 4; MuSK, muscle specific kinase; IST, immunosuppressive therapies.

De Bleecker JL, et al. *Acta Neurol Belg*. 2024;124:1371–83.

How can we integrate new and emerging agents for the treatment of generalized myasthenia gravis into clinical practice?

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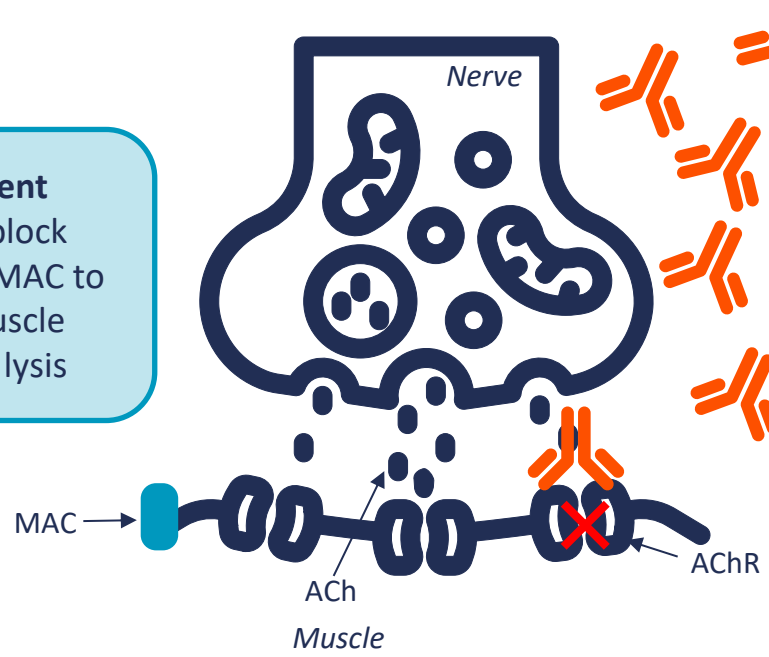
Advanced therapies for generalized myasthenia gravis: Mechanisms of action



Complement inhibitors block formation of MAC to prevent muscle membrane lysis

Plasma cell

B cell

AChR, MuSK or LRP4 antibodies

FcRn inhibitors decrease circulating antibody levels by disrupting antibody recycling

Rituximab leads to B-cell depletion and modulation

AChR, acetylcholine; AChR, ACh receptor; FcRn, neonatal Fc receptor; LRP4, low-density lipoprotein receptor-related protein 4; MAC, membrane attack complex; MuSK, muscle specific kinase. Burton LB, Guidon AC. 2020. Available at: https://practicalneurology.com/diseases-diagnoses/neuromuscular/neuromuscular-notes-next-generation-treatments-for-myasthenia-gravis/31666/ (accessed 22 April 2025).

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Recently approved advanced therapies for generalized myasthenia gravis[1]

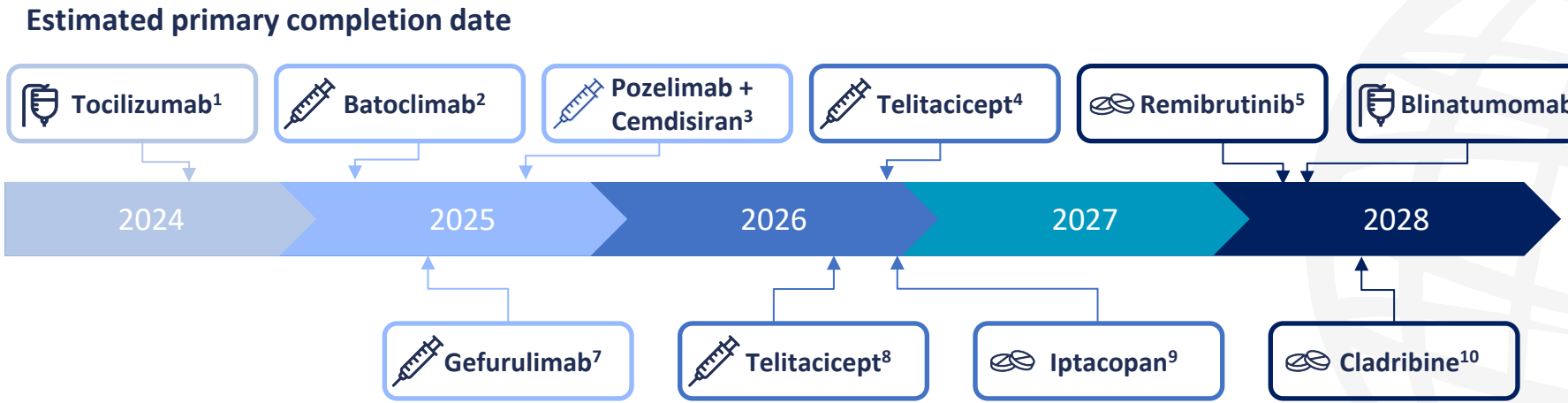
Drug	Composition	Indication	MoA	RoA
Eculizumab	mAb	AChR+	Complement inhibitor	IV
Ravulizumab	mAb	AChR+	Complement inhibitor	IV
Zilucoplan	Macrocyclic peptide	AChR+	Complement inhibitor	SC
Efgartigimod	IgG Ab fragment	AChR+	FcRn antagonist	IV, SC (including prefilled syringe*)
Rozanolixizumab	mAb	AChR+, MuSK+	FcRn antagonist	SC

*A prefilled syringe formulation was approved on 10 April 2025 allowing for administration by patients and/or caregivers.[2]

Ab, antibody, AChR, acetylcholine; FcRn, neonatal Fc receptor; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; IV, intravenous, mAb, monoclonal Ab; MoA, mechanism of action; MuSK, muscle-specific tyrosine kinase; RoA, route of administration; SC, subcutaneous.

