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# TARGETED THERAPIES IN GENERALIZED MYASTHENIA GRAVIS – A NARRATIVE REVIEW

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## ABSTRACT

### Background

Generalized myasthenia gravis (gMG) is a clinically and immunologically heterogeneous autoimmune disorder that can cause substantial functional impairment and life-threatening myasthenic crisis. Although symptomatic therapy and broad immunosuppression remain the basis of management, long-term treatment may be limited by incomplete disease control and treatment-related toxicity. Advances in understanding disease mechanisms have led to the development of therapies targeting specific immune pathways.

## Aim

To summarize and critically evaluate the evidence on the efficacy and safety of existing and emerging targeted therapies for generalized myasthenia gravis.

## Materials and Methods

A narrative review was conducted using PubMed, Google Scholar, and ClinicalTrials.gov, covering English-language sources from January 2016 to September 2026, with earlier landmark and mechanistic studies considered when relevant. A total of 87 sources were included. Evidence was grouped by therapeutic target and synthesized qualitatively, considering study design, autoantibody status, previous treatment exposure, and follow-up duration. Preliminary findings from conference abstracts and trial registries were distinguished from full peer-reviewed publications.

## Results

FcRn and complement inhibitors improved clinical outcomes in several randomized trials, although study populations, endpoints, and treatment effects differed. Evidence for complement inhibition was concentrated in AChR-Ab-positive gMG; the primary endpoint of the pivotal eculizumab REGAIN trial did not reach statistical significance. Evidence for B-cell-directed therapies varied by agent and antibody subgroup. Support for rituximab in MuSK-Ab-positive disease came predominantly from observational studies, whereas inebilizumab demonstrated efficacy in a phase III trial involving AChR-Ab-positive and MuSK-Ab-positive patients. Findings for cytokine and intracellular signaling inhibitors were heterogeneous. CAR-T therapies showed preliminary clinical activity, but long-term safety and durability remained uncertain.

## Conclusions

Targeted therapies have expanded treatment options for gMG, with the most extensive clinical evidence supporting FcRn and complement inhibition. The applicability of this evidence depends on autoantibody status, disease characteristics, previous treatment exposure, and agent-specific safety considerations. Differences between trials and limited direct comparisons prevent identification of an optimal treatment sequence. Further comparative and long-term studies are needed to clarify safety, sustained reductions in corticosteroid exposure, and the potential for durable treatment-free remission.

**Keywords:** generalized myasthenia gravis; targeted therapy; FcRn inhibitors; complement inhibitors; rituximab; CAR-T cell therapy

## INTRODUCTION

Myasthenia gravis (MG) is a chronic autoimmune disorder of the neuromuscular junction caused by autoantibodies targeting proteins involved in postsynaptic neuromuscular transmission. A recent systematic review estimated a mean prevalence of 173.3 cases per million population and a mean incidence of 15.7 cases per million person-years [1]. MG occurs at all ages, with earlier-onset disease more common in women and late-onset disease more frequently observed in men [2]. The clinical presentation is heterogeneous and includes ocular and generalized forms. Ptosis and diplopia are the most common manifestations, occurring in approximately 60% of patients at disease onset [3]. Generalized MG involves bulbar, facial, axial, limb, and respiratory muscles and may lead to severe functional impairment or myasthenic crisis. A systematic review and meta-analysis found that approximately 39% of patients with ocular MG subsequently develop generalized disease. AChR antibody positivity, older age at onset, thymoma, and abnormal electrophysiological findings have been associated with an increased risk of generalization [4].

MG is immunologically heterogeneous. AChR antibodies are detected in approximately 80-85% of patients with generalized MG, while MuSK antibodies occur in approximately 5-10% and LRP4 antibodies in approximately 1-5% [5,6]. AChR antibodies, predominantly IgG1 and IgG3, impair neuromuscular transmission through receptor blockade, internalization, and complement-mediated destruction of the postsynaptic membrane. In contrast, MuSK antibodies, predominantly IgG4, disrupt the LRP4-MuSK signaling pathway required for maintenance of acetylcholine receptor clustering and are associated with limited complement activation. B cells, plasmablasts, and plasma cells contribute to autoantibody production, while T-cell-dependent mechanisms support B-cell activation and differentiation. The neonatal Fc receptor (FcRn) additionally prolongs the half-life of circulating IgG [7,8]. These mechanisms provide distinct therapeutic targets, including B cells, plasma cells, complement activation, FcRn-mediated IgG recycling, and cytokine signaling.

Conventional treatment combines symptomatic therapy with pyridostigmine and immunosuppression using corticosteroids and steroid-sparing agents such as azathioprine, mycophenolate mofetil, tacrolimus, cyclosporine, or methotrexate. Intravenous

immunoglobulin and plasma exchange are used for rapid immunomodulation, particularly in severe exacerbations and myasthenic crisis, while thymectomy is indicated in selected patients [9].

However, long-term immunosuppression is associated with substantial toxicity, including infections, osteoporosis, metabolic complications, cytopenias, hepatotoxicity, and nephrotoxicity. Corticosteroid exposure is also associated with increased risks of diabetes, cardiovascular disease, glaucoma, and other complications [10,11]. Approximately 10-20% of patients with MG have refractory disease despite conventional treatment [12]. These patients often require multiple immunosuppressive therapies and remain at increased risk of disease exacerbations and treatment-related toxicity.

The limitations of conventional immunosuppression, together with the biological heterogeneity of MG, have driven the development of targeted therapies designed to selectively interfere with pathogenic immune pathways. The rapid expansion of targeted treatment strategies and the growing body of clinical evidence from recently completed and ongoing trials highlight the need for an updated synthesis of the current evidence regarding their mechanisms, efficacy, safety, and clinical development in generalized myasthenia gravis.

## AIM

To summarize and critically evaluate the evidence on the efficacy and safety of existing and emerging targeted therapies for generalized myasthenia gravis.

### Objectives

1. To describe the mechanisms of action and stages of clinical development of targeted drugs and cellular therapies.
2. To analyze efficacy and safety data in relation to patients' autoantibody status and study characteristics.
3. To examine the role of targeted therapies in disease management and the limitations of the evidence regarding treatment selection and sequencing.

# METHODS

A narrative literature review was conducted based on English-language publications and clinical trial records relevant to targeted therapies in generalized myasthenia gravis. PubMed and Google Scholar were searched for publications from January 2016 to September 2026. Earlier landmark and mechanistic studies were considered when relevant to the biological rationale or development of targeted therapies. ClinicalTrials.gov was additionally searched to identify registered trials and ongoing clinical development programs. Searches were completed in September 2026.

The search strategy included combinations of the terms “myasthenia gravis,” “generalized myasthenia gravis,” “gMG,” “targeted therapy,” “FcRn inhibitor,” “complement inhibitor,” “B-cell therapy,” “plasma-cell therapy,” “cytokine signaling,” “intracellular signaling,” and “CAR-T,” together with the names of individual therapeutic agents. Additional searches were performed for individual drugs and specific trials to identify relevant publications and updated results.

Sources were selected for their relevance to the mechanisms of action, clinical efficacy, safety, or development of targeted therapies for generalized myasthenia gravis. Eligible sources included randomized controlled trials, phase I–III trials, open-label extension studies, subgroup analyses, observational studies, systematic reviews, meta-analyses, clinical guidelines, expert consensus statements, conference abstracts, and clinical trial registry records. Systematic reviews and meta-analyses were used for contextual information. ClinicalTrials.gov records were included particularly for ongoing or recently initiated studies when peer-reviewed clinical results were not yet available. Mechanistic and preclinical studies were included to explain the biological rationale for emerging approaches, including MuSK-specific cellular therapy. Publications unrelated to these therapeutic approaches were excluded. Findings available only in conference abstracts or registry records were treated as preliminary and distinguished from results reported in full peer-reviewed publications.

