

## New and emerging treatments for myasthenia gravis

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New immunomodulatory therapeutics hold promise for the future treatment of myasthenia gravis, say DeHart-McCoyle and colleagues

### Introduction

Myasthenia gravis is an antibody mediated autoimmune disorder affecting the function of the neuromuscular junction, leading to fluctuating weakness of ocular, facial, bulbar, limb, and respiratory muscles. The disorder has an estimated prevalence of 70-300 per million people worldwide. Uncontrolled myasthenia gravis can lead to substantial disability and recurrent hospital admissions, with an estimated mortality rate of about 2%. Although many patients with myasthenia gravis benefit from standard treatments, including cholinesterase inhibitors, corticosteroids, and steroid sparing immunosuppressants (eg, azathioprine and mycophenolate mofetil), 8.5-15% of patients still have varying degrees of disability because of insufficiently controlled clinical symptoms or unacceptable side effects. In recent years, research has identified promising new treatments, including targeted treatments with new mechanisms of action that have the potential to improve efficacy and tolerability. Here, we consider the broad spectrum of emerging therapeutics, including B cell depletion, complement and T cell inhibition, and neonatal Fc receptor (FcRn) antagonists.

### Pathophysiology

Autoantibodies directed against the acetylcholine receptor (AChR) on the postsynaptic membrane of the neuromuscular junction are the pathological mechanism responsible for generalised myasthenia gravis in about 85% of patients.<sup>1</sup> Thymus dysfunction is considered an important source of immune intolerance in acetylcholine receptor antibody positive myasthenia gravis (AChR+MG). AChR antibodies are predominantly immunoglobulin (Ig) G1 and IgG3. At the neuromuscular junction, these autoantibodies block the binding of acetylcholine

to AChR, crosslinking the receptors, leading to their internalisation and degradation, while also activating the complement cascade to form the membrane attack complex that destroys postsynaptic membrane folds. Consequently, transmission across the neuromuscular junction cannot generate reliable muscle activation, resulting in fatigable weakness (figure 1).

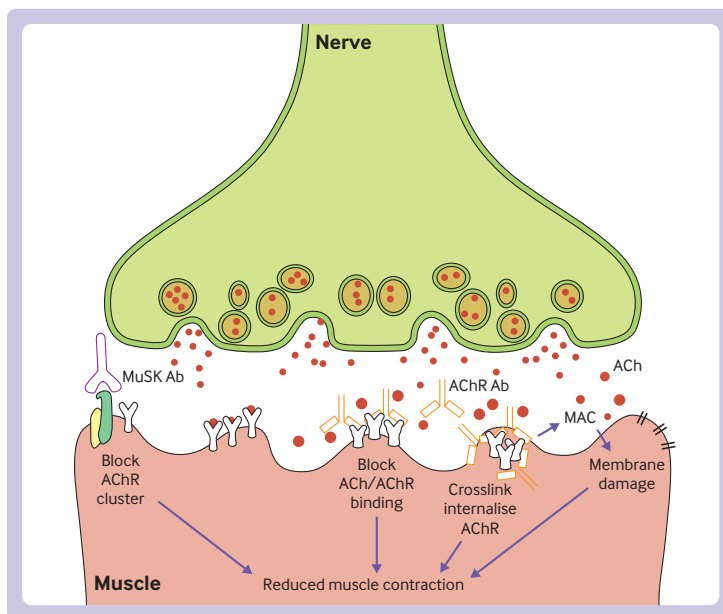
Autoantibodies directed against muscle specific tyrosine kinase (MuSK) and low density lipoprotein receptor related protein 4 occur in about 10% of all patients with myasthenia gravis. Under normal circumstances, interactions between MuSK and low density lipoprotein receptor related protein 4 cause clustering of AChRs.<sup>2</sup> MuSK antibodies are mainly IgG4. In contrast with the IgG1 or IgG3 antibodies associated with AChR+MG, IgG4 antibodies do not activate the complement cascade. Therefore, complement inhibition will not be an effective treatment strategy in MuSK antibody positive myasthenia gravis (MuSK+MG). Autoantibodies against low density lipoprotein receptor related protein 4 are believed to be pathogenic by disrupting activation of MuSK.

