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REVIEW ARTICLE

Refocusing generalized myasthenia gravis: Patient burden, disease profiles, and the role of evolving therapy

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Abstract

Background and purpose: Generalized myasthenia gravis (gMG) continues to present significant challenges for clinical management due to an unpredictable disease course, frequent disease fluctuations, and varying response to therapy. The recent availability of new pharmacologic therapies presents a valuable opportunity to reevaluate how this disease is classified, assessed, and managed and identify new ways to improve the clinical care of patients with gMG.

Methods: Narrative review was made of publications identified via searches of PubMed and selected congresses (January 2000–September 2022).

Results: New consensus definitions are required to ensure consistency, to better characterize patients, and to identify patients who will benefit from specific drugs and earlier use of these agents. There is a need for more frequent, standardized patient assessment to identify the cause of motor function deficits, provide a clearer picture of the disease burden and its impact on daily living and quality of life (QoL), and better support treatment decision-making. Novel approaches that target different components of the immune system will play a role in more precise treatment of patients with gMG, alongside the development of new algorithms to guide individualized patient management.

Conclusions: gMG has a physical, mental, and social impact, resulting in a considerable burden of disease and substantially decreased QoL, despite standard treatments. The availability of novel, targeted treatments that influence key pathological mediators of gMG, together with new biomarkers, offers the potential to optimize patient management and ultimately enables a greater number of patients to achieve minimal manifestation status and a reduced burden of disease.

KEYWORDS
classification, disease burden, generalized myasthenia gravis, pathophysiology, targeted therapy

INTRODUCTION

Generalized myasthenia gravis (gMG) is a rare, chronic immunoglobulin G-mediated neuromuscular autoimmune disease that causes debilitating muscle weakness [1, 2]. Up to 18% of patients with gMG will experience a potentially life-threatening myasthenic crisis with respiratory failure requiring mechanical ventilation [3].

gMG is characterized by the presence of antibodies to acetylcholine receptors (AChRs) in approximately 80% of patients, leading to signaling blockade, internalization and destruction of AChRs, and complement activation, all of which result in impaired neuromuscular transmission (Figure 1) [4, 5]. A small number of patients have antibodies against muscle-specific kinase (MuSK) or lipoprotein receptor-related protein 4 (LRP4) [6]. Patients with gMG are classified into subgroups based on the presence of serum antibodies and clinical features (Table 1) [6]. MuSK-MG exhibits more focal muscle involvement and muscle wasting than AChR-MG [7], whereas LRP4-MG seems to have an earlier disease onset and milder disease severity than AChR-MG; both MuSK-MG and LRP4-MG have a predominance in females [8].

Despite an advanced understanding of the pathophysiology of gMG and an increasing spectrum of therapeutic approaches, including symptomatic treatment, immunomodulating therapies, and thymectomy, this disease still presents significant challenges for patients and their physicians. These include a variable, unpredictable disease course, differing response to specific therapies, and frequent diurnal disease fluctuations that impact patients' ability to perform daily activities.

A proportion of patients with gMG (generally considered to be approximately 15%) do not respond to standard therapies and are considered to have so-called "refractory" MG [13]. The proportion of individuals reported as having refractory MG is highly variable, depending on the criteria used [14]. In refractory patients, disease burden

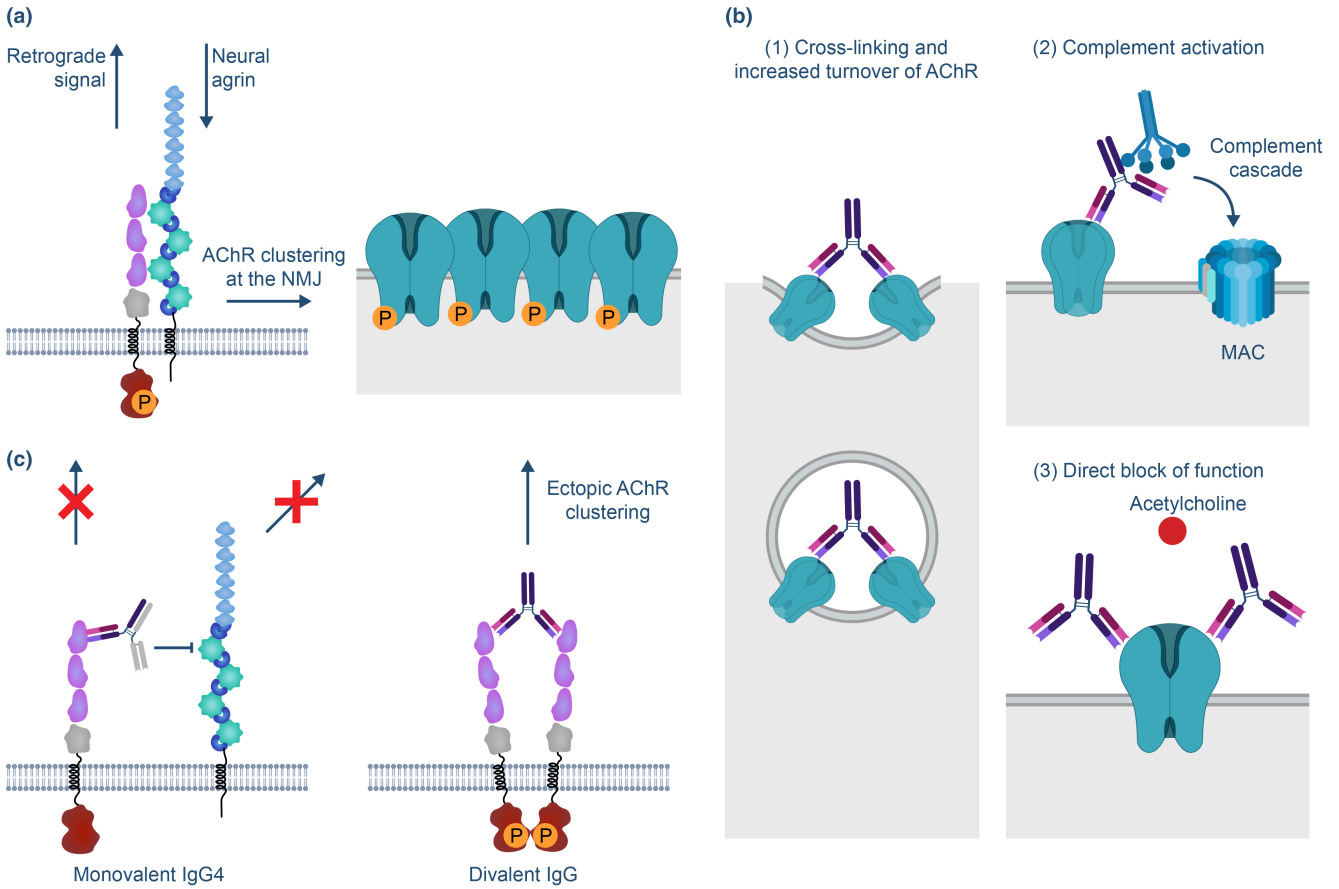

FIGURE 1 Main immunopathogenic mechanisms of the acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) myasthenia gravis (MG) disease subgroups. Pathogenic mechanisms of MG autoantibodies at the neuromuscular junction (NMJ). (a) At the healthy NMJ, neural agrin stimulation induces interaction between lipoprotein receptor-related protein 4 (LRP4) and MuSK, leading to MuSK autophosphorylation and activation and the phosphorylation and clustering of AChRs. A retrograde signal for presynaptic development is sent via LRP4. (b) MG antibodies of immunoglobulin (Ig) G1 and IgG3 subclass against AChR have three pathogenic mechanisms: (i) cross-linking and increased turnover of AChR leading to reduced AChR levels at the NMJ [23]; (ii) activation of the classical complement cascade, formation of the membrane attack complex (MAC), and complement-mediated damage of the postsynaptic membrane; and (iii) direct block of function by preventing the binding of acetylcholine [19]. (c) Bispecific IgG4 antibodies of IgG4 subclass against MuSK bind monovalently to MuSK and block LRP4–MuSK interaction, thus interrupting the agrin–LRP4–MuSK–Dok7 signaling axis and causing reduced densities of AChR at the synapse. A further effect is the disruption of a retrograde signal from LRP4 to the motor neuron. Divalent binding of MuSK IgG leads to dimerization, autophosphorylation, and activation of MuSK independent of agrin stimulation and causes the formation of ectopic AChR clusters. Created with BioRender. Reproduced from: Koneczny I, Herbst R. Myasthenia gravis: pathogenic effects of autoantibodies on neuromuscular architecture. Cells. 2019;8(7):671; doi:10.3390/cells8070671. Licensed under CC BY 4.