For each relevant therapy, information was extracted on the mechanism of action, trial design and phase, patient population, sample size, autoantibody status, treatment regimen, background therapy, treatment duration, efficacy outcomes, and safety. Where available, numerical data for MG-ADL, QMG, MGC, MG-QOL15r, minimal manifestation status, exacerbations, rescue treatment, and corticosteroid-sparing effects were recorded.

The evidence was grouped by therapeutic target and synthesized qualitatively, taking into account study design, autoantibody status, previous treatment exposure, and duration of follow-up. Randomized trial findings were distinguished from observational data, open-label extensions, preliminary clinical reports, and preclinical evidence. Differences between study populations and outcome definitions were considered when interpreting results across therapies.

A total of 87 sources were included in the narrative synthesis. Source selection was descriptive and was not conducted according to a formal systematic review protocol.

# RESULTS

## FcRn inhibitors

Efgartigimod is a human IgG1 Fc fragment that selectively binds to the neonatal Fc receptor (FcRn), thereby inhibiting immunoglobulin G (IgG) recycling and accelerating the clearance of circulating IgG autoantibodies.

Its efficacy was evaluated in the phase III ADAPT trial, which included 167 adults with generalized myasthenia gravis (gMG), classified as Myasthenia Gravis Foundation of America (MGFA) class II–IV, with clinically significant disease despite stable conventional therapy, including acetylcholinesterase inhibitors, corticosteroids, and/or nonsteroidal immunosuppressive therapies. Patients were eligible regardless of acetylcholine receptor antibody (AChR-Ab) status, although the primary efficacy analysis was performed in the AChR-Ab-positive population. In this group, efgartigimod significantly increased the proportion of patients achieving a clinically meaningful response on the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale compared with placebo (68% vs. 30%; odds ratio [OR], 4.95; $p < 0.0001$). Efgartigimod also significantly improved Quantitative Myasthenia Gravis (QMG) outcomes, with 63% of patients achieving a QMG response compared with 14% in the placebo group ($p < 0.0001$).

Most clinical responses became apparent within the first two weeks of treatment, with improvements in limb, bulbar, respiratory, and ocular manifestations of MG, while improvements in health-related quality of life (HRQoL) were detectable as early as the first week and were maintained during subsequent treatment cycles. Significant improvements were observed in both MG-specific and generic quality-of-life measures, including the Myasthenia Gravis Quality of Life 15-item revised (MG-QOL15r) and

EuroQol 5-Dimensions 5-Levels (EQ-5D-5L), and changes in HRQoL correlated with reductions in serum IgG concentrations and improvements in clinical outcomes. The safety profile was generally favorable, with headache and nasopharyngitis among the most frequently reported adverse events [13,14].

The subcutaneous formulation of efgartigimod was evaluated in the phase III ADAPT-SC trial, which compared subcutaneous efgartigimod PH20 with intravenous efgartigimod in adults with generalized myasthenia gravis (gMG). The primary endpoint was the percentage change from baseline in total IgG concentration at week 4, and noninferiority was established for IgG reduction, with mean reductions of 66.4% and 62.2%, respectively (between-group difference, −4.2 percentage points; 95% CI, −7.73 to −0.66). Clinical efficacy was assessed using secondary endpoints, which showed similar MG-ADL and QMG responses between the formulations.

Among AChR-Ab-positive patients, MG-ADL responses were achieved by 71.1% of patients receiving subcutaneous treatment and 71.7% receiving intravenous treatment [15]. More recently, the phase IIIb ADAPT NXT study evaluated alternative intravenous dosing regimens of efgartigimod in 69 AChR-Ab-positive patients with generalized myasthenia gravis. Both fixed treatment cycles and every-other-week dosing resulted in rapid and sustained, clinically meaningful improvements in Myasthenia Gravis Activities of Daily Living (MG-ADL) scores, with least-squares mean changes from baseline over 21 weeks of −5.1 (95% CI, −6.5 to −3.8) and −4.6 (95% CI, −5.4 to −3.8), respectively. Improvements were observed as early as week 1 and were maintained throughout the study, while minimal symptom expression (MG-ADL score 0–1) was achieved by 47.1% and 44.2% of patients, respectively. Efgartigimod was well tolerated, with a safety profile consistent with previous studies [16]. Subgroup analyses of ADAPT further demonstrated that the clinical efficacy of efgartigimod was consistent across a broad range of patient and disease characteristics, including previous nonsteroidal immunosuppressive treatment, concomitant therapies, age, disease duration, baseline MG-ADL severity, sex, and prior thymectomy, with a similar safety profile across subgroups [17]. Long-term data from the open-label ADAPT+ extension study further confirmed the sustained efficacy of efgartigimod, with clinically meaningful improvements in MG-ADL and QMG scores observed as early as 1 week after treatment initiation and maintained across repeated treatment cycles in both AChR-Ab-positive and AChR-Ab-negative patients. Among AChR-Ab-positive patients, more than 90% achieved a clinically meaningful MG-ADL response during each of the first 10 treatment cycles, while clinical improvements corresponded with reductions in total IgG and AChR-Ab levels. The long-term safety profile remained consistent with that observed

in ADAPT [18]. In a prospective open-label study, efgartigimod was evaluated in 30 patients with double-seronegative generalized myasthenia gravis, defined by the absence of antibodies against the acetylcholine receptor (AChR-Ab) and muscle-specific tyrosine kinase (MuSK-Ab), who remained symptomatic despite previous treatment with corticosteroids, nonsteroidal immunosuppressants, and intravenous immunoglobulin or plasma exchange.

The Myasthenia Gravis Impairment Index (MGII), the primary endpoint, improved significantly, with a mean reduction of 11.92 points (95% CI, 5.19–18.65; $p < 0.001$). Significant improvements were also observed in Myasthenia Gravis Activities of Daily Living (MG-ADL) and health-related quality of life, while the change in Quantitative Myasthenia Gravis (QMG) score was not statistically significant. Overall, 72% of patients achieved a clinically meaningful MGII response and 76% achieved an MG-ADL response, with 31% classified as early responders. Adverse events were reported in 25 of 30 patients (83.3%), with headache being the most frequently reported event; most adverse events were mild [19]. Ongoing studies are further evaluating efgartigimod in pediatric patients with generalized myasthenia gravis and in adults with newly diagnosed generalized disease, including subcutaneous administration [20–22].

Rozanolixizumab, another neonatal Fc receptor (FcRn) inhibitor, was evaluated in the phase III MycarinG trial, which included 200 adults with generalized myasthenia gravis (gMG), classified as Myasthenia Gravis Foundation of America class II–IVa, with clinically relevant symptoms despite stable background therapy. Patients were positive for either acetylcholine receptor antibodies (AChR-Ab) or muscle-specific tyrosine kinase antibodies (MuSK-Ab). Both rozanolixizumab doses significantly improved Myasthenia Gravis Activities of Daily Living (MG-ADL) scores compared with placebo, with least-squares mean differences of −2.59 points (95% CI, −4.09 to −1.25; $p < 0.0001$) for 7 mg/kg and −2.62 points (95% CI, −3.99 to −1.16; $p < 0.0001$) for 10 mg/kg. A clinically meaningful MG-ADL response was achieved by 68.2% of patients receiving 7 mg/kg compared with 28.4% receiving placebo (odds ratio [OR], 5.77; 95% CI, 2.10–14.88; $p < 0.001$), while significant improvements were also observed in Quantitative Myasthenia Gravis (QMG) and Myasthenia Gravis Composite (MGC) scores. Importantly, a subsequent subgroup analysis demonstrated significant clinical benefit in the MuSK-Ab-positive population, although this subgroup comprised only 21 patients. Treatment-emergent adverse events were reported in 109 of 133 patients receiving rozanolixizumab (82%), compared with 45 of 67 patients receiving placebo (67%). Most of them were mild to moderate, with headache, diarrhea, and pyrexia being the most frequently reported events. No deaths occurred [23,24]. Long-term

pooled data from the MycarinG trial and its open-label extension studies confirmed sustained efficacy of repeated rozanolixizumab treatment, with clinically meaningful improvements in MG-ADL, MGC, and QMG scores maintained across repeated treatment cycles and already evident after the first week of treatment. Among patients who responded according to MG-ADL during the first cycle, the response was maintained in subsequent cycles, with a weighted mean response rate of 80.1% across cycles 2–13; similarly, the weighted mean QMG response rate was 71.9% [25]. Ongoing studies are further evaluating rozanolixizumab in ocular myasthenia gravis and in pediatric patients with generalized disease [26,27].