### New treatments on the horizon

Traditionally, patients with myasthenia gravis have been treated with pyridostigmine, corticosteroids, immunosuppressants (eg, azathioprine and mycophenolate mofetil), and intravenous immunoglobulins or plasmapheresis during episodes of myasthenia gravis crisis or severe myasthenia gravis symptoms. These treatments are the foundation of myasthenia gravis treatment and the backbone of the 2020 international consensus guidance for management of myasthenia gravis and the Association of British Neurologists' guidelines on myasthenia gravis.<sup>3,4</sup> The international consensus guidance recommends early consideration of thymectomy in patients with AChR antibody positive generalised myasthenia gravis (AChR+gMG), aged 18-50 years, although the guideline from the Association of British Neurologists emphasises early thymectomy in patients with general and ocular myasthenia gravis who are younger than 45 years. Despite these treatments, 8.5-15% of individuals with myasthenia gravis continue to have symptoms that negatively affect their quality of life or have unwanted adverse effects related to the treatments.<sup>5,6</sup> Our understanding of the pathophysiology of myasthenia gravis has enabled the development of new targeted therapeutics with more favourable side effect profiles. Possibly future treatment algorithms might not resemble our current approach (table 1).

### KEY MESSAGES

- ⇒ Myasthenia gravis is an antibody mediated autoimmune disorder affecting the neuromuscular junction function that leads to muscle weakness and functional disability
- ⇒ Treatments targeting the underlying pathophysiological pathway are rapidly evolving and have improved management of myasthenia gravis
- ⇒ The most appropriate selection of treatments considers the mechanisms, indications, risks and benefits, and costs of each treatment along with patients' preference
- ⇒ Targeting different pathomechanisms of the disease simultaneously will likely lead to improved outcomes, particularly in the severe cases



**Figure 1 | Illustration of antibody mediated pathogenesis in myasthenia gravis. Ab=antibody; ACh=acetylcholine; AChR=acetylcholine receptor; MAC=membrane attack complex; MuSK=muscle specific tyrosine kinase**

**Table 1 | New and emerging treatments for myasthenia gravis by therapeutic class**

Class	Mechanism of action	Drug name	Route	Recommendations	Studies*
B cell depletion	Target CD20, lead to B cell depletion	Rituximab: chimeric monoclonal antibody	Intravenous	Early consideration in MuSK+MG, third line for AChR+gMG	Blinded prospective study for MuSK+MG and retrospective studies. Phase 2 BeatMG trial
	Target CD19, lead to B cell depletion	Inebilizumab: humanised monoclonal antibody	Intravenous	TBD	Phase 3 randomised controlled trial of AChR+gMG and MuSK+MG ongoing
Complement inhibition	Block cleavage of C5 into C5a and C5b and prevent formation of membrane attack complex	Eculizumab: humanised monoclonal antibody	Intravenous	Refractory AChR+gMG	Phase 3 REGAIN trial completed. FDA approval for AChR+gMG in 2017
		Ravulizumab: humanised monoclonal antibody	Intravenous	AChR+gMG	Phase 3 CHAMPION study completed. FDA approval for AChR+gMG in 2022
		Zilucoplan: 15 amino acid peptide	Subcutaneous	TBD	Phase 3 RAISE trial AChR+gMG completed, and primary and key secondary endpoints met
Neonatal Fc receptor inhibition	Bind and block neonatal Fc receptor, reduce IgG recycling and level of IgG antibodies	Efgartigimod alfa: Fc fragment of human IgG1	Intravenous	AChR+gMG	ADAPT trial completed. FDA approval for AChR+gMG in 2021
		Rozanolixizumab: humanised IgG4	Subcutaneous	AChR+MG and MuSK+MG are enrolled	Phase 3 MycarinG study completed, and primary and key secondary endpoints met
		Batoclimab: humanised IgG1	Subcutaneous	TBD	Phase 3 randomised controlled trial of generalised myasthenia gravis ongoing
		Nipocalimab: humanised IgG1	Intravenous	TBD	Phase 3 randomised controlled trial of generalised myasthenia gravis ongoing
Interleukin 6 inhibition	Block interleukin 6 receptor, reduce proinflammatory T cell and B cell differentiation	Satralizumab: humanised IgG2	Subcutaneous	TBD	Phase 3 randomised controlled trial of AChR+gMG ongoing
Chimeric antigen receptor T cell treatment	Modify T cells and their regulation of B cell maturation	Descartes-08	Subcutaneous	TBD	Phase 1/2 trial ongoing

