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REVIEW ARTICLE

# Pharmacotherapy of Generalized Myasthenia Gravis with Special Emphasis on Newer Biologicals

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## Abstract

Myasthenia gravis (MG) is a chronic, fluctuating, antibody-mediated autoimmune disorder directed against the post-synaptic neuromuscular junctions of skeletal muscles, resulting in a wide spectrum of manifestations ranging from mild to potentially fatal. Given its unique natural course, designing an ideal trial design for MG has been wrought with difficulties and evidence in favour of several of the conventional agents is weak as per current standards. Despite this, acetylcholinesterases and corticosteroids have remained the cornerstones of treatment for several decades with intravenous immunoglobulins (IVIG) and therapeutic plasma exchange (PLEX) offering rapid treatment response, especially in crises. However, the treatment of MG entails long-term immunosuppression and conventional agents are viable options but take longer to act and have a number of class-specific adverse effects. Advances in immunology, translational medicine and drug development have seen the emergence of several newer biological agents which offer selective, target-specific immunotherapy with fewer side effects and rapid onset of action. Eculizumab is one of the newer agents that belong to the class of complement inhibitors and has been approved for the treatment of refractory general MG. Zilucoplan and ravulizumab are other agents in this group in clinical trials. Neisseria meningitis is a concern with all complement inhibitors, mandating vaccination. Neonatal Fc receptor (FcRn) inhibitors prevent immunoglobulin recycling and cause rapid reduction in antibody levels. Efgartigimod is an FcRn inhibitor recently approved for MG treatment, and rozanolixizumab, nipocalimab and batoclimab are other agents in clinical trial development. Although lacking high quality evidence from randomized clinical trials, clinical experience with the use of anti-CD20 rituximab has led to its use in refractory MG. Among novel targets, interleukin 6 (IL6) inhibitors such as satralizumab are promising and currently undergoing evaluation. Cutting-edge therapies include genetically modifying T cells to recognise chimeric antigen receptors (CAR) and chimeric autoantibody receptors (CAAR). These may offer sustained and long-term remissions, but are still in very early stages of evaluation. Hematopoietic stem cell transplantation (HSCT) allows immune resetting and offers sustained remission, but the induction regimens often involve serious systemic toxicity. While MG treatment is moving beyond conventional agents towards target-specific biologicals, lack of knowledge as to the initiation, maintenance, switching, tapering and long-term safety profile necessitates further research. These concerns and the high financial burden of novel agents may hamper widespread clinical use in the near future.

## 1 Introduction

Myasthenia gravis (MG) is a chronic, fluctuating, potentially fatal, autoimmune disorder directed against the post-synaptic neuromuscular junction (NMJ) of skeletal muscles [1]. It

**Key Points**

The treatment of myasthenia gravis is essentially based on long-term immunomodulation.

Conventional immunosuppressive agents are effective but in general have a delayed onset of action and have several side effects.

Novel biological agents offer selective, target-specific immunotherapy and are the future of myasthenia gravis treatment.

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is an antibody-mediated disease which impairs NMJ transmission and can manifest in a spectrum ranging from mild ptosis and ocular symptoms to profound bulbar, limb and respiratory muscle weakness, and the presentation can be broadly classified as ocular or generalized MG. MG has a bimodal age distribution and, in young adults, causes major disease and treatment-related burdens and significant impairment in quality of life (QOL) [2, 3]. Although a relatively rare disease with an incidence of 0.3 to 2.8 per 100,000 and prevalence of 5.3 to 35 per 100,000, these rates have been increasing across the world at 3% per year with a doubling of prevalence since the 1970s, although the incidence has remained stable in some areas [4, 5]. Improved diagnosis, aging of the population and longer patient survival with novel treatments are reasons underlying the increased prevalence.

Understanding the nuances of immunopathology underlying MG has been the cornerstone of treatment advances in MG. MG is the prototype of an antibody-mediated disease and the pathogenic antibody is directed against the post-synaptic acetylcholine receptor (AChR) in up to 85% of cases of generalized MG, against muscle-specific kinase (MUSK) in 6% and against low-density lipoprotein receptor-related protein 4 (LRP4) in 1–2% of cases [6]. A breakdown of immunotolerance by an unknown trigger sets in motion CD4+ T-cell upregulation, which drives the pathogenesis [7]. The CD4+ T-cell mediated upregulation of proinflammatory cytokines leads to proliferation and differentiation of B cells to antibody secreting plasma cells, memory B cells and long-lived plasma cells [8]. The antibodies in AChR-positive MG are subclass IgG1 and IgG3 and their binding with the post-synaptic AChR receptor leads to the complement cascade, formation of the membrane attack complex, reduced end-plate potentials and failure of action potential transmission [1, 9, 10]. The pathogenesis differs in MUSK MG in that the antibodies belong to the IgG4 subclass and do not activate the complement pathway, but act by masking the site of normal MUSK-LRP4 interaction and thus prevent AChR clustering [1]. The thymus plays a central role in anti-AChR antibody-mediated MG. The process of central tolerance, with elimination of autoreactive T cells, occurs in the thymus. In MG, thymic abnormalities lead to deficient elimination of autoreactive T cells, thereby perpetuating autoimmunity [11].