Nipocalimab is a monoclonal antibody targeting the neonatal Fc receptor (FcRn), investigated in the phase II Vivacity-MG trial in 68 adults with generalized myasthenia gravis (gMG) who had an inadequate response to stable standard-of-care therapy. The study population was predominantly acetylcholine receptor antibody (AChR-Ab)-positive (94%), with a small subgroup of muscle-specific tyrosine kinase antibody (MuSK-Ab)-positive patients. Although none of the individual nipocalimab doses produced a statistically significant improvement in Myasthenia Gravis Activities of Daily Living (MG-ADL) compared with placebo, a significant dose-response relationship was observed for the change in MG-ADL at day 57 ($p=0.031$) [28]. These findings were subsequently confirmed in the phase III Vivacity-MG3 trial, which included 199 adults with gMG inadequately controlled despite standard-of-care therapy, including patients with AChR, MuSK, or LRP4 antibodies. In contrast to the phase II study, the primary endpoint was met, with nipocalimab producing a significantly greater improvement in MG-ADL than placebo over weeks 22–24 (least-squares mean change, −4.70 vs −3.25; difference, −1.45 points; 95% CI, −2.38 to −0.52; $p=0.0024$). Significant improvements were also observed in QMG, supporting an improvement in both functional disability and muscle weakness [29]. Nipocalimab was generally well tolerated, with a safety profile comparable to placebo [28,29]. A subsequent analysis of Vivacity-MG3 further demonstrated sustained clinical benefit, with nipocalimab significantly increasing the likelihood of maintaining a clinically meaningful MG-ADL and QMG response for at least 12 weeks compared with placebo [30]. Ongoing studies are further evaluating nipocalimab in pediatric generalized myasthenia gravis and directly comparing its efficacy with efgartigimod in adults with AChR-Ab-positive disease [31,32].

Batoclimab is a monoclonal IgG1 antibody targeting the neonatal Fc receptor (FcRn) and was evaluated in a multicenter randomized phase III trial involving adults with antibody-positive generalized myasthenia gravis (gMG). Sustained improvement in Myasthenia Gravis Activities of Daily Living (MG-ADL), defined as a reduction of at

least 3 points maintained for 4 or more consecutive weeks, was achieved by 58.2% of patients receiving batoclimab compared with 31.3% receiving placebo (odds ratio [OR], 3.45; 95% CI, 1.62–7.35; p=0.001). The MG-ADL scores began to diverge from placebo as early as week 2, with the greatest difference in mean MG-ADL reduction observed at day 43 (−1.9 points; 95% CI, −2.8 to −1.0; nominal p < 0.001). Improvements were also observed in Quantitative Myasthenia Gravis (QMG), Myasthenia Gravis Composite (MGC), and MG-QOL15r scores, accompanied by a reduction in serum IgG levels. However, FcRn inhibition also affects albumin recycling, resulting in a clinically relevant decrease in serum albumin. In the phase III trial, mean serum albumin decreased by approximately 31%, from 45.3 g/L at baseline to 31.2 g/L at week 6. Peripheral edema was reported in 38.8% of patients receiving batoclimab compared with 4.6% receiving placebo; these events were mild or moderate and were not considered clinically significant. Albumin concentrations increased toward baseline after treatment discontinuation [33]. Further evaluation of batoclimab is ongoing in a phase III extension study, focusing on its efficacy and safety when used for both induction and maintenance treatment of generalized myasthenia gravis [34].

## Complement inhibitors

Eculizumab is a monoclonal antibody targeting complement component C5, thereby inhibiting terminal complement activation and formation of the membrane attack complex. Its efficacy was evaluated in the phase III REGAIN trial, which included 125 adults with acetylcholine receptor antibody (AChR-Ab)-positive generalized myasthenia gravis (gMG) with refractory disease, classified as Myasthenia Gravis Foundation of America (MGFA) class II–IV and inadequately controlled despite treatment with at least two immunosuppressive therapies or one immunosuppressant combined with chronic intravenous immunoglobulin or plasma exchange. Although the primary endpoint, the change in the Myasthenia Gravis Activities of Daily Living (MG-ADL) score at week 26, did not reach statistical significance (p=0.0698), sensitivity analyses supported a treatment effect, and significant improvements were observed in secondary clinical outcomes, including Quantitative Myasthenia Gravis (QMG), Myasthenia Gravis Composite (MGC), and MG-QOL15 scores. Clinically meaningful improvement was also reflected by a greater proportion of patients achieving minimal manifestations of disease compared with placebo [35].

These benefits were sustained during the open-label extension for up to 3 years, with improvements in daily functioning, muscle strength, and quality of life observed across ocular, bulbar, respiratory, and limb muscle groups through 130 weeks of treatment.

The rate of disease exacerbations was reduced by 75% compared with the year preceding REGAIN ($p<0.0001$), while 56% of patients achieved minimal manifestation (MM) or pharmacological remission (PR). MM was defined as the absence of symptoms or functional limitations attributable to myasthenia gravis, although mild weakness could still be detected on examination, whereas PR referred to the absence of clinical symptoms or signs of disease while remaining on stable immunosuppressive therapy. The most frequently reported adverse events during long-term treatment were headache, nasopharyngitis, and upper respiratory tract infections. No meningococcal infections were reported, although meningococcal vaccination was required because of the increased susceptibility to Neisseria meningitidis associated with terminal complement inhibition [36,37].

More recent real-world data in patients with late-onset myasthenia gravis (LOMG) further supported the effectiveness of eculizumab. After 12 months of treatment, the mean MG-ADL score decreased by 5.43 points ($p<0.001$), with 96.4% of patients achieving a clinically meaningful improvement, while the mean daily prednisone dose was reduced by approximately 7.6 mg ($p<0.001$). However, these findings should be interpreted cautiously given the retrospective design and small study population [38].

In a separate prospective cohort, eculizumab was evaluated in patients with gMG who had shown an inadequate early response to efgartigimod. Following the switch to eculizumab, mean MG-ADL scores decreased from 7.9 to 2.6 (mean change, −5.3; $p<0.001$), while QMG scores decreased from 14.1 to 6.5 (mean change, −7.4; $p<0.001$). All patients achieved a clinically meaningful improvement in MG-ADL, and after 16 weeks, 58.3% achieved minimal symptom expression [39].

In adolescents with refractory AChR-Ab-positive gMG, a phase III open-label study also demonstrated significant improvements in QMG and MG-ADL scores at week 26 ($p=0.0004$ and $p=0.0017$, respectively), with efficacy maintained throughout the study period. All treatment-emergent adverse events were mild or moderate, and most were considered unrelated to eculizumab [40].