TABLE 1 Characteristics of MG disease subgroups [5, 6, 9–12].

MG subtype	Antibody	IgG subtype	Age at onset	Sex	Thymus pathology
Early onset	AChR	Mainly IgG1 and IgG3	<50 years	More frequent in females than males (F:M ratio 3:1)	Thymic lymphofollicular hyperplasia
Late onset	AChR	Mainly IgG1 and IgG3	>50 years	Slightly more frequent in males than females (F:M ratio 1:1.15) especially after 60 years of age	Usually normal (age-related thymus atrophy); rarely hyperplasia
Thymoma	AChR	Mainly IgG1 and IgG3	Varies		Thymoma
Ocular	AChR in 50% of patients; rarely MuSK	AChR: mainly IgG1 and IgG3; MuSK: mainly IgG4	Varies		Variable; hyperplasia in some patients
MuSK	MuSK	Mainly IgG4	Usually young adults; rarely in very old or children	85% female	Normal
Seronegative	None		Varies		Hyperplasia in some patients
LRP4	LRP4	IgG1 and IgG2	Varies but patients tend to present before 50 years of age	Female predominance (F:M ratio 5:1)	Variable (normal, thymoma, thymic lymphofollicular hyperplasia)
East Asian	Low titer AChR		Prepubertal; <10–15 years but also very early onset (e.g., 1 year)	F:M ratio 1.3–1.6:1	Variable; hyperplasia in some patients

Abbreviations: AChR, acetylcholine receptor; F, female; IgG, immunoglobulin G; LRP4, lipoprotein-related protein 4; M, male; MG, myasthenia gravis; MuSK, muscle-specific kinase.

is particularly high and is related to disability from the disease itself, the need for regular use of treatments and their associated side effects, and the psychological and socioeconomic consequences of gMG that impact daily living, employment, and quality of life (QoL) [15].

Novel treatments that influence key pathological mediators of gMG are in development or have recently been approved. The availability of new pharmacologic therapies for this challenging neuromuscular disease offers an opportunity to reevaluate and improve how it is classified, assessed, and managed, as well as address particular needs and challenges to enhance the clinical care of patients with this disease.

This narrative review examines current challenges in the management of gMG for both physicians and patients and considers how recent and continuing advances will impact the treatment landscape and patient outcomes.

METHODS

A nonsystematic search of PubMed and selected congresses was performed to identify relevant English language publications published between 1 January 2000 and 30 September 2022 using the terms "generalized myasthenia gravis", "burden", "classification", "quality of life", and "treatment OR therapy". Key areas of focus identified by the authors for this review were patient characteristics, current approaches to management, disease and socioeconomic burden, and new pharmacologic therapies recently approved or under investigation for gMG.

RESULTS

Currently available treatments for gMG

Symptoms of gMG are typically managed by acetylcholinesterase inhibitors, such as pyridostigmine (first approved for medical use in 1955), and immunosuppressive drugs, such as corticosteroids, azathioprine, and mycophenolate mofetil [16]. Although these drugs are widely used off-label in several countries and have been used in clinic over many years [17], some randomized controlled trials have not provided evidence of their efficacy in gMG (see Table S1). Adverse events (AEs) with the use of standard immunosuppressive therapies include gastrointestinal events, infections, leukopenia, pancreatitis, and an increased risk of neoplasms.

Thymectomy is recommended for adults aged <50 years with nonthymomatous gMG and AChR-antibody (AChR-Ab)-positive gMG early in the disease course to improve clinical outcomes [18], but is used in patients aged up to 65 years in clinical practice. Thymectomy may also be considered in patients without detectable AChR-Ab if they fail to respond adequately to immunosuppressive therapy or to minimize intolerable side effects [18]. In the randomized MGTX trial

in adults with nonthymomatous gMG (disease duration < 5 years), thymectomy plus prednisone was associated with a lower average Quantitative Myasthenia Gravis (QMG) score compared with prednisone alone over a 3-year period ($p < 0.001$) [19]. Patients who underwent thymectomy had a lower average requirement for prednisone, and fewer patients required immunosuppression with azathioprine or hospitalization for exacerbations compared with those who received prednisone only [19]. A recent meta-analysis found that patients with late onset nonthymomatous MG had a lower chance of achieving clinical remission after thymectomy than patients with early onset disease. Compared with conservative treatment, thymectomy did not show a superior benefit in terms of clinical and pharmacological remission in patients with late onset MG [20].

For patients in myasthenic crisis, pharmacologic interventions include intravenous immunoglobulin G (IgG), plasma exchange, or immunoadsorption. Common side effects associated with intravenous IgG include headache, fever, nausea, and injection site discomfort, and serious complications include aseptic meningitis, cardiac arrhythmia, thrombocytopenia, and arterial or venous thrombosis [3]. Common side effects of plasma exchange include fever, symptoms from hypocalcemia, transient decreases in blood pressure, and tachycardia, and serious complications include hemodynamic instability, cardiac arrhythmia, myocardial infarction, and hemolysis [3]. In addition, for plasma exchange, infections arising from the use of percutaneous central catheters is a serious common consequence that limits their long-term use.

The anti-CD20 monoclonal antibody (mAb) rituximab is recommended for off-label use in some national guidelines for gMG. This drug failed to demonstrate efficacy across several outcomes in patients who were AChR-Ab-positive in the phase 2 BEATMG randomized controlled trial [21]. However, data from the RINOMAX randomized controlled trial suggested some benefit after early treatment with rituximab, despite no improvement in Myasthenia Gravis Activities of Daily Living (MG-ADL) and QMG scale scores. In contrast, several observational studies and meta-analyses suggest that rituximab is effective in patients with MuSK-MG and may provide long-term benefit [22–26]. Based on this evidence, rituximab is increasingly being used early in the disease course in patients with MuSK-positive MG with the aim of inducing rapid and sustained remission [27]. Commonly reported AEs with rituximab include infusion-related reactions and infections [22, 24, 28]. Progressive multifocal encephalopathy is extremely rare in patients with MG, including those with exposure to rituximab [18, 29]. Secondary hypogammaglobulinemia and an associated increased risk of infection have also been reported with long-term rituximab use [30].

Eculizumab is a humanized mAb that binds to terminal C5 complement protein, prevents membrane attack complex formation, and reduces damage caused by complement-fixing AChR antibodies [18, 31, 32]. Eculizumab is approved by the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan for the treatment of refractory gMG in patients who are AChR-Ab-positive. In the phase 3 REGAIN study, the primary analysis for change in the MG-ADL score from baseline to week 26 (measured by worst-rank analysis of covariance) showed no significant difference between eculizumab and placebo ($p = 0.0698$) in patients with AChR-positive refractory gMG [33]. Prespecified and post hoc sensitivity analyses did show improvements in MG-ADL score with eculizumab relative to placebo, regardless of background immunosuppressive therapy, which were maintained through 3 years of eculizumab treatment in the long-term extension study [34]. Common treatment-related AEs with eculizumab include headache, upper respiratory tract infection, and nasopharyngitis. The most frequent serious AEs were infections [33]. Ravulizumab, a longer acting complement inhibitor that is administered intravenously, has recently been approved by the EMA and zilucoplan, which inhibits C5 and C6 and is administered subcutaneously, may become available in Europe in the near future. Other complement inhibitors are also in development (Table 2).