1. Silvestri NJ. *Practical Neurology (US)*. 2024;23:29–32; 2. Efgartigimod Prescribing Information. Available at: https://bit.ly/4dtv71i (accessed 20 May 2025).

Emerging treatments for generalized myasthenia gravis in phase III trials



Actual primary completion date

- **Nipocalimab[11]** November 2023
- **Inebilizumab[12]** May 2024

1. NCT05716035; 2. NCT05403541; 3. NCT05070858; 4. NCT05737160; 5. NCT06744920; 6. NCT06836973; 7. NCT05556096; 8. NCT06456580; 9. NCT06517758; 10. NCT06463587; 11. NCT04951622; 12. NCT04524273. Information on clinical trials can be found by searching their NCT number at ClinicalTrials.gov (accessed 6 May 2025).

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Question 1

Several new agents have recently been approved and others soon to follow. Is there any way to personalize treatment, and can these new agents be combined with other immunosuppressants?

Question 2

What are the future targets of emerging treatments for myasthenia gravis?

Mechanisms of action of emerging treatments

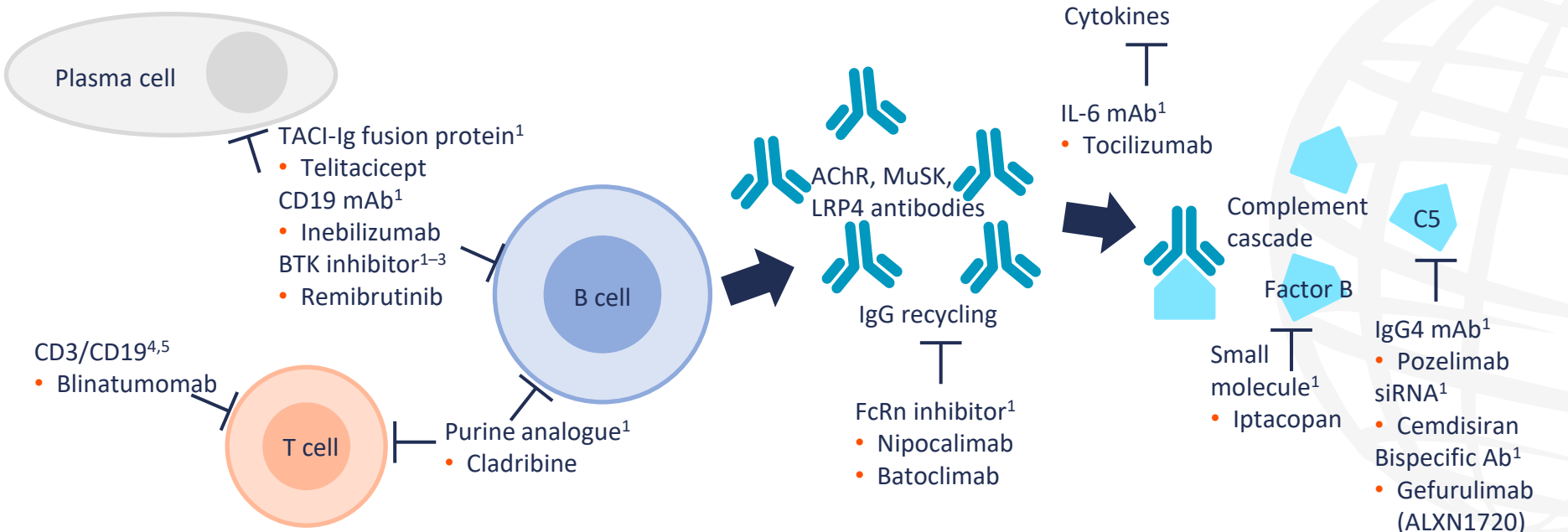

Figure adapted from DeHart-McCoyle M, et al. *BMJ Med*. 2023 and Mantegazza R, Antozzi C. *Front Neurol*. 2020.[6,7]

Ab, antibody; AChR, acetylcholine receptor; BTK, Bruton's tyrosine kinase; FcRn, neonatal Fc receptor; Ig, immunoglobulin; IL-6, interleukin 6; LRP4, low-density lipoprotein receptor-related protein 4; mAb, monoclonal Ab; MuSK, muscle specific kinase; siRNA, small interfering RNA; TACI, transmembrane activator and cancer-associated macrophage-like cells interactor. 1. Gerischer L, et al. *BioDrugs*. 2025;39:185–213; 2. Williams K, et al. *Neurology*. 2023;100(Suppl. 2):P7-3.015; 3. NCT06744920. Available at: https://clinicaltrials.gov/ (accessed 19 March 2025); 4. Subklewe M, et al. *Eur J Cancer*. 2024;204:114071; 5. NCT06836973. Available at: https://clinicaltrials.gov/ (accessed 19 March 2025); 6. DeHart-McCoyle M, et al. *BMJ Med*. 2023;2:e000241; 7. Mantegazza R, Antozzi C. *Front Neurol*. 2020;11:981.

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Question 3

Are there any oral therapies for generalized myasthenia gravis in development?