Ravulizumab is a long-acting monoclonal antibody targeting complement component C5. Its extended half-life allows administration every 8 weeks, providing a less frequent dosing schedule than eculizumab. Its efficacy was evaluated in the phase III CHAMPION-MG trial, which included 175 adults with anti-acetylcholine receptor antibody (AChR-Ab)-positive generalized myasthenia gravis (gMG), classified as Myasthenia Gravis Foundation of America (MGFA) class II–IV and with clinically significant disease despite stable standard-of-care therapy. Ravulizumab significantly im-

proved Myasthenia Gravis Activities of Daily Living (MG-ADL) scores at week 26 compared with placebo (least-squares mean change, −3.1 vs −1.4; difference, −1.6 points; 95% CI, −2.6 to −0.7; $p<0.001$). Significant improvement was also observed in Quantitative Myasthenia Gravis (QMG) scores (−2.8 vs −0.8; difference, −2.0 points; 95% CI, −3.1 to −0.8; $p<0.001$), with clinical improvement evident as early as week 1 and sustained through week 26. Ravulizumab was generally well tolerated, with adverse events occurring at a similar frequency to placebo and no new safety concerns identified [41]. Long-term follow-up from the CHAMPION-MG open-label extension confirmed the durability of the clinical benefit, with improvements in MG-ADL maintained for up to 4 years. Overall, 88.1% of patients achieved at least a 2-point improvement in MG-ADL, while 41.8% of responders reached an MG-ADL score of 0 or 1, with more than half maintaining this level of disease control for over half of their remaining follow-up. These findings were supported by sustained improvements in QMG, MG-QOL15r, and fatigue measures, together with reduced rates of clinical deterioration and lower corticosteroid use [42]. Ongoing studies are further evaluating ravulizumab in routine clinical practice, pediatric gMG, and as a strategy for reducing oral corticosteroid exposure in AChR-Ab-positive disease [43,44].

Zilucoplan is a macrocyclic peptide inhibitor of complement component C5 that blocks terminal complement activation and is administered by once-daily subcutaneous injection. Its efficacy was evaluated in the phase III RAISE trial, which included 174 adults with acetylcholine receptor antibody (AChR-Ab)-positive generalized myasthenia gravis (gMG) with clinically significant disease despite stable standard-of-care treatment. At week 12, the least-squares mean change in MG-ADL score was −4.39 points with zilucoplan and −2.30 points with placebo; the between-group difference was −2.09 points (95% CI, −3.24 to −0.95; $p=0.0004$). The corresponding changes in QMG score were −6.19 and −3.25 points, respectively, with a between-group difference of −2.94 points (95% CI, −4.39 to −1.49; $p<0.0001$). An MG-ADL response, defined as a ≥3-point improvement without rescue therapy, was achieved by 73.1% of patients receiving zilucoplan versus 46.1% receiving placebo. A QMG response, defined as a ≥5-point improvement without rescue therapy, was achieved by 58.0% versus 33.3%, respectively. Clinical improvement was evident as early as week 1 and was maintained throughout the 12-week treatment period [45]. Long-term follow-up from the ongoing RAISE-XT open-label extension demonstrated sustained efficacy through 96 weeks, with mean MG-ADL improvements of 6.33 points in patients continuing zilucoplan and 7.83 points in those switched from placebo [46]. Zilucoplan was generally well tolerated, with injection-site reactions being the most frequently reported adverse event [45,46]. A subsequent RAISE subgroup analysis showed that zilucoplan also improved

MG-specific outcomes in patients without previous immunoglobulin or plasma exchange exposure, with efficacy comparable to that observed in patients with prior treatment, supporting its potential use earlier in the treatment pathway [47]. A phase IIIb open-label study evaluated switching from intravenous C5 inhibitors to subcutaneous zilucoplan in clinically stable AChR-Ab-positive gMG. Among 26 patients, 16 switched from eculizumab and 10 from ravulizumab. After 12 weeks, MG-ADL scores improved significantly overall (mean change, −1.15; p=0.0217), while the greatest benefit was observed in patients switching from ravulizumab, with significant improvements in both MG-ADL (−2.41; p=0.0307) and QMG (−3.52; p=0.0149). Importantly, 76.9% of patients preferred daily subcutaneous zilucoplan over intravenous treatment [48]. The clinical development program is now expanding the use of zilucoplan beyond the established adult population, with ongoing studies addressing pediatric gMG and treatment during severe exacerbations requiring hospitalization [49,50].

Gefurulimab is a novel dual-binding nanobody targeting complement component C5. Its albumin-binding capacity extends its half-life and enables once-weekly subcutaneous self-administration. The phase III PREVAIL trial enrolled 260 adults with AChR-Ab-positive generalized myasthenia gravis (gMG), representing patients with MGFA class II–IV disease and clinically significant symptoms despite standard treatment. At week 26, gefurulimab significantly improved Myasthenia Gravis Activities of Daily Living (MG-ADL) scores compared with placebo (least-squares mean change, −4.2 vs −2.6; treatment difference, −1.6; 95% CI, −2.4 to −0.8; $p<0.001$). A significant improvement was also observed in Quantitative Myasthenia Gravis (QMG) scores (−4.5 vs −2.4; treatment difference, −2.1; 95% CI, −3.1 to −1.1; $p<0.001$). Clinical improvement in MG-ADL was already evident after the first week, while QMG improvement emerged by week 4, and both effects were maintained through week 26 with favorable safety profile [51]. The clinical development of gefurulimab is also extending into the pediatric population, with an ongoing phase III study evaluating its pharmacokinetics, safety, and clinical activity in AChR-Ab-positive children and adolescents with gMG [52].

Cemdisiran is a N-acetylgalactosamine-conjugated small interfering RNA (siRNA) that targets hepatic C5 mRNA, thereby reducing circulating C5 levels and complement activation. Its efficacy was assessed in the phase III NIMBLE trial as shown in Table 1, which included 284 adults with generalized myasthenia gravis (gMG) who were seropositive for anti-acetylcholine receptor (AChR) or anti-low-density lipoprotein receptor-related protein 4 (LRP4) antibodies. Cemdisiran administered subcutaneously every 12 weeks significantly improved Myasthenia Gravis Activities of Daily Living (MG-ADL) scores at week 24 compared with placebo (least-squares mean change, −4.5 vs −2.2; placebo-

adjusted difference, −2.3; 95% CI, −3.6 to −1.0; p=0.0005). A significant improvement was also demonstrated in Quantitative Myasthenia Gravis (QMG) scores (placebo-adjusted difference, −2.8; p=0.002), with 76.6% of patients achieving a ≥3-point improvement in MG-ADL compared with 44.1% receiving placebo, while 48.4% achieved a ≥5-point improvement in QMG versus 19.0%, respectively. Notably, clinical efficacy was observed despite approximately 74% inhibition of complement activity, indicating that substantial clinical benefit may be achieved without complete suppression of the terminal complement pathway. The trial also evaluated cemdisiran in combination with pozelimab, a monoclonal antibody that directly binds circulating C5 and prevents its cleavage into C5a and C5b, thereby providing complementary inhibition of C5 production and activity. The combination achieved near-complete complement inhibition of approximately 99%. The placebo-adjusted MG-ADL difference was −1.7 points (p=0.0086) with combination therapy, compared with −2.3 points (p=0.0005) with cemdisiran monotherapy, while the corresponding placebo-adjusted QMG differences were −1.9 and −2.8 points, respectively. The prespecified statistical testing strategy assessed each regimen against placebo rather than directly comparing combination therapy with cemdisiran monotherapy. Therefore, these numerical differences should be interpreted descriptively and do not establish the comparative superiority of either regimen. The safety profile was comparable to placebo, with no meningococcal infections or treatment-related deaths reported during the 24-week double-blind period [53].

Longer-term follow-up from the NIMBLE program is ongoing, with extended treatment and post-treatment observation planned to further characterize the durability of clinical benefit and long-term safety of cemdisiran [54].