Efgartigimod is a novel antagonist of the neonatal Fc receptor (FcRn), which is responsible for recycling IgG antibodies and autoantibodies [35]. It was approved by the FDA in December 2021 for the treatment of gMG in patients who are AChR-Ab-positive, and by the EMA as an add-on therapy in the same patient population in August 2022 (Table 2). Approval was granted by the PMDA in January 2022 for the treatment of gMG in patients who do not have sufficient response to glucocorticoids or nonsteroidal immunosuppressive therapies. In the phase 3 ADAPT trial, a significantly higher proportion of AChR-positive patients were MG-ADL responders during the first treatment cycle with efgartigimod versus placebo (68% vs. 30%, $p < 0.0001$) [35]. Similarly, a higher proportion of patients in the efgartigimod arm were QMG responders in the first cycle compared with those in the placebo arm (63% vs. 14%, $p < 0.0001$). Efgartigimod was well tolerated, with most AEs being mild or moderate in severity, and a low incidence of infusion reactions (efgartigimod 4% vs. placebo 10%). Infections occurred in 46% of patients treated with efgartigimod and 37% of placebo-treated patients [35]. Other FcRn inhibitors have been investigated or are under evaluation in clinical trials (Table 2).

Disease burden in gMG

Despite the use of recommended therapies within the current gMG treatment paradigm, some patients continue to experience a substantial disease burden, reduced QoL, and diminished social functioning and emotional well-being. The burden of gMG may be related to clinical aspects of the disease (e.g., unpredictability of the disease course, treatment burden, persistence of symptoms), its broader physical and psychosocial impact, or the ability of the individual patient to cope with the consequences of gMG.

Owing to the chronic nature of gMG, regular long-term treatment is required. Although immunosuppressive therapies are effective in many patients with gMG, their prolonged use is associated with safety issues, and for many patients, immune system suppression is not sufficient to adequately control symptoms or restore

their QoL. Unsurprisingly, patient-reported outcome (PRO) studies indicate that 33%–47% of patients with gMG are dissatisfied with the management of their symptoms [48, 49]. Patients with gMG also frequently have comorbidities or develop treatment-related complications, both of which may impact outcomes and further contribute to the overall patient burden.

An analysis of qualitative data describing patients' lived experience of gMG identified several key themes relating to the burden of disease [50]. These include the impact of living with fluctuating and unpredictable muscle weakness requiring constant adaptation of daily routines together with feelings of social isolation and loss of life control due to unresolved symptoms, which in turn may cause anxiety, frustration, guilt, anger, loneliness, and depression [50]. There may be reluctance among patients and their physicians to make changes to treatment, even if symptoms are not optimally managed. This may be due to the length of time needed to see the benefits of newly initiated treatments, concerns over side effects, or patients having adapted to coping with their disability and having resilience [50]. Patients, particularly those not being treated by specialists, sometimes feel that health care providers do not always fully understand their disease and its impact and only assess clinically relevant symptoms and AEs, without considering those aspects of the condition with the greatest impact on patients' daily lives. There may also be a disconnect between patients and physicians in their perceptions of what is considered a satisfactory level of symptom control and QoL [50]. Although the limitations inherent in qualitative research should be acknowledged, these findings nonetheless make a valuable contribution to our understanding of the burden of gMG.

The ongoing MyRealWorld MG study is being conducted in nine countries across Asia, Europe, and North America to better understand the impact and burden of MG on adult patients and their families. Data on diagnosis, symptoms, treatment, daily activities, and QoL are being collected via a patient app and self-report questionnaires.

Socioeconomic consequences of gMG

MG has a typical age at onset of 20–40 years, placing a heavy socioeconomic burden on people of working age [51]. Physical impairments such as reduced muscle strength and fatigue, mobility problems, decreased ability to communicate, diplopia, and an inability to drive can impact patients' ability to work, leading to loss of productivity, reduced working hours, and early retirement from the workplace [15, 51]. A systematic review and meta-analysis of data published between 2000 and 2019 found that overall, half of patients with MG were unemployed, with even higher levels of unemployment among younger patients with gMG [51]. In a multicenter, cross-sectional study in Japan in which patients completed a questionnaire on social disadvantages resulting from MG and its treatment, unemployment or a job transfer against their will was experienced by 31.3% of patients following the onset of MG, and 35.9% of patients experienced a decrease in income [52]. Factors contributing to adverse socioeconomic outcomes were illness severity, prednisolone dose and duration, long-term treatment, and a depressive state and change in appearance after treatment with oral corticosteroids.

Opportunities to improve the management of gMG

Need for improved clinical assessment and assessment of disease burden

There is a need for more frequent, thorough, and standardized patient assessment to identify the cause of motor function deficits (which may not be directly related to gMG), evaluate the impact of the disease on daily living and QoL, better support decisions regarding choice of treatment, and ultimately improve patient management.

Inconsistent methods of assessment and use of nonobjective tools for assessing disease severity and prognosis combined with infrequent assessment mean that patients' level of motor disability is not always fully recognized in gMG. Furthermore, there is an underappreciation of the value of PROs for measuring QoL and the achievement of life milestones.

Disease fluctuations in gMG mean that objective assessments may not adequately reflect patients' experienced symptom burden. Furthermore, the clinical presentation of MG can be complex, and broader symptoms are not always considered. General fatigue (i.e., lack of energy, physically and mentally) is a common symptom of gMG that is strongly correlated with disease severity and has a negative impact on QoL; however, there is poor awareness of this symptom among some physicians [53].

Consensus on approaches to the assessment of gMG symptoms is needed to provide a clearer picture of the disease burden and better support treatment decisions. A more consistent use of information and communication technology in clinical practice could help to fill the gaps that result from infrequent and inconsistent assessment and will allow for remote assessment of treatment efficacy and safety. This will soon become an essential tool for use with the pulsed treatment efgartigimod, as well as for home-infused and self-administered therapies.

Management of challenging disease profiles

The international consensus guidelines for the management of MG were updated in 2020 [18]. However, there remains no clear understanding of which patients have the most challenging-to-manage disease, which patients will require multiple treatments, and which patients may benefit from earlier treatment with alternative agents.

Furthermore, definitions of treatment-refractory MG are inconsistent, and use of this term is controversial. Older definitions fail to take into account the improved outcomes that are achievable with newer MG therapies [15]. Current descriptions of treatment-refractory MG focus on factors such as insufficient symptom response to standard care, frequent relapses requiring long-term treatment with immunosuppressive drugs, and inability to tolerate standard therapies. For example, the following definition of

TABLE 2 Current and recent clinical trials in patients with gMG.