FDA=US Food and Drug Administration; AChR+MG=acetylcholine receptor antibody positive myasthenia gravis; AChR+gMG=acetylcholine receptor antibody positive generalised myasthenia gravis; MuSK+MG=muscle specific tyrosine kinase antibody positive myasthenia gravis; TBD=to be determined.

\*Study names: BeatMG=B Cell Targeted Treatment in Myasthenia Gravis; REGAIN=Safety and Efficacy of Eculizumab in Refractory Generalised Myasthenia Gravis; CHAMPION=Safety and Efficacy Study of Ravulizumab in Adults With Generalised Myasthenia Gravis; RAISE=Safety, Tolerability, and Efficacy of Zilucoplan in Subjects With Generalised Myasthenia Gravis; ADAPT=An Efficacy and Safety Study of ARGX-113 in Patients With Myasthenia Gravis Who Have Generalised Muscle Weakness; MycarinG=A Study to Evaluate Rozanolixizumab in Study Participants With Generalised Myasthenia Gravis.

### B cell depletion treatments

Treatments targeted at B cell depletion have received substantial attention because autoreactive B cells have important role in the immunopathogenesis of myasthenia gravis by producing pathogenic autoantibodies. Rituximab is a chimeric monoclonal antibody against CD20 that depletes circulating B cells. Several retrospective and prospective studies of rituximab in AChR+gMG and MuSK antibody positive generalised myasthenia gravis (MuSK+gMG) have recently been published, focusing on new onset disease, refractory disease, or both. In a retrospective cohort study of 72 non-MuSK+gMG patients with either new onset or refractory disease treated with rituximab, 55 of 72 patients fulfilled the criteria for clinical remission.<sup>7</sup> Time to remission was shorter in those with new onset generalised myasthenia gravis compared with those with refractory disease (7 v 16 months,  $P=0.009$ ). The new onset group treated with rituximab achieved clinical remission at a faster rate than the control group receiving conventional treatment (7 v 11 months,  $P=0.004$ ).

A large systematic review of 165 patients with AChR+gMG treated with rituximab from 13 different studies reported substantial clinical improvement in 68% of patients (113/165); one study showed a remission rate of 36% (14/39), four studies found that 27-64% (mean 54%) of patients had minimal manifestation status, whereas nine studies reported a significant reduction in immunosuppressive treatment burden.<sup>8</sup> Several meta-analyses investigating the role of rituximab specifically in refractory generalised myasthenia gravis have supported the efficacy of rituximab in this context.<sup>9-11</sup> One retrospective case series exploring rituximab in new onset generalised myasthenia gravis reported that 89% (17/19) of treated patients were relapse free after a mean follow-up of 51.3 months, although the study was confounded by thymectomy (47%) before the start of treatment with rituximab and a high incidence of thymoma (37%).<sup>12</sup>

A prospective open label multicentre study of 34 patients with refractory generalised myasthenia gravis treated with Zytux (a rituximab biosimilar)

showed reduced disease activity and improved quality of life.<sup>13</sup> Although these data are encouraging, the BeatMG (B Cell Targeted Treatment in Myasthenia Gravis) study, a phase 2 randomised controlled trial designed to examine the safety and efficacy of rituximab in AChR+gMG, failed to show a significant steroid sparing effect compared with placebo, although the safety profile was favourable.<sup>14</sup> This study had some limitations, however, including a higher than anticipated response rate in the placebo group, low B cell counts from baseline immunosuppressive treatment, and a mild level of disease severity. These limitations could have affected the results of the study.