Claseprubart is an investigational monoclonal antibody that selectively inhibits the active form of complement component C1s, thereby blocking the classical complement pathway upstream of C4 cleavage and subsequent membrane attack complex formation. This mechanism may be particularly relevant in generalized myasthenia gravis (gMG) with acetylcholine receptor antibodies (AChR-Ab), in which complement activation contributes to damage of the postsynaptic neuromuscular junction [55].

Claseprubart was evaluated in the phase II MaGic trial, a randomized, double-blind, placebo-controlled study that included 65 adults with AChR antibody-positive gMG. Patients received claseprubart at doses of 300 or 600 mg every 2 weeks or placebo for 13 weeks, followed by a 52-week open-label extension. Preliminary results showed that, at week 13, the mean improvement in MG-ADL score from baseline was 4.6 points in the 300-mg group and 5.4 points in the 600-mg group, compared with 2.8 points

with placebo, corresponding to placebo-adjusted differences of 1.8 and 2.6 points, respectively (p=0.0113 and p=0.0006). Similar improvements were observed in QMG scores, with placebo-adjusted differences of 2.4 and 2.5 points in the 300- and 600-mg groups, respectively (p=0.0144 and p=0.0111). Claseprubart was generally well tolerated, with no major safety signals identified during the randomized treatment period [56]. The phase III EMERGE trial is currently evaluating claseprubart in adults with AChR antibody-positive gMG, with change in MG-ADL score from baseline as the primary endpoint [57].

Empasiprubart is a monoclonal antibody targeting complement component C2, thereby inhibiting the classical and lectin complement pathways. It is currently being investigated in patients with AChR antibody-positive generalized myasthenia gravis (gMG), including in combination with efgartigimod in patients with partial response to FcRn inhibition [58,59].

## B-cell and plasma-cell inhibitors

Iptacopan is an oral, selective inhibitor of complement factor B that blocks activation and amplification of the alternative complement pathway, representing a potential oral complement-targeted therapy for gMG. Its efficacy and safety are currently being evaluated in the phase III trial in adults with AChR antibody-positive gMG receiving stable background therapy [60].

Rituximab is a chimeric monoclonal antibody targeting CD20, resulting in depletion of CD20-positive B cells. Although it is not specifically approved for the treatment of myasthenia gravis, clinical evidence suggests particular benefit in patients with MuSK antibodies and in some patients with treatment-refractory generalized myasthenia gravis [61]. In the randomized RINOMAX trial, a single course of rituximab in patients with newly diagnosed gMG resulted in a greater proportion of patients achieving minimal disease manifestations compared with placebo. At week 16, the primary endpoint was achieved by 71% of patients receiving rituximab compared with 29% receiving placebo (p=0.007) [62]. In contrast, the phase II BeatMG trial evaluated rituximab in 52 patients with established, mild-to-moderate AChR-antibody-positive gMG receiving background prednisone therapy. At week 52, the primary steroid-sparing endpoint, defined as a reduction of at least 75% in mean daily prednisone dose without significant clinical worsening, was achieved by 60% of patients receiving rituximab and 56% receiving placebo. The study met its prespecified futility criterion, indicating a low prob-

ability of demonstrating the predefined clinically meaningful steroid-sparing effect in a larger trial involving a similar population [63].

Long-term follow-up of the RINOMAX trial demonstrated sustained clinical benefit, with lower time-weighted QMG scores in the rituximab group compared with the original placebo group at 12 months (mean difference, 2.9 points; p=0.005) and 24 months (mean difference, 2.6 points; p=0.027) [64]. Recent real-world data further support a greater and more sustained response in MuSK-positive disease, with 66.7% of MuSK-positive and 33.3% of AChR-positive patients achieving MGFA post-intervention status success at 60 months; steroid reduction was achieved in 90.9% and 76.2% of patients, respectively [65].

Inebilizumab is a humanized monoclonal antibody targeting CD19 and inducing depletion of a broad spectrum of B-lineage cells, including plasmablasts. As demonstrated in Table 1, its efficacy was evaluated in the phase III MINT trial, which included 238 patients with generalized myasthenia gravis who were AChR-Ab- or MuSK-Ab-positive. At week 26, the mean change in MG-ADL score was −4.2 with inebilizumab and −2.2 with placebo, corresponding to an adjusted between-group difference of −1.9 points (95% CI, −2.9 to −1.0; $p<0.001$). For QMG, the corresponding changes were −4.8 and −2.3 points, with an adjusted between-group difference of −2.5 points (95% CI, −3.8 to −1.2; $p<0.001$) [66].

Among AChR-Ab-positive patients, the treatment effect was sustained through week 52, with adjusted between-group differences of −2.8 points for MG-ADL and −4.3 points for QMG (both $p<0.001$) [67]. Inebilizumab also reduced the risk of exacerbations compared with placebo, with a hazard ratio of 0.41 (95% CI, 0.24–0.70) in the overall population at week 26 [68]. The most frequently reported adverse events included headache, cough, nasopharyngitis, infusion-related reactions, and urinary tract infections [66].

Belimumab is a fully human IgG1λ monoclonal antibody targeting B-cell activating factor (BAFF), a key regulator of B-cell survival and differentiation. In a randomized phase II study of patients with generalized myasthenia gravis, belimumab did not significantly improve the primary endpoint of change in Quantitative Myasthenia Gravis (QMG) score at week 24 compared with placebo, and no significant differences were observed in secondary clinical outcomes, including MG-ADL and MG Composite scores [69].

Mezagitamab (TAK-079) is a fully human monoclonal antibody targeting CD38, which is highly expressed on plasmablasts and plasma cells, thereby directly targeting anti-

body-producing cells. In the phase II NCT04159805 trial, 36 patients with gMG received mezagitamab at doses of 300 or 600 mg or placebo. Available results did not demonstrate a clear clinical benefit, with no significant improvements in MG-ADL or QMG compared with placebo. Although the trial has been completed, no full peer-reviewed publication of the clinical results is currently available; therefore, these findings should be interpreted with caution [70].

Telitacicept is a recombinant fusion protein containing the extracellular domain of transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) linked to an Fc fragment, thereby inhibiting both B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL). By targeting both cytokines, telitacicept may interfere with B-cell survival and differentiation, plasmablast formation, and plasma-cell maintenance. In a randomized, open-label phase II study involving 29 patients with generalized myasthenia gravis, subcutaneous telitacicept was administered at doses of 160 or 240 mg once weekly for 24 weeks. The study did not include a placebo group. At week 24, mean QMG scores decreased from baseline by 7.7 points in the 160-mg group and by 9.6 points in the 240-mg group, with improvements observed from week 12. Treatment was also associated with reductions in serum IgG, IgA, and IgM concentrations [71]. Telitacicept is currently being further evaluated in phase III randomized, placebo-controlled trials in patients with generalized myasthenia gravis [72].

Povetacicept, another engineered TACI-Fc fusion protein targeting both BAFF and APRIL, is currently being evaluated in a phase II trial in adults with generalized myasthenia gravis [73].

Iscalimab is a fully human monoclonal antibody targeting CD40, thereby blocking CD40–CD154 costimulatory signaling involved in T-cell-dependent B-cell activation and germinal-center formation. In a randomized, double-blind, placebo-controlled phase II study involving 44 patients with moderate-to-severe generalized myasthenia gravis, iscalimab did not significantly improve the primary endpoint of QMG score at week 25 compared with placebo. Although transient improvements in MG Composite and MG-ADL scores were observed, particularly among non-thymectomized patients, the overall results did not support further clinical development of iscalimab in myasthenia gravis [74].