Drug and mechanism of action	Mode of administration and dosing	Current or recent trial	Trial/approval status	Population
FcRn inhibitors				
Efgartigimod Human anti-FcRn IgG1 Fc fragment Reduces autoantibody levels and recycling	IV infusion, 4 per cycle (1 infusion per week) for a maximum of 3 cycles during the 26-week study [35]	ADAPT (phase 3) NCT03669588 and ADAPT+ OLE [36]	ADAPT completed and published [35] ADAPT+ ongoing [36] Approved by EMA, FDA, and PMDA (Japan)	Adults with MG (with or without AChR+) on a stable dose of ≥1 SOC treatment for MG ($N=167$) [35]; $n=151$ (91%) entered ADAPT+ [36]
Rozanolixizumab Human anti-FcRn IgG4 mAb Reduces autoantibody levels	SC injection, once weekly [37]	Phase 2a NCT03052751	Phase 2a Completed and published [37]	Phase 2a Adults with MG (AChR+ or MuSK+; $N=43$) [37]
		Phase 3 NCT03971422	Phase 3 Completed; interim results published [38]	Phase 3 Adults with gMG (AChR+ or MuSK+; $N=200$) [38]
Nipocalimab Human anti-FcRn deglycosylated IgG1 mAb Reduces autoantibody levels	IV infusion, once every 2 weeks for up to 24 weeks (blinded phase) then following entry to the OLE phase, once every 2 weeks (transitioning to once every 4 weeks if stable on prior dosing regimen) for up to 56 months	Phase 3 NCT04951622	Ongoing	Adults with MG ($N\approx180$)
Batoclimab (HBM9161) Human anti-FcRn IgG1 mAb Reduces autoantibody levels	SC injection, once weekly for 6 weeks (double-blind treatment phase) then every other week for 6 weeks (OLE phase) [39]	Phase 2 NCT04346888	Completed and published	Chinese adults with moderate to severe gMG (AChR+ or MuSK+; $N=30$) [39]
Complement inhibitors				
Eculizumab Humanized anti-C5 mAb Inhibits cleavage of C5 complement into C5a and C5b [17]	IV infusion, 900 mg once every week for 4 weeks (induction phase), 1200 mg for 1 week (interim phase), then regular maintenance doses of 1200 mg every 2 weeks (maintenance phase) [40]	REGAIN (phase 3) (NCT01997229) and OLE	Completed and published Approved by FDA for AChR+ gMG [17]	Adults with gMG ($N=125$) [33, 34]

Key primary and secondary end points and efficacy results in clinical trials	Key safety results in clinical trials
Primary: significantly higher proportion of MG-ADL responders during first treatment cycle with efgartigimod vs. placebo (68% vs. 30%; OR = 4.95, 95% CI = 2.21–11.53, $p < 0.0001$) [35] Secondary: higher proportion QMG responders in the first cycle with efgartigimod vs. placebo (63% vs. 14%, $p < 0.0001$) [35] In ADAPT+, the magnitude of clinically meaningful improvements in MG-ADL and QMG mirrored those observed at week 3 of cycle 1 [36]	Comparable incidence of TEAEs for efgartigimod (77%) vs. placebo (84%) Most frequently reported TEAEs for efgartigimod and placebo were headache (29% vs. 28%) and nasopharyngitis (12% vs. 18%) SAEs were reported in 4 (5%) and 7 (8%) patients in the efgartigimod and placebo groups Three patients per treatment group discontinued due to AEs [35] Similar incidence rates per year of SAEs between ADAPT and ADAPT+ (mean study duration = 363 days) [36]
Phase 2a Primary: improvements from baseline to day 29 in QMG for rozanolixizumab vs. placebo were not statistically significant (LS mean = −1.8 vs. −1.2, $p = 0.221$) [37] Secondary: Improvements in MG-ADL (LS mean = −1.8 vs. −0.4) and MGC (LS mean = −3.1 vs. −1.2) scores [37]	Phase 2a Comparable AE incidence for rozanolixizumab vs. placebo SAEs not reported with rozanolixizumab vs. 9% with placebo Most common TRAE was headache: 38% vs. 9% with placebo [37]
Phase 3 Significant reduction from baseline in MG-ADL at day 43 for rozanolixizumab at doses of ~7 and ~10 mg/kg vs. placebo; placebo-corrected mean improvement in MG-ADL of 2.586 points for ~7 mg/kg dose and 2.619 points for ~10 mg/kg dose (both $p < 0.001$ vs. placebo) [38]	Phase 3 Most TEAEs mild to moderate in intensity with rozanolixizumab [38] Higher proportion of TEAEs in active treatment arms vs. placebo (81.3% for ~7 mg/kg, 82.6% for ~10 mg/kg, and 67.2% for placebo) [38] Most frequently reported TEAEs were headache, diarrhea, pyrexia, and nausea [38]
Primary: change from baseline in MG-ADL score at 24 weeks Secondary: change over weeks 22 and 24 in QMG score; proportion of patients with ≥2-point improvement from baseline in MG-ADL score over weeks 22–24; MG-ADL score at weeks 1 and 2; or MG-ADL score at weeks 2–24 with ≤2 losses of improvement in MG-ADL score of ≥2 points during weeks 3–23; proportion of patients with MG-ADL score 0/1 over weeks 22–24 Efficacy results not yet published	Safety results not yet published
Primary: significantly greater reduction from baseline in MG-ADL score on day 43 with batoclimab vs. placebo ($p = 0.043$) [39] MG-ADL score changes from baseline to day 43 were −2.2 ± 0.9, −4.7 ± 0.6, and −4.4 ± 1.0 in the placebo, batoclimab 340 mg, and batoclimab 680 mg groups, respectively [39] Secondary: substantial and persistent clinical improvements in MGC, QMG, MG-ADL, and MG-QoL15r scores at day 43 [39]	Comparable AE incidence for batoclimab vs. placebo [39] Most AEs were mild [39] Serum albumin decreased dose-dependently with batoclimab, returning to normal range 6 weeks after study drug discontinuation [39] Serum cholesterol levels were increased with batoclimab [39] No SAEs reported [39] No discontinuations due to TEAEs [39] No deaths [39]
Primary: no significant difference between eculizumab and placebo for mean change from baseline in MG-ADL total score measured by worst-rank ANCOVA at 26 weeks ($p = 0.0698$) [33] Secondary: significant improvements in QMG, MGC and MG-QoL15 scores at week 26 [33] Beneficial treatment effects with eculizumab were sustained over the 3-year OLE [34]	Similar AE incidence for eculizumab vs. placebo [33] Most common AEs were headache, upper respiratory tract infection, nasopharyngitis, and gastrointestinal upset (nausea and diarrhea) [33] SAEs occurred in 15% vs. 29% of patients receiving eculizumab or placebo, respectively; most common were infections (3% with eculizumab vs. 10% with placebo) [33] No deaths or meningococcal infections occurred [33] Safety profile remained consistent between REGAIN and its OLE [34]

TABLE 2 (Continued)