The indication for rituximab in MuSK+MG is clearer. A multicentre, blinded, prospective review compared 24 patients with MuSK+MG who received rituximab with 31 controls receiving the current standard of care. The study found that 58% of patients treated with rituximab met the primary endpoint of a score of  $\leq 2$  on the myasthenia gravis status and treatment intensity scale, compared with 16% of controls ( $P=0.002$ ). The number needed to treat to achieve this primary endpoint was 2.4.<sup>15</sup> The 2020 update of the international myasthenia gravis consensus guidelines recommend consideration of rituximab as an early treatment option for those with MuSK+MG who have had an unsatisfactory response to initial immunotherapy. For AChR+generalised myasthenia gravis, the efficacy of rituximab is unclear, but remains an option if patients fail other immunosuppressive treatments.<sup>4</sup>

Inebilizumab, an anti-CD19 monoclonal antibody, targets and depletes pro-B cells, plasmablasts, and plasma cells.<sup>16</sup> A phase 3 randomised controlled trial of 270 patients with generalised myasthenia gravis (188 with AChR+gMG and 82 with MuSK+gMG) is underway (NCT04524273) and the primary outcome measure is change in score on the myasthenia gravis-activities of daily living (MG-ADL) scale from baseline at week 52 for patients with AChR+gMG and at week 26 for patients with MuSK+gMG (NCT04524273). Figure 2 illustrates the mechanisms of action of the different treatments described in this article.

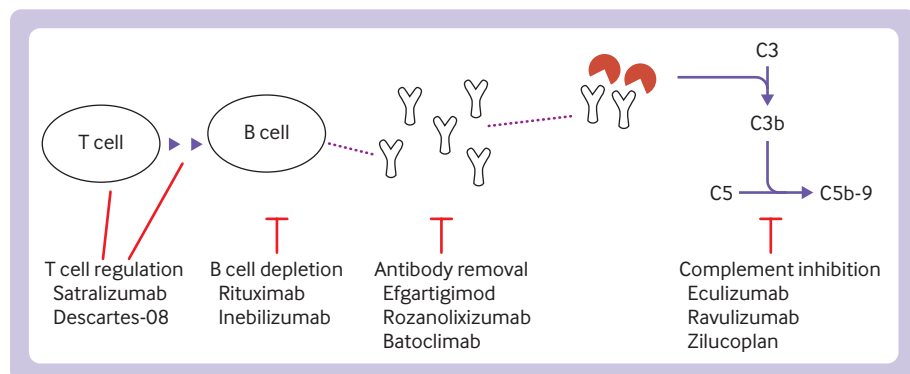


Figure 2 | Illustration of sites of action targeted by emerging and current treatments for myasthenia gravis

### Complement inhibitors

The complement cascade plays an important part in the pathogenesis of AChR+MG, and hence, complement inhibition has been identified as a therapeutic target. Eculizumab is a recombinant monoclonal antibody that binds to C5, inhibits enzymatic cleavage to C5a and C5b, and ultimately prevents formation of the membrane attack complex. Eculizumab was approved by the US Food and Drug Administration in 2017 for use in AChR+gMG. This approval ushered in the next chapter of myasthenia gravis biological therapeutics, representing the first FDA approved drug for myasthenia gravis in more than 60 years. The pivotal phase 3 study, REGAIN (Safety and Efficacy of Eculizumab in Refractory Generalised Myasthenia Gravis), explored the efficacy and safety of eculizumab in refractory AChR+gMG.<sup>17</sup> Although the primary endpoint of change in score on the MG-ADL scale from baseline to week 26 was not met, post hoc analysis of this outcome and secondary endpoints, including change in the total quantitative myasthenia gravis score, supported the efficacy of eculizumab. In the subsequent open label extension study, those treated with eculizumab reported improvements in muscle strength, activities of daily living, functional ability, and quality of life for up to three years.<sup>18</sup>