## Cytokine inhibitors

Tocilizumab is a humanized monoclonal antibody targeting the interleukin-6 receptor (IL-6R), thereby inhibiting IL-6-mediated signaling involved in B-cell differentiation,

plasmablast formation, and inflammatory responses. Its clinical use in myasthenia gravis has been investigated primarily in patients with treatment-refractory disease. In a prospective cohort study of 34 patients with refractory AChR antibody-positive generalized myasthenia gravis, 20 patients received tocilizumab and 14 conventional immunotherapy. Tocilizumab was associated with greater improvements in MG-ADL and QMG scores and a greater reduction in daily prednisone dose over 24 weeks [75].

Satralizumab is a humanized monoclonal antibody targeting the interleukin-6 receptor (IL-6R), thereby inhibiting IL-6-mediated signaling involved in inflammatory and B-cell-mediated immune responses. Its efficacy was evaluated in the randomized, double-blind, placebo-controlled phase III LUMINESCE trial, which included 188 patients with seropositive generalized myasthenia gravis; 166 AChR-IgG-positive patients constituted the primary efficacy population. At week 24, the adjusted mean change in MG-ADL score was −3.59 with satralizumab compared with −2.57 with placebo, corresponding to a between-group difference of −1.02 points (95% CI, −1.88 to −0.16; p=0.012). Adverse events occurred in 90% and 73% of patients, respectively, while serious adverse events were reported in 3% and 7%, with no deaths. Although satralizumab demonstrated a statistically significant improvement in MG-ADL, the magnitude of the treatment effect was modest, and further development of satralizumab for generalized myasthenia gravis was subsequently discontinued [76].

Tofacitinib, an oral JAK inhibitor targeting intracellular cytokine signaling, has also been investigated as a potential therapy for refractory MG. In a prospective pilot study of 19 patients with refractory MG, 24 weeks of tofacitinib treatment was associated with improvements in MG clinical scores and quality of life, as well as reduced glucocorticoid requirements; however, the single-arm design and small sample size limit the interpretation of these findings [77]. Another small-molecule targeted therapy is remibrutinib, a highly selective, covalent inhibitor of Bruton's tyrosine kinase (BTK), which mediates B-cell receptor signaling and B-cell activation. It is currently being evaluated in the phase III RELIEVE trial in adults with generalized myasthenia gravis receiving stable background therapy [78].

Cellular therapies represent an emerging therapeutic strategy in generalized myasthenia gravis, aiming to achieve profound and potentially durable depletion of pathogenic B-cell and plasma-cell populations and thereby induce a sustained immune reset. Among these approaches, Descartes-08 is an autologous BCMA-directed mRNA CAR-T therapy targeting antibody-producing plasma cells. In a randomized, double-blind, placebo-controlled phase IIb trial including 26 patients with gMG, 66.7% of patients receiving Descartes-08 achieved a ≥5-point improvement in MG Composite

score at month 3 compared with 27.3% receiving placebo (p=0.0472), with clinical benefits maintained through 12 months. The most common adverse events were infusion-related reactions, including chills (60%), fever (55%), headache (50%), nausea (45%), and myalgia (35%), which generally resolved within 24 hours. Serious adverse events occurred in five patients (25.0%) receiving Descartes-08 and three (18.8%) receiving placebo; only one event in the Descartes-08 group, a severe infusion-related reaction presenting with fever of 40°C, was considered possibly treatment-related and resolved within 48 hours. No new treatment-related adverse events were reported during months 4–12 of follow-up [79]. KYV-101 and CABA-201 (rese-cel) are fully human, autologous CD19-directed CAR-T therapies designed to induce profound B-cell depletion; early clinical studies have reported improvements in MG-ADL and QMG scores, together with substantial reductions in immunosuppressive treatment, although efficacy data remain preliminary. In an interim analysis of six patients treated with KYV-101, no immune effector cell-associated neurotoxicity syndrome (ICANS) or high-grade cytokine release syndrome (CRS) was reported. Follow-up ranged from 28 days to 9 months; however, the conference abstract did not provide a comprehensive breakdown of adverse events or serious adverse events [80].

In an interim analysis of rese-cel, four patients had received treatment and completed at least one month of follow-up as of September 2025. One patient developed grade 2 CRS. The limited sample size and short follow-up preclude a comprehensive assessment of the treatment's safety profile [81]. A dual-target CD19/BCMA CAR-T approach has been developed to simultaneously target B cells and antibody-producing plasma cells. In a phase I study of 18 patients with refractory AChR antibody-positive gMG, treatment was associated with a mean improvement of 8.6 points in MG-ADL and 15.4 points in QMG by day 180; 82% achieved minimal manifestations, 88% discontinued glucocorticoids, and 47% became seronegative for AChR antibodies. CRS occurred in seven patients (39%), was transient, and resolved within 1–3 days; no ICANS or deaths were reported. The main adverse events were hematological, particularly lymphopenia, leukopenia, and neutropenia; anemia and thrombocytopenia were also reported. These abnormalities were generally transient and manageable, although some patients required supportive treatment. Three patients developed bacterial pneumonia during follow-up. Seventeen of the 18 patients completed follow-up through day 180; the publication did not provide a consolidated overall count of serious adverse events [82]. A more antigen-specific strategy is represented by MuSK-CAAR-T, which is engineered to selectively recognize B cells bearing MuSK-specific B-cell receptors, but remains at the preclinical stage [83]. Table 1 summarizes the mechanisms, efficacy, safety, and key clinical evidence for targeted therapies in generalized myasthenia gravis.

Table 1. Overview of targeted therapeutic agents in generalized myasthenia gravis

| THERAPEUTIC AGENT | MECHANISM OF ACTION | MAIN CLINICAL EVIDENCE | KEY EFFICACY FINDING | ADVERSE EFFECTS | KEY REFERENCES |
|---|---|---|---|---|---|
| Efgartigimod | FcRn inhibitor | ADAPT; ADAPT NXT; ADAPT+ | MG-ADL response: 68% vs 30% placebo; QMG: 63% vs 14%; sustained responses | Generally well tolerated; headache, nasopharyngitis | [13–19] |
| Rozanolixizumab | FcRn inhibitor | MycarinG and its long-term extensions | MG-ADL response 68.2% vs 28.4% placebo | Mostly mild–moderate; headache, diarrhea, pyrexia | [23–25] |
| Nipocalimab | FcRn inhibitor | Vivacity-MG; Vivacity-MG3 | MG-ADL response −4.70 vs −3.25 placebo; QMG also improved | Generally well tolerated | [28–30] |
| Batoclimab | FcRn inhibitor | Phase III Randomised Clinical Trial | MG-ADL response 58.2% vs 31.3% placebo; QMG/MGC also improved | Generally well tolerated; albumin reduction and peripheral edema more frequent than placebo | [33,34] |
| Eculizumab | C5 inhibitor | REGAIN | MG-ADL response: not significant; QMG, MGC, MG-QOL15 significant improvements | Headache, nasopharyngitis, URTIs; meningococcal infection risk | [35–37] |
| Ravulizumab | C5 inhibitor | CHAMPION-MG and its long-term extension | MG-ADL response −3.1 vs −1.4 placebo; QMG −2.8 vs −0.8 | Generally well tolerated | [41,42] |
| Zilucoplan | C5 inhibitor | RAISE; RAISE-XT | MG-ADL change: −4.39 vs −2.30 with placebo; QMG change: −6.19 vs −3.25 with placebo at week 12 | Generally well tolerated; injection-site reactions | [45,46] |
| Gefurulimab | C5 inhibitor | PREVAIL | MG-ADL response −4.2 vs −2.6 placebo; QMG −4.5 vs −2.4 | Generally well tolerated | [51] |
| Cemdisiran | C5 inhibitor | NIMBLE | MG-ADL response −4.5 vs −2.2 placebo; QMG also improved | Comparable to placebo | [53] |
| Claseprubart | C1s inhibitor | MaGic phase II; EMERGE phase III | Placebo-adjusted MG-ADL: +1.8/+2.6; QMG also improved | Generally well tolerated | [55–57] |
| Iptacopan | Factor B inhibitor | Phase III trial | Not reported | Not reported | [60] |
| Rituximab | CD20 inhibitor | RINOMAX and its long-term extension | Primary endpoint achieved by 71% patient receiving rituximab vs 29% placebo | Not reported | [62–64] |
| Inebilizumab | CD19 inhibitor | MINT | MG-ADL response −4.2 vs −2.2 placebo; QMG: −4.8 vs −2.3 | Headache, cough, nasopharyngitis, infusion reactions, UTI | [66] |
| Belimumab | BAFF inhibitor | Phase II Randomised Clinical Trial | MG-ADL, QMG, MGC: not significant | Not reported | [69] |