Drug and mechanism of action	Mode of administration and dosing	Current or recent trial	Trial/approval status	Population
Ravulizumab Humanized anti-C5 IgG2/4 mAb Inhibits cleavage of C5 complement into C5a and C5b [41]	IV infusion, single loading dose on day 1, then regular maintenance doses from day 15 [42]	Phase 3 NCT03920293	Completed and published [42] Approved by EMA and FDA	Adults with MG, without prior treatment with a complement inhibitor, use of rituximab within 6 months of screening, or IVIg or plasma exchange within 4 weeks of randomization ($N = 175$) [42]
Zilucoplan Short 35-kDa macrocyclic peptide targeting C5/C5b Inhibits terminal complement/MAC activation	SC injection, daily [43]	RAISE (phase 3) NCT04115293	Completed	Adults with MG (AChR+; $N = 174$) [43]
B-cell inhibitors				
Belimumab Human anti-BlyS IgG1λ mAb Reduces B-cell differentiation and depletes circulating CD19 cell levels	IV infusion on weeks 0, 2, 4, 8, 12, 16, and 20 (plus SOC treatment for MG) [44]	Phase 2 NCT01480596	Completed and published [44]	Adults with MG (AChR+ or MuSK+), receiving a stable dose of ≥1 SOC treatment for MG ($N = 40$) [44]
Rituximab Chimeric anti-CD20 mAb Depletes CD20 cell levels	IV infusion, 4 per cycle (1 infusion per week) for 2 cycles (given during weeks 0–3 and 24–27) [21]	BeatMG (phase 2) NCT02110706	Completed and published [21]	Adults with MG (AChR+) receiving prednisone ≥15 mg/day ($N = 52$) [21]
	Single IV infusion [26]	RINOMAX (phase 3) NCT02950155	Completed and published [26]	Adults with new onset gMG ($N = 47$) [26]
Inebilizumab Humanized anti-CD19 IgGκ mAb Depletes CD19 cell levels	IV infusion on days 1, 15, and 183	MINT (phase 3) NCT04524273	Ongoing	Adults with MG (AChR+ or MuSK+), receiving a stable dose of corticosteroids, NSIT, or both ($N \approx 270$)
Mezagitamab Humanized anti-CD38 mAb [17] Depletes CD38 cell levels	SC injection 600 mg, once weekly [17]	Phase 2 NCT04159805	Ongoing	Adults with gMG ($N \approx 32$)
Satralizumab Humanized anti-IL-6 IgG2 recycling mAb Reduces inflammation and inhibits T- and B-cell activation and B-cell differentiation Engineered to have a prolonged half-life by dissociating from IL-6 in the acidic endosome, and recycling to the cell membrane to bind another IL-6 molecule in plasma [45]	SC injection 120 mg at weeks 0, 2, and 4 (loading dose), then every 4 weeks thereafter (maintenance dose) [45]	Phase 3 NCT04963270	Ongoing	Patients aged ≥12 years with gMG ($N \approx 240$) on a stable dose of therapy for gMG

Key primary and secondary end points and efficacy results in clinical trials	Key safety results in clinical trials
Primary: significant improvement from baseline in MG-ADL total score at week 26 (ravulizumab −3.1 vs. placebo −1.4; $p < 0.001$) Secondary: significant improvement from baseline through week 26 in QMG total score for ravulizumab vs. placebo ($p < 0.001$) [42] Improvements in MG-ADL and QMG scores observed within 1 week and maintained through week 26 [42]	No notable differences in AEs between the treatment groups [42]
Primary: placebo-corrected mean improvement of 2.12 points in MG-ADL score at week 12 ($p < 0.001$) Significant improvement in MG-ADL from week 1 Secondary: significant improvements in QMG, MGC, and MG-QoL15r from week 1 [43]	Similar rate of TEAEs with zilucoplan (76.7%) vs. placebo (70.5%); most common TEAEs were injection site bruising, headache, diarrhea, and MG worsening [43]
Primary: no significant difference between belimumab and placebo for mean change from baseline in QMG at 24 weeks ($p = 0.256$) Secondary: no significant differences between belimumab and placebo groups in MGC or MG-ADL scores at 24 or 36 weeks [44]	Similar incidence for belimumab vs. placebo in all AEs (78% vs. 91%) and treatment-related AEs (28% vs. 32%) SAEs not reported with belimumab vs. 5 events with placebo [44]
Primary: 60% of patients on rituximab achieved ≥75% reduction in mean daily prednisone dose during weeks 49–52 with clinical improvement or no significant worsening of symptoms in the 4 weeks prior to week 52% vs. 56% of those on placebo [21]	No safety signals were observed [21]
Primary: 71% of patients on rituximab vs. 29% on placebo had minimal disease manifestations defined as a QMG score of ≤4 and a daily dose of prednisolone of ≤10 mg/day at week 16, with no need of rescue treatment procedures during study weeks 9–16 ($p = 0.007$, probability ratio = 2.48, 95% CI = 1.20–5.11) [26]	Number of AEs and serious AEs greater with rituximab vs. placebo (81 vs. 44 and 6 vs. 4, respectively) [26] One patient on placebo arm had a myocardial infarction with cardiac arrest and one patient on rituximab experienced a fatal cardiac event [26]
Primary: change from baseline in MG-ADL at 52 (AChR+) and 26 weeks (MuSK+) Secondary: change in QMG, MGC, MG-QoL15r, and PGIC scores; time to first MG exacerbation; change in MG-ADL score (AChR+ only) at 52 (AChR+) and 26 weeks (MuSK+) Efficacy results not yet published	Safety results not yet published
Secondary: change from baseline in MG-ADL, QMG, MGC, or MG-QoL15r score up to 32 weeks; change from baseline in anti-AChR or anti-MuSK antibody levels up to 32 weeks; percentage of participants meeting minimal clinically important difference criteria in MG-ADL, QMG, or MGC scores up to 32 weeks Efficacy results not yet published	Primary: percentage of participants with TEAEs and SAEs, grade ≥3 TEAEs, AEs leading to mezagitamab discontinuation up to 32 weeks Safety results not yet published
Primary: change from baseline in MG-ADL score at 24 weeks in AChR+ population Secondary: change from baseline in QMG, MG-QoL15r, Neuro-QoL, or MGC scores at 24 weeks; proportion of MG-ADL, QMG, or MGC responders at 24 weeks; proportion of participants achieving minimal disease manifestation (total MG-ADL score = 0 or 1) at 24 weeks Efficacy results not yet published	Safety results not yet published

TABLE 2 (Continued)

Drug and mechanism of action	Mode of administration and dosing	Current or recent trial	Trial/approval status	Population
Cladribine Synthetic chlorinated analog of deoxyadenosine, converted to its active metabolite by deoxycytidine kinase and inactivated by 5′-nucleotidase (the ratio of these enzymes is high in lymphocytes vs. other cell types, making them a preferential target) [46] Elimination of autoreactive T and B cells, reduced inflammation [47]	SC injection 0.30 mg/kg over 2 consecutive days, repeated monthly until clinical response [46]	Prospective, open-label, pilot study [46]	Completed and published [46]	Adults with refractory, difficult-to-treat MG ($N = 13$) [46]
T-cell inhibitors				
CAR-T-cell therapy Descartes-08 (CD8+ investigational CAR-T-cell therapy: T cells expressing a chimeric antigen receptor directed against B-cell maturation antigen) Engineered to have a limited, predictable half-life [17]	IV infusion	Phase 1 NCT04146051	Ongoing	Adults with gMG ($N \approx 30$)
CAAR-T-cell therapy MuSK-CAAR T cells expressing a chimeric autoantibody receptor directed against autoreactive B cells Elimination of autoreactive B cells [17]	IV infusion	Phase 1 NCT05451212	Ongoing	Adults with MuSK+ MG and active disease ($N \approx 24$)
HSCT				
Elimination of autoreactive T and B cells [17]	IV infusion	Phase 1 NCT00424489	Terminated due to poor recruitment	Patients aged 15–65 years with refractory/severe autoimmune MG ($N = 9$)
		Phase 2 NCT00716066	Ongoing	Patients aged ≤70 years with a variety of autoimmune neurologic disorders, including MG ($N \approx 80$)