The role of eculizumab in AChR+gMG is still being determined and currently this treatment tends to be reserved for those with refractory symptoms. Because patients receiving eculizumab have shown benefit as early as one week after the start of treatment, however, it might eventually have a role in treating myasthenia gravis crisis.<sup>19</sup>

An unwanted complication of complement inhibition is a greatly increased risk of infection caused by encapsulated bacteria, particularly *Neisseria meningitidis*. Patients receiving complement inhibitors should receive double meningococcal vaccination with ACYW conjugate and serogroup B vaccine at least two weeks before the first drug infusion. Antibiotic prophylaxis is mandatory if the drug is started within two weeks of vaccination.

Ravulizumab is a long acting C5 complement inhibitor engineered over the backbone of eculizumab. The phase 3 CHAMPION (Safety and Efficacy Study of Ravulizumab in Adults With Generalised Myasthenia Gravis) study evaluating the safety and efficacy of ravulizumab in patients with AChR+gMG showed significant improvement in the total score on the MG-ADL scale ( $P<0.001$ ) and in the quantitative myasthenia gravis score from baseline to week 26 ( $P<0.001$ ) compared with placebo.<sup>19</sup> The benefits were seen within one week after the start of treatment and were sustained up to week 26. Ravulizumab is well tolerated and has the benefit of dosing every eight weeks, compared with every two weeks for eculizumab. The FDA approved its use for the treatment of AChR+gMG in April 2022.

Zilucoplan is a small 15 amino acid macrocyclic peptide that binds to C5 with high affinity, preventing the cleavage of C5 and assembly of the membrane attack complex. Zilucoplan is self-administered subcutaneously. Preliminary results from the phase 3 RAISE (Safety, Tolerability, and Efficacy of Zilucoplan in Subjects With Generalised Myasthenia Gravis) trial in patients with AChR+gMG were recently released. The study met its primary endpoint, showing a placebo corrected mean improvement of 2.12 points in the MG-ADL at week 12 ( $P<0.001$ ). All key secondary endpoints, including improvement in the quantitative myasthenia gravis score, were met. A favourable safety profile and good tolerability were reported. Regulatory submission was accepted by the FDA.

### Neonatal Fc receptor antagonists

FcRn has a central regulatory role in the humoral immune response. FcRn selectively binds to IgG antibodies, protects the antibodies from lysosomal degradation, and recycles them into the circulation. Blocking FcRn therefore promotes breakdown of IgG antibodies and is a prime target to reduce pathogenic autoantibodies in myasthenia gravis.

In December 2021, the FDA approved the first in class efgartigimod alfa, an IgG1 Fc fragment, for the treatment of AChR+gMG after the pivotal phase 3 ADAPT (An Efficacy and Safety Study of ARGX-113 in Patients With Myasthenia Gravis) trial.<sup>20</sup> In this randomised controlled trial, patients with generalised myasthenia gravis were assigned in a 1:1 ratio to efgartigimod alfa or placebo for four weekly infusions for each cycle and repeated as needed. The primary endpoint was the proportion of patients with AChR+gMG who achieved a response on the MG-ADL scale of at least a two point improvement for four or more consecutive weeks. Of the MG-ADL responders in cycle 1, more were in the efgartigimod alfa group (44/65, 68%) than in the placebo group (19/64, 30%;  $P<0.0001$ ). The safety profile of efgartigimod alfa was comparable with placebo. The open label extension study (ADAPT+) is ongoing (NCT03770403).