| | | | | | |
|---|---|---|---|---|---|
| Mezagitamab | CD38 inhibitor | Phase II Randomised Clinical Trial | MG-ADL, QMG: not significant | Not reported | [70] |
| Telitacicept | BAFF and APRIL inhibitor | Phase II; phase III Randomised Clinical Trial ongoing | QMG reduction: −7.7/−9.6 points at 160/240 mg; reduced IgG, IgA and IgM | Not reported | [71,72] |
| Povetacicept | BAFF and APRIL inhibitor | Phase II | Not reported | Not reported | [73] |
| Iscalimab | CD40 inhibitor | Phase II Randomised Clinical Trial | QMG: not significant; transient MG-ADL/MGC effects | Not reported | [74] |
| Tocilizumab | IL-6R inhibitor | Prospective cohort study | Greater MG-ADL/QMG improvement and prednisone reduction vs conventional therapy | Not reported | [75] |
| Satralizumab | IL-6R inhibitor | LUMINESCE | MG-ADL response −3.59 vs −2.57 placebo | AEs: 90% vs 73% placebo; serious AEs: 3% vs 7%; no deaths | [76] |
| Tofacitinib | JAK inhibitor | Prospective pilot study | Improved clinical scores, quality of life, and glucocorticoid requirements | Not reported | [77] |
| Remibrutinib | BTK inhibitor | RELIEVE | Not reported | Not reported | [78] |
| Descartes-08 | BCMA-directed mRNA CAR-T; targets plasma cells | Phase IIb Randomised Clinical Trial | ≥5-point MGC improvement: 66.7% vs 27.3% placebo | Infusion-related reactions; chills, fever, headache, nausea, myalgia | [79] |
| KYV-101 | CD19-directed CAR-T | Early clinical studies | Improvements in MG-ADL/QMG | No ICANS or high-grade CRS reported; complete AE/SAE data unavailable | [80] |
| CABA-201 (resecel) | CD19-directed CAR-T | Early clinical studies | Improvements in MG-ADL/QMG | Grade 2 CRS in one patient; limited safety data | [81] |
| CD19/BCMA CAR-T | Dual B-cell/plasma-cell targeting | Phase I | MG-ADL mean improvement of 8.6 points; QMG: 15.4 | CRS, lymphopenia, leukopenia, and neutropenia, bacterial pneumonia | [82] |
| MuSK-CAAR-T | MuSK-specific B-cell targeting | Preclinical | No clinical efficacy data | Not reported | [83] |

# DISCUSSION

The development of targeted therapies has substantially expanded the treatment options for generalized myasthenia gravis (gMG). The available evidence supports several distinct therapeutic targets, but their clinical relevance differs according to disease phenotype, autoantibody status, previous treatment exposure, and stage of disease. These factors are particularly important when interpreting results from separate

placebo-controlled trials, as differences in study populations limit direct comparisons between therapies.

FcRn inhibitors currently have a broad and consistent evidence base. Efgartigimod, rozanolixizumab, nipocalimab and batoclimab have demonstrated clinically meaningful benefit in patients with active gMG despite background treatment. Their relatively rapid onset of action is consistent with the reduction of circulating IgG achieved through FcRn blockade. However, most pivotal studies primarily enrolled patients with established disease receiving stable conventional therapy, and therefore provide limited information regarding the role of FcRn inhibition early after diagnosis. In addition, although efficacy has been demonstrated across different antibody profiles, the numbers of MuSK-Ab-positive, LRP4-Ab-positive, and seronegative patients remain considerably smaller than those of AChR-Ab-positive patients [13,23,29,33].

The evidence is therefore strongest for the latter population. The requirement for repeated treatment also raises the question of whether FcRn inhibition provides sustained disease modification or predominantly controls disease activity while treatment is continued. From a safety perspective, FcRn inhibitors are generally associated with manageable adverse events, although headache, infections and, for some agents, infusion- or injection-related reactions may affect tolerability. Because FcRn blockade reduces circulating IgG, the consequences of repeated treatment for protective antibody levels and infection susceptibility warrant continued monitoring. Longer-term extension studies provide additional reassurance, but their design and selected populations limit conclusions regarding uncommon adverse events and the consequences of prolonged or repeated exposure.

Complement inhibition is similarly supported by substantial clinical evidence, but its applicability is more clearly linked to antibody status. Eculizumab, ravulizumab, and zilucoplan have presented efficacy predominantly in AChR-Ab-positive gMG [35,41,42,45]. This is consistent with the pathogenic role of complement activation in AChR-Ab-mediated disease but limits extrapolation to MuSK-Ab-positive gMG, in which IgG4 antibodies have limited complement-activating capacity. Importantly, the pivotal trials did not enroll identical patient populations. REGAIN focused on highly refractory disease, whereas CHAMPION-MG and RAISE included patients with clinically significant disease despite stable standard therapy [35,42,45]. Consequently, the magnitude of treatment effects across these studies cannot be interpreted as a direct comparison of efficacy. Newer complement-directed approaches, including gefurulimab, cemdisiran, claseprubart, and iptacopan, are expanding the therapeutic pos-

sibilities, but their optimal position in relation to established C5 inhibition remains uncertain [51,53,56,58,60].

The principal class-specific safety concern is the increased susceptibility to invasive infections caused by Neisseria species, particularly meningococcal disease. Vaccination and appropriate risk-mitigation measures are therefore essential, although vaccination does not eliminate the risk entirely [35,41,42,45]. The available trial and extension data also remain insufficient to quantify rare infectious complications reliably over prolonged treatment periods.

B-cell-directed therapies demonstrate greater heterogeneity. Rituximab has the strongest clinical rationale in MuSK-Ab-positive disease, where depletion of CD20-positive B cells is supported by both pathophysiological considerations and clinical observations. However, evidence in this subgroup is derived predominantly from observational studies, which are limited by small sample sizes, differences in concomitant immunosuppression, and the absence of randomized controlled comparisons. The randomized RINOMAX trial demonstrated clinical benefit in newly diagnosed gMG, supporting the potential role of rituximab early in the disease course. However, the trial enrolled predominantly AChR-Ab-positive patients and included too few patients with other antibody profiles to establish efficacy specifically in MuSK-Ab-positive disease [62].

These findings should be interpreted alongside those of the BeatMG trial, which evaluated rituximab in patients with established, mild-to-moderate AChR-Ab-positive gMG receiving background prednisone therapy. BeatMG did not demonstrate a clinically meaningful steroid-sparing effect over 52 weeks and met its prespecified futility criterion [63]. The findings of these trials are not necessarily contradictory, as they differed in disease duration, treatment context, follow-up, and primary endpoints: RINOMAX assessed the achievement of minimal disease manifestations in newly diagnosed patients, whereas BeatMG primarily evaluated steroid reduction in established disease.