Abbreviations: AChR, acetylcholine receptor; AE, adverse event; ANCOVA, analysis of covariance; BlyS, B-lymphocyte stimulator; CAAR-T, chimeric autoantigen receptor; CAR-T, chimeric antigen receptor; CI, confidence interval; DLT, dose-limiting toxicity; EMA, European Medicines Agency; FcRn, neonatal Fc receptor; FDA, US Food and Drug Administration; gMG, generalized myasthenia gravis; HSCT, hematopoietic stem cell transplantation; Ig, immunoglobulin; IL, interleukin; IV, intravenous; IVIg, intravenous immunoglobulin; LS, least squares; mAb, monoclonal antibody; MAC, membrane attack complex; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis–Composite; MGFA-PIS, Myasthenia Gravis Foundation of America Post-intervention Status; MG-QoL15, Myasthenia Gravis Quality of Life 15-Item Scale; MG-QoL15r, Myasthenia Gravis Quality of Life 15-Item Scale–Revised; MuSK, muscle-specific kinase; Neuro-QoL, Quality of Life in Neurological Disorders; NSIT, nonsteroidal immunosuppressive therapy; OLE, open-label extension; OR, odds ratio; PGIC, Patient Global Impression of Change; PMDA, Pharmaceuticals and Medical Devices Agency; QMG, Quantitative Myasthenia Gravis; SAE, serious adverse event; SC, subcutaneous; SOC, standard of care; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

refractory MG was proposed by an international panel of experts in 2016: "status is unchanged or worse after corticosteroids and at least two other immunosuppressive agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning as defined by patient and physician" [54]. These definitions do not acknowledge that concomitant conditions (including depressive symptoms and other psychological factors), which may have arisen separately or as a result of living with a chronic disease such as gMG, will impact assessment and how patients experience their disease [50]. Depending on the criteria used,

Key primary and secondary end points and efficacy results in clinical trials	Key safety results in clinical trials
Primary: 11 of 13 patients achieved significant clinical improvement in MGC score at 6 months vs. baseline (mean MGC score of 6.3 vs. 15.1) Secondary: 9 of 13 patients reduced their dose of steroids at 6 months vs. baseline (prednisolone dose decreased from 9.5 to 1.9 mg) All 13 patients had decreased lymphocyte levels No patients required IVIg or plasma exchange treatments [46]	No AEs occurred on-study [46]
Primary: change from baseline in MG-ADL score at 12 weeks Secondary: change from baseline in QMG, MG-QoL15r, or MG composite scores, or MGFA-PIS at 12 weeks (overall and in crossover patients); change from baseline in MG-specific autoantibody titers at 24 weeks; effect of single or multiple infusions of Descartes-08 by standard clinical assessment scales (QMG, MG-QoL15r, or MG composite scores, MGFA-PIS) over 24 weeks Efficacy results not yet published	Primary: safety and tolerability Safety results not yet published
Other outcomes: use of concomitant MG therapies; clinical symptom assessment using MG-ADL, QMG, or MGC scores up to 36 months; quality-of-life assessment using MG-QoL15r up to 36 months Efficacy results not yet published	Primary: incidence of AEs, DLTs, and MuSK-CAART-related AEs Safety results not yet published
Primary: survival for up to 5 years At termination, 3/9 patients had died ($n=1$ late lymphoma, $n=1$ insulin-induced hypoglycemia, $n=1$ sepsis bacteremia)	At termination, AEs: $n=1$ bowel obstruction (resolved without surgical intervention), $n=2$ pneumonia (resolved with antibiotics)
Secondary: disease response Efficacy results not yet published	Primary: incidence of grade 4/5 regimen-related toxicity Secondary: transplant-related mortality; exacerbation of disease symptoms Safety results not yet published

the proportion of patients defined as having refractory MG can vary from 3.0% to 40.1% [14].

As new treatments for gMG continue to become available, further consensus definitions will be needed to better characterize patients, define those patients who may become refractory to treatment in the future, and evaluate which patients will benefit from specific drugs and earlier use of these agents. In the future, failure of off-label immunosuppressive drugs should be considered as a mandatory transition to starting new, approved treatments.

The guideline-recommended treatment goal for MG defined in 2016 is at least minimal manifestation status (i.e., no symptoms or functional limitations from MG but some weakness of some muscles on examination), with no more than grade 1 AEs [54]. Current treatment approaches require a compromise between disease improvement and side effects, meaning that some patients with gMG are unable to meet these criteria. With the availability of new treatment options, it is anticipated that more patients will be able to achieve a minimal symptom burden.

Various individual patient characteristics can make the effective management of gMG more challenging. These include the presence of comorbidities, treatment-related complications, thymoma, pregnancy, and poor response to standard therapies. Considerations for the management of patients with challenging gMG disease profiles are summarized in Table 3.

Additional challenges include the assessment and management of symptoms that may not be readily measured using typical tools and determination of the optimal sequence of therapies, particular as more treatments become available.

The evaluation of new treatments for MG presents an opportunity to reassess the objectives of clinical trials and the outcome measures used. End points of clinical trials in MG are often remission or minimal manifestation status, which is based more on physician examination than the patient's assessment of their own health. The MG-ADL has typically been included in clinical trials as a secondary end point but is increasingly used as a primary end point, analyzed as change from baseline in total score, using a responder threshold to indicate clinical improvement, or by using a cutoff to indicate minimal symptoms [55]. However, a limitation of this instrument is that it does not capture the entire patient experience. The minimal symptom expression (MSE), which occurs when MG symptoms are expressed at a minimal level, is an emerging clinical trial end point to assess treatment efficacy [55]. The patient-acceptable symptom state (PASS) is a holistic evaluation of the patient's satisfaction with their overall disease burden determined by a single question that identifies health scores associated with feeling well, rather than just better, after treatment. A study has established PASS thresholds for commonly used MG health scales in a validation cohort of 257 patients with MG [56]. Using these thresholds, patients who self-reported acceptable health states had lower scores in all measures of disease severity and better QoL than those who did not [56]. The use of thresholds based on the patient's perspective will be of great interest to better define secondary end points in clinical trials.

DISCUSSION

gMG has a physical, mental, and social impact on a diverse patient population, resulting in a considerable burden of disease and substantially decreased QoL despite available treatments. Notwithstanding advances in our knowledge of the pathophysiology of gMG and the introduction of different therapeutic approaches, many unmet needs remain.

To fully understand patient needs and support improved clinical assessment and treatment decision-making, new PRO instruments are required that can accurately assess aspects of gMG such as disease fluctuations, fatigue, anxiety, and depression. Objective assessment measures that are reproducible, reliable, and easy to use by both physicians and patients are also needed.

Recently, there has been a focus on developing novel, targeted therapies with the potential to optimize the management of patients with gMG, and ultimately enable more patients to achieve minimal manifestation status and a reduced burden of disease. Three newly approved treatment options are available that offer the potential to address some of the current unmet needs in gMG: the complement inhibitors eculizumab and ravulizumab and the first-in-class FcRn antagonist efgartigimod. The latter has a more selective action than broadly immunosuppressive steroids, nonsteroidal immunosuppressive therapies, and complement inhibitors and, in the global clinical development program, demonstrated rapid efficacy in a broad population of patients with gMG with a durable clinical benefit.

Ongoing and recently completed trials are evaluating various immunotherapies in MG including (i) the complement inhibitor zilucoplan; (ii) the FcRn inhibitors batoclimab, nipocalimab, and rozanolixizumab; (iii) the B-cell inhibitors belimumab, inebilizumab, mezagitamab, and satralizumab; (iv) T-cell inhibitors (chimeric autoantibody receptor T-cell therapy and chimeric antigen receptor T-cell therapy); and (v) hematopoietic stem cell transplantation (Table 2). Several other narrative reviews also provide an overview of emerging novel therapies for gMG/MG [17, 27, 57–60].

The introduction of eculizumab, ravulizumab, and efgartigimod, and evidence from ongoing trials, will inform the positioning of new therapies within the gMG treatment pathway and identify further opportunities to improve patient management. These new therapies provide hope for patients with drug-refractory gMG. Other patients who may derive benefit from emergent new drugs include those with moderate or severe side effects or comorbidities that limit the use of currently available drugs and patients who have acute, severe weakness, because one of the benefits of these new drugs is that they have a relatively rapid onset of action compared with conventional treatments [61]. The availability of new drugs with different mechanisms of action that may be used earlier in the disease course could reduce or even eliminate the need for chronic corticosteroid-based treatments and off-label therapies as well as offering possibilities to personalize treatment. Novel treatment approaches that target different immune system components will play a role in the more precise treatment of patients with gMG, alongside the development of new algorithms based on age, sex, thymus histopathology, antibody subtype, additional biomarkers, and treatment options for comorbid autoimmune diseases for more individualized management.