Efgartigimod alfa can be prescribed to eligible patients with generalised myasthenia gravis through the Early Access to Medicines Scheme in the UK. Also, ADAPT NXT (An Open-label Study to Investigate the Clinical Efficacy of Different Dosing Regimens of Efgartigimod IV in Patients With Generalised Myasthenia Gravis, NCT04980495) has recently commenced. In this open label study, the clinical efficacy of two different dosing regimens (10 mg/kg every two weeks v 10 mg/kg every seven days for four infusions, with repeated cycles every four weeks) is being investigated. A long term, single arm, open label multicentre trial of efgartigimod alfa given subcutaneously in generalised myasthenia gravis is also ongoing (NCT04818671).



Rozanolixizumab is a subcutaneously infused monoclonal antibody that targets FcRn. Preliminary data from the phase 3 MycarinG study (NCT04650854) investigating the efficacy and safety of rozanolixizumab in patients with AChR+gMG or MuSK+gMG has been announced. The primary endpoint of change in MG-ADL score and all secondary endpoints, including the quantitative myasthenia gravis score, myasthenia gravis composite scale, and patient reported outcomes, were found to be significant ( $P < 0.0001$ ). Rozanolixizumab was granted FDA approval for the treatment of AChR+gMG in June 2023. Two more FcRn therapeutics, batoclimab (NCT05039190) and nipocalimab (NCT04951622), both fully human IgG1 antibodies, are in phase 3 studies in generalised myasthenia gravis.

### T cell directed treatments

Because T cells promote B cell proliferation and differentiation into plasma cells through cytokines, drugs targeting T cells and cytokines could have a potential role in the treatment of myasthenia gravis. Satralizumab is a humanised monoclonal antibody that binds the interleukin 6 receptor, inhibiting interleukin 6 signalling and T cell activation. A phase 3 study, with the goal of enrolling 240 patients with AChR+gMG, is currently ongoing (NCT04963270). Satralizumab is given every two weeks by subcutaneous injection followed by monthly injections. Tocilizumab, another interleukin 6 receptor antagonist, is being investigated in a phase 2 trial for the treatment of AChR+gMG (NCT05067348).

Chimeric antigen receptor T cell treatment is a new technology that equips autologous T cells with a specially engineered receptor (ie, chimeric antigen receptor), thereby enabling T cells to effectively destroy cells of interest. Descartes-08, a treatment that modifies T cells with chimeric antigen receptors targeting the B cell maturation antigen found on antibody producing plasma cells, is currently in a phase 1/2 trial (NCT04146051).

### Future treatment landscape

Treatment for myasthenia gravis is rapidly evolving, with particularly notable developments for patients with moderate to severe AChR+gMG. Considering the drugs recently approved by the FDA and new treatments on the horizon, selection of the ideal therapeutic might seem daunting. Although drawing comparisons in efficacy across different clinical trials is tempting, especially when the same primary and secondary endpoints are used, caution is recommended. Differences in baseline patient characteristics, including antibody status, severity of disease, concomitant drugs on entry to the trial, previously attempted drug treatments, and duration of time since thymectomy are likely to mean that the results are not directly comparable.

Ultimately, incorporation of newer therapeutics will require comprehensive assessment of costs

versus benefits, potential risks, patient preference, and medical comorbidities. Considering the high costs of these newer treatments, whether they will replace the traditional first line treatment approach remains to be seen. The long term efficacy, safety, and tolerability of these treatments have yet to be determined but use of these newer therapeutics and traditional treatments might not need to be mutually exclusive. We might ultimately find that a combined approach, targeting different pathomechanisms of the disease simultaneously, will lead to improved outcomes. Complement inhibitors, especially eculizumab, have been used increasingly in the clinical management of patients with refractory AChR+gMG since its approval; efgartigimod alfa is getting lots of attention for its new mechanism and safety profile; and rituximab is now considered an effective early intervention in MuSK+MG by many specialists, and its use in the management of patients with refractory AChR+MG is also increasing. The guidelines that direct the clinical care of our patients with myasthenia gravis will need to be updated frequently to reflect the rapidly changing tools available to treat these patients.

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