Inebilizumab provides phase III evidence for broader B-lineage depletion and supports this therapeutic concept beyond CD20 targeting [66]. In contrast, negative findings with belimumab and iscalimab indicate that targeting B-cell survival or T-cell-dependent B-cell activation does not uniformly translate into clinical efficacy [69,74]. These negative results should be distinguished from the preliminary positive findings reported with telitacicept and other emerging agents, for which the evidence remains limited by study size, design, or publication status. For mezagitamab and povetacicept, the available evidence should be characterized according to the specific clinical data pub-

lished for each agent rather than grouped with therapies that failed their primary endpoints [70,73].

The lack of clinical benefit with iscalimab, despite direct inhibition of CD40–CD154 signaling involved in T-cell-dependent B-cell activation, further illustrates that targeting a biologically relevant pathway does not necessarily result in meaningful clinical improvement. Differences in the immune-cell populations affected, the extent of pathogenic antibody suppression, and the stage or phenotype of disease may contribute to these divergent results. Safety considerations for B-cell- and plasma-cell-directed therapies include infusion reactions, infections, and, with sustained B-cell depletion, hypogammaglobulinemia, and other uncommon but potentially serious complications are also relevant to clinical monitoring. The duration of B-cell depletion and recovery of immunoglobulin levels may extend beyond the period assessed in pivotal trials, making longer-term observational data important when evaluating cumulative risks [84].

Evidence for cytokine and intracellular signaling therapies remains less mature. Tocilizumab has shown potential in refractory AChR-Ab-positive disease, but evidence remains largely non-randomized [75]. In the phase III LUMINESCE trial, satralizumab produced a statistically significant but relatively small improvement in MG-ADL compared with placebo in AChR-Ab-positive patients. Further development for gMG was subsequently discontinued by the sponsor; this decision should not be interpreted as proof that the drug has no biological or clinical effect, but it does limit its current therapeutic relevance [76]. Evidence for tofacitinib is limited by a small single-arm study, while remibrutinib remains under investigation [77,78]. These findings suggest that biological plausibility alone is insufficient to establish the clinical value of a targeted pathway and that future studies may need to identify patients with a more specific dependence on the pathway being targeted.

CAR-T therapy represents a different therapeutic concept, aiming to achieve profound depletion of pathogenic B-cell or plasma-cell populations rather than transiently suppressing downstream immune mechanisms. Early results with Descartes-08, KYV-101, CABA-201, and dual CD19/BCMA-directed approaches are promising, but the evidence remains preliminary. Most studies have enrolled small numbers of highly selected patients with severe or refractory disease and extensive previous treatment exposure. The safety profile also differs from that of conventional targeted therapies. Cytokine release syndrome, cytopenias, infections, and potential neurotoxicity require attention, while lymphodepleting conditioning may contribute to early hematological and infectious complications. The small numbers of patients studied and relatively short follow-up preclude reliable estimates of rare or delayed adverse events. Long-term sur-

veillance is particularly important to assess persistent immune-cell depletion, hypogammaglobulinemia, secondary infections, and potential late cellular-therapy complications [79–82].

Differences in CAR-T constructs, conditioning regimens, cellular targets, and follow-up further limit cross-study interpretation. Whether the clinical responses observed to date will translate into durable treatment-free remission or meaningful disease modification remains unknown. Antigen-specific strategies such as MuSK-CAAR-T may ultimately provide greater immunological selectivity, but remain preclinical [83].

Across therapeutic classes, safety and durability should therefore be considered alongside short-term efficacy. FcRn and complement inhibitors have a more extensive clinical evidence base than most emerging therapies, but their long-term risks and the consequences of continued treatment require ongoing evaluation. B-cell-directed therapies may produce more prolonged immunological effects, accompanied by risks related to sustained B-cell depletion and reduced immunoglobulin levels. CAR-T therapies may offer durable responses after a single treatment course, but their long-term safety and the possibility of treatment-free remission remain uncertain. These differences are clinically relevant when selecting therapy, particularly in patients requiring repeated treatment, those with recurrent infections, and those for whom prolonged immunosuppression is undesirable.

Current treatment recommendations reflect the increasing role of targeted therapies in selected patients with gMG. The 2020 International Consensus Guidance recommended rituximab for refractory MuSK-Ab-positive disease and eculizumab for AChR-Ab-positive patients with severe, refractory gMG [9]. The 2023 German guideline subsequently incorporated newer therapies, recommending eculizumab, ravulizumab, or efgartigimod for highly active AChR-Ab-positive gMG, while recommending rituximab for highly active MuSK-Ab-positive disease. For LRP4-Ab-positive and seronegative gMG, targeted treatment remains supported by substantially less clinical evidence [85].

More recent consensus work has shifted the focus from whether targeted therapies are effective to when they should be introduced and how treatment should be adapted over time. The 2026 international Delphi consensus supports consideration of novel therapies when clinically relevant symptoms persist despite conventional treatment, when treatment-related toxicity limits long-term management, or when rapid disease control is required [86]. The 2026 German-Austrian expert opinion provides more specific guidance for patients already receiving targeted therapy. In patients with an inad-

equate or waning response to an FcRn inhibitor, switching to another FcRn inhibitor or to a C5 inhibitor may be considered, while patients with an inadequate response to C5 inhibition may be switched to another C5 inhibitor or to FcRn inhibition. The choice of the subsequent agent should take into account the reason for treatment change, previous response, treatment duration, safety, and practical aspects of administration [87].

These recommendations address an important gap in the clinical trial literature, as most pivotal studies evaluated individual agents against placebo rather than directly comparing treatment sequences.

The major unmet need is therefore the definition of optimal treatment sequencing. Pivotal trials have generally evaluated individual therapies against placebo rather than against other targeted agents, and their populations differ substantially in antibody status, disease duration, previous treatment exposure, and disease severity. It remains unclear whether inadequate response or loss of response to one mechanism should preferentially prompt switching within the same therapeutic class or a change to a different immunological target. Future studies should prioritize head-to-head comparisons and prospective sequencing strategies, particularly in MuSK-Ab-positive, LRP4-Ab-positive, and seronegative gMG. Long-term studies are also needed to determine whether targeted therapies can reduce cumulative corticosteroid exposure, permit sustained treatment-free remission, or modify the long-term course of disease.

### Limitations

This narrative review was limited by the non-systematic selection of sources and restriction to English-language publications, which may have introduced selection and language bias. Some emerging therapies were represented by conference abstracts or clinical trial registry records rather than full peer-reviewed publications, limiting the completeness and certainty of the available information. Differences in study design, patient populations, outcome definitions, and follow-up duration also limited comparisons across therapies.

## CONCLUSIONS

Targeted therapies acting on IgG recycling, complement activation, and B-cell pathways have expanded treatment options for generalized myasthenia gravis. The most

extensive clinical evidence supports FcRn and complement inhibition, although its applicability varies by autoantibody status and study population. Evidence for B-cell-directed therapies differs by agent and antibody subgroup; support for rituximab in MuSK-Ab-positive disease comes predominantly from observational studies. Evidence for cytokine and intracellular signaling inhibitors remains heterogeneous, and their clinical role is uncertain. CAR-T cell therapies remain experimental, with preliminary clinical results and unresolved questions regarding long-term safety and durability of response.

The applicability of the available evidence depends on autoantibody status, disease activity, previous treatment exposure, and agent-specific safety considerations. Differences in trial populations and the scarcity of direct comparisons prevent reliable ranking of therapies or identification of an optimal treatment sequence. Further comparative and long-term studies are needed to establish optimal treatment sequencing, characterize long-term safety, and determine whether clinical benefits translate into sustained reductions in cumulative corticosteroid exposure or durable treatment-free remission.

## DISCLOSURE

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All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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## Conflict of Interest

The authors declare no conflict of interest.

## Use of Artificial Intelligence

Artificial intelligence tools, including ChatGPT and other OpenAI systems, were used for language refinement and structural improvement. All changes made with the assistance of artificial intelligence were reviewed and verified by the authors. The authors take full responsibility for the final content of the manuscript.

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