Although these new drugs have demonstrated considerable potential, they are not without their limitations. Newer agents have all been evaluated in patients on stable immunomodulatory treatment with conventional agents and not as standalone therapies [17]. Additional data from open-label extension studies and the real-world setting will be needed to address unanswered questions

TABLE 3 Considerations for the management of challenging gMG disease profiles.

Patient characteristic	Key points for consideration
Side effects on pyridostigmine therapy	• Although pyridostigmine is the most widely used symptomatic therapy, side effects—particularly gastrointestinal events—are very common and are intolerable in some patients; these are usually dose dependent and may require dose reduction or slower titration. • Severe side effects are rare with pyridostigmine treatment. • Elderly patients may experience syncope even with low doses of pyridostigmine. High doses of pyridostigmine can lead to cholinergic crisis that results in worsening of neuromuscular weakening due to an excess of acetylcholine. • Pyridostigmine may exacerbate MuSK gMG.
Inadequate disease control or side effects on corticosteroid therapy	• Corticosteroids remain the cornerstone of gMG therapy alongside symptomatic medication. However, these drugs do not provide sufficient disease control for many patients. For example, less than half (44%) of patients with AChR-Ab-positive gMG achieved a satisfactory response (i.e., remission/MMS) after 2 years of low-dose prednisone monotherapy. • Many patients require long-term corticosteroid treatment, which is associated with the risk of serious side effects through both mineralocorticoid (e.g., water retention, hypertension) and glucocorticoid (e.g., diabetes mellitus, osteoporosis, hormonal and mood disorders) activity. • Patients on corticosteroid therapy require regular monitoring to ensure early identification and management of AEs. • Patients not responding to high-dose or long-term corticosteroids are usually treated with one or more other immunosuppressive drugs or, less commonly, chronic IVIg. These patients require further clinical and analytical assessment and monitoring of drug side effects and have an increased hospital dependence that, together, increase their overall disease burden.

Poor compliance/ adherence	• AEs with both traditional and newer gMG treatments may contribute to poor compliance and adherence with medication.
	  • In a prospective study of patients with MG followed from 2003 to 2007, almost one quarter reported poor treatment compliance, and this was associated with unsatisfactory outcomes. In cross-sectional studies, 45%–61% of patients with MG were not treatment adherent, and these patients tended to have greater muscle weakness, poorer QoL, and higher risk of depression.
	  • AEs with IVIg include headache, urticaria, nephrotoxicity, thrombotic events, myalgia, fever, and influenzalike symptoms.
	  • When PLEX is administered on an outpatient basis with peripheral access, typical AEs include hypocalcemia, hypotension, fever, coagulopathy, and allergic reactions. However, PLEX is often considered to be a complex treatment with a need for hospitalization and central venous access, which may be associated with complications such as pneumothorax, line infection, and thromboembolism.
	  • AEs with eculizumab include headache, nausea, diarrhea, infusion-related reactions, nasopharyngitis, arthralgia, severe meningococcal infection, other infections, and musculoskeletal pain.
	  • AEs with ravulizumab include headache, diarrhea, upper respiratory tract infection, and nasopharyngitis.
	  • AEs with efgartigimod include headaches, allergic reactions, infections, leukopenia, and myalgia.
	• The convenience of a particular dosing regimen (i.e., subcutaneous vs. intravenous and at-home vs. in-hospital administration) may be associated with the likelihood of therapeutic compliance and adherence.
	• These findings emphasize the need to consider the patient's motivation/desire for use of a particular treatment/mode of administration and for routine assessment of medication compliance and adherence.
	• Some newer treatments being inaccessible or unfunded for some patients will also impact compliance and adherence to a recommended treatment regimen.

Comorbidities	• There is a high prevalence of comorbidities in patients with gMG, particularly among elderly people, and this can limit the treatment options available because of contraindications. The presence of multiple comorbidities is associated with poorer outcomes in MG.
	• Diabetes mellitus is a common comorbidity of late onset MG, posing one of the greatest challenges for patient management. Recent research conducted using a rat model found that diabetes promotes both adaptive and innate immunity and worsens symptoms of experimental MG.
	• Corticosteroids are usually contraindicated in patients with diabetes due to the risk of glucose control disruption leading to acute decompensation.
	• More than half of patients with MG report weight gain as a side effect of treatment with medications such as prednisone, which can increase appetite. Muscle weakness also limits activity, which increases the risk of weight gain.
	  • A cross-sectional prevalence cohort study based on patient-reported symptom severity showed that obesity was associated with high MG-ADL scores, which may reflect that the treatment of patients with obesity is challenging, particularly as they often have other cardiovascular comorbidities, such as high blood pressure and diabetes mellitus.
	  • Corticosteroids are contraindicated in patients with obesity. For these patients, immunosuppressive therapy may be prescribed; in the case of failure, newer therapies (e.g., efgartigimod or eculizumab) could be considered.
	  • In patients with severe obesity, IVIg may be administered on a regular basis while awaiting the effect of immunosuppressants. IVIg dosing should be based primarily on lean body mass.

(Continues)

TABLE 3 (Continued)

Patient characteristic	Key points for consideration
Other autoimmune conditions	• Coexisting autoimmune conditions are frequent in patients with MG (9%–23%), most commonly thyroid disease, RA, or SLE, reflecting shared pathogenic mechanisms. • Concordant autoimmune disease occurs most frequently in females and those with early onset gMG, and is associated with a poorer prognosis compared with patients with MG alone. • In these patients, a common treatment strategy is sometimes possible. The choice of immunosuppressive treatment, when necessary, must be discussed in a multidisciplinary manner with specialists in charge of the other autoimmune diseases (e.g., rheumatologists). • The spectrum of drugs that may be effective in patients with MG and concordant autoimmune diseases will be enlarged by the availability of new B-cell-depleting drugs and FcRn and complement inhibitors, as well as T-cell-directed approaches including the anti-CD40 antibody iscalimab and interleukin inhibitors such as satralizumab, which is already approved for the treatment of AQP4 antibody-positive NOSD. • In addition, BTK inhibitors currently in development (e.g., tolebrutinib) may be used in the future for the treatment of both gMG and RA, or gMG and multiple sclerosis.
Pregnancy	• In this population, there are concerns about administering classic immunosuppressive therapies due to potential effects on fertility and pregnancy outcomes. • Furthermore, MG shows a variable course during pregnancy that is difficult to predict, with exacerbations most likely to occur during the first trimester and postpartum period. • Females with MG are also at increased risk of requiring assisted vaginal or caesarean delivery compared with the general population. • Optimal care of patients with MG of childbearing age includes counseling on the risks of pregnancy and planning, regular follow-up during pregnancy, multidisciplinary care during the birth, and close postpartum follow-up, with treatment decisions made on an individual basis. • Mycophenolate mofetil should not be used during pregnancy because of an association with an increased number of congenital malformations. • If needed, continuation of azathioprine can be considered. • Rituximab is currently contraindicated in pregnancy; eculizumab has the potential to be used in women of childbearing age, and efgartigimod has also shown promise in this population. • Transfer of maternal antibodies relevant for neuromuscular transmission via the placenta may lead to the development of transient neonatal myasthenic syndrome in babies of women with AChR-Ab- or MuSK-Ab-positive MG, requiring care from experienced pediatricians.
Ocular manifestations	• A high proportion of patients with gMG have ocular manifestations either at presentation or during the disease course. • Many patients with ocular forms of MG tend to be neglected, despite a substantial burden on daily life work productivity. • For patients with ocular MG (which is confined to the extrinsic ocular muscles), corticosteroids should be the initial immunosuppressive therapy, after trying symptomatic treatments like pyridostigmine. • Earlier, more aggressive treatment is required if corticosteroids alone are ineffective, contraindicated, or poorly tolerated. • Up to 80% of patients with ocular manifestations go on to develop generalized disease, usually within 2 years after the onset of ocular symptoms. • Although most patients respond favorably to treatment, some patients develop ocular sequelae that require the assessment of expert neuro-ophthalmologists to improve ptosis and diplopia due to prisms; rarely, patients may require surgery.
Thymoma	• Thymomas are rare epithelial tumors located in the anterior mediastinum. • MG is present in 30%–50% of patients with thymoma and often manifests with differing clinical and autoimmune traits compared with the typical presentation. • Thymomas associated with MG require surgical removal and sometimes radiotherapy or chemotherapy with oncological follow-up, which increases the disease burden.
Patients without AChR-Ab and MuSK-Ab	• The treatment of seronegative patients presents a major challenge, with the lack of a diagnostic biomarker leading to delays in diagnosis and treatment initiation. • The unknown pathophysiology underlying seronegative MG means it is not possible to determine the most effective therapy for each patient. • The psychological burden associated with an often-lengthy patient journey and diagnostic uncertainty may negatively impact patients' clinical disease course. • Currently, seronegative patients are managed in a similar way to AChR-Ab- and MuSK-Ab-positive patients, but clinicians should be alert to other potential conditions that can mimic MG, particularly if the patient's response to treatment is inadequate.
Overtreated for many years and unwilling to wean off medication	• Some patients develop an intense fear of their disease worsening and are not willing to wean off medication or change therapy. • A patient–physician relationship based on trust and communication is needed to achieve understanding; however, it may sometimes be difficult for the two parties to reach agreement. • Some patients on long-term corticosteroid therapy may find it difficult to wean off corticosteroids, and corticosteroid withdrawal symptoms (e.g., fatigue) can often mimic MG; however, with expert clinical review, it should be possible to distinguish between the two states.

TABLE 3 (Continued)

Patient characteristic	Key points for consideration
Irreversible symptoms	• Some patients develop ophthalmoplegia as a fixed defect, particularly if their MG is untreated for several years or occurs due to an underlying genetic predisposition, and this subphenotype remains resistant to treatment. • Atrophy of the tongue has been described in some patients with MuSK-Ab-positive gMG.
Mental health problems	• Corticosteroids can worsen mental health issues, and psychological well-being is crucial for any patient with a chronic neurological illness. • Patient support groups, specialist nurses, and therapists are often very useful in helping patients through their illness.

Abbreviations: Ab, antibody; AChR, acetylcholine receptor; AE, adverse event; AQP4, anti-aquaporin-4; BTK, Bruton's tyrosine kinase; FcRn, neonatal Fc receptor; gMG, generalized myasthenia gravis; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MMS, minimal manifestation status; MuSK, muscle-specific kinase; NOSD, neuromyelitis optica spectrum disorder; PLEX, plasma exchange; QoL, quality of life; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

relating to long-term efficacy, safety, and patient adherence, strategies for treatment initiation and discontinuation, optimal duration of therapy, treatment sequencing, method and timing of switching from one agent to another, and the potential for drug–drug interactions [17, 27]. Finally, newly approved treatments come at a high cost [17, 62], and cost-effectiveness based on accurate pricing and real-world outcomes needs to be determined.

The introduction of targeted therapies has kickstarted the search for new prognostic biomarkers in gMG, with several markers currently in early stages of development. Calprotectin (CLP) has shown promise as a biomarker of disease activity. Levels of CLP appear to correlate with level of dysbiosis, which plays a pivotal role in MG. CLP levels are significantly higher in patients with MG compared with controls ($p < 0.0001$), and higher CLP levels are correlated with greater clinical disease severity [63]. MicroRNAs (miRNAs) have emerged as potential biomarkers owing to their ease of accessibility in body fluids and unique profiles in autoimmune disorders [64]. Studies on circulating miRNAs have identified specific miRNA profiles in different MG subtypes, and these could play a future role as markers of disease progression [64]. Multilabel metabolomics profiling has been used to identify biomarkers with potential utility in following the clinical course of MG. Research has found markedly different metabolic profiles in patients with seropositive MG compared with healthy controls, with six metabolites significantly upregulated and six downregulated in patients with MG [65]. Limited evidence suggests a correlation between decreased levels of AChR, MuSK, and titin autoantibodies and improvements in disease severity in MG. However, further investigation is required to enable more definitive conclusions to be drawn. Plasma complement protein analysis revealed a plasma profile of C2, C3, C5, C3b, and C5a associated with AChR-Ab-positive MG that offers potential as a biomarker of complement activation status with utility in tailoring anticomplement therapy in gMG [66]. Additional research and validation may provide a basis for using biomarkers to improve the diagnosis of gMG, predict the clinical course and response to treatment, and guide individualized patient management, paving the way for personalized medicine.

A limitation of this informative review is the nonsystematic approach taken for the literature search. The selection of publications included was based on a subjective critical appraisal, synthesis, and analysis of the search results and as such, may be subject to bias. Nonetheless, the findings contribute to a better understanding of the current state of the field.

In conclusion, gMG is associated with a heavy burden for patients and presents significant challenges for clinical management. There is a need for more frequent, standardized patient assessment to identify the cause of motor function deficits, provide a clearer picture of the disease burden and its impact on daily living and QoL, and better support decisions regarding choice of treatment. The availability of novel, targeted treatments that influence key pathological mediators of gMG together with new biomarkers offers the potential to optimize patient management and ultimately enable more patients to achieve minimal manifestation status and a reduced burden of disease.

AUTHOR CONTRIBUTIONS

Francesco Saccà: Conceptualization; writing – review and editing. **Emmanuelle Salort-Campana:** Conceptualization; writing – review and editing. **Saiju Jacob:** Conceptualization; writing – review and editing. **Elena Cortés-Vicente:** Conceptualization; writing – review and editing. **Christiane Schneider-Gold:** Conceptualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

E.C.-V. has received public speaking honoraria and compensation for advisory boards and/or consultation fees from argenx and UCB. S.J. has served as an international advisory board member for Alexion, Alnylam, argenx, Immunovant, Regeneron, and UCB; is currently an expert panel member of the Myasthenia Gravis Consortium for argenx; and has received speaker fees from Eisai Pharmaceuticals and Terumo BCT. F.S. has received public speaking honoraria from Alexion Pharmaceuticals, Biogen, Mylan, Novartis, Roche Pharma, Sanofi, and Teva Pharmaceuticals; he has also received compensation for advisory boards and/or consultation fees from Alexion Pharmaceuticals, Almirall, argenx, AveXis, Biogen, Forward Pharma,

Lexeo Therapeutics, Merck, Novartis, Novatek, Pomona, Roche, Sanofi, and Takeda and is currently the principal investigator in clinical trials sponsored by Alexion Pharmaceuticals, argenx, Prilenia, and Sanofi. E.S.-C. has received public speaking honoraria from Biogen and Sanofi; she has also received compensation for advisory boards and/or consultation fees from Amicus, argenx, Biogen, Lupin, Roche, and Sanofi. CS.-G. has received public speaking honoraria and/or compensation for advisory boards/consultation fees from Alexion Pharmaceuticals, Amicus Therapeutics, argenx, Bayer Schering, Hormosan Pharma, Immunovant, Janssen, Lupin Pharmaceuticals, Roche Pharma, Teva Pharmaceuticals, and UCB.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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