The treatment of MG is firmly based on immunosuppressive or immunomodulatory mechanisms, which range in the case of conventional agents from having a wide and non-targeted action to recent highly selective target-specific biologicals [12]. The latter have several potential advantages in offering minimal adverse effects, rapid response and patient- and disease-specific personalized treatment [13]. In this review, we elaborate on the various pharmacotherapeutic agents, with special emphasis on novel and investigational biological agents employed in the treatment of generalized MG, and examine their mechanisms of action and the existing efficacy, safety and tolerability data. PubMed, Google Scholar and ClinicalTrials.gov searches were performed from October 2021 to a final search in April 2022 with search words 'myasthenia gravis' and 'trials' for newer agents and 'myasthenia gravis' and 'steroids', 'azathioprine', 'mycophenolate', 'tacrolimus', 'cyclosporine', 'cyclophosphamide', 'intravenous immunoglobulin', 'subcutaneous immunoglobulin' and 'plasma exchange' for conventional agents.

## 2 Clinical Trial Considerations in Myasthenia Gravis

There are several challenges in designing an ideal treatment trial for MG and this is apparent by the wide heterogeneity in clinical trial design and assessment methodologies over the decades. As a chronic but fluctuating disorder with diverse clinical manifestations, variable serological status and different treatment modalities at any given time point, choosing appropriate selection criteria sufficiently narrow to be representative and fairly homogeneous but broad enough to include patient subpopulations, enable successful study recruitment and allow generalization of study results to the entire MG population, is often difficult [14]. Most of the recent MG clinical trials have recruited adult patients with AChR antibody-positive generalized MG who have been on stable doses of corticosteroids (typically for 4 weeks) or conventional immunosuppressive agents for 3–6 months, and excluded patients with recent thymectomy, thymoma or requiring maintenance intravenous immunoglobulin (IVIG) or therapeutic plasma exchange (PLEX). Determining the ideal trial duration that would confirm or refute drug efficacy is often based on preclinical studies and pharmacokinetic analyses but these are lacking in earlier trials [15].

The early lack of consensus on ideal outcome measures led to the Medical Scientific Advisory Board (MSAB) of the Myasthenia Gravis Foundation of America (MGFA) forming a task force that recommended certain clinical measures of MG severity and response to treatment [14, 16]. There are no ideal biomarkers for MG as antibody levels do not reflect clinical severity on the patient level [17]. Single-fibre electromyography (SFEMG) provides quantitative data on neuromuscular transmission but is invasive, time consuming and not universally performed, so is not feasible in a clinical trial setting. Several clinical measures that are usually a composite of examiner-determined physical examination scores—such as the quantitative myasthenia gravis (QMG) score, myasthenia gravis composite (MGC), myasthenia muscle score (MMS) and manual muscle test (MMT)—or patient-determined disability or QOL measures such as

myasthenia gravis quality of life (MG QOL) and myasthenia gravis activities of daily living (MG ADL), have been employed frequently in recent clinical trials [18]. Steroid sparing or acetylcholinesterase sparing are other endpoints that can be used to determine the efficacy of an immunosuppressive agent. Despite all these instruments, a single gold standard trial design for MG is still not feasible. Furthermore, current trial designs fail to address multiple relevant questions concerning initiation and discontinuation of novel agents, inter-class and intra-class switching, synergistic or antagonistic actions and application in vulnerable populations such as pregnant women and the paediatric age group [13]. Other considerations are cost effectiveness of novel therapies, access to care and equity of care.

## 3 Agents Used for Symptomatic Treatment

The discovery of therapeutic application of acetylcholinesterase inhibitors (AChEIs) in the 1930s has remained one of the greatest advances in neuropharmacology [19]. The initial AChEI in use was physostigmine, which was subsequently replaced by pyridostigmine and neostigmine and these remain the first-line agents for symptomatic treatment of MG [20]. They are synthetic quaternary ammonium compounds that reversibly inhibit acetylcholinesterase and thus prolong the action of acetylcholine at the NMJ [21]. There are several formulations, especially of pyridostigmine, such as oral sustained-release preparations, syrup for paediatric use and also injectables for parenteral administration. Peak plasma levels are attained 1–2 h after an oral dose with clinical benefit starting in 0.5 hours and wearing off in 3–4 h due to plasma cholinesterase activity [22]. There are no large-scale trials evaluating AChEIs and most of the evidence is from retrospective case series and clinical experience. In mild forms of MG, AChEI may be the sole treatment, although in most series the proportion of patients maintained on pyridostigmine alone ranges from 30 to 50% [23–25].

The adverse effects of AChEI are mild, frequent (observed in 30% of patients) and more common in older patients [23, 26]. These are related to muscarinic receptor stimulation in the autonomic glands and smooth muscles manifesting as increased sweating, hypersalivation and excess bronchial secretions and increased gut motility resulting in abdominal cramps and diarrhoea. AChEIs are contraindicated in gastrointestinal or bladder obstruction. The nicotinic receptor side effects are less common and consist of muscle cramps and fasciculations. Our practice is to initiate pyridostigmine at 30 mg three or four times daily with subsequent upward titration of the dose depending on the patient's symptoms and tolerability to 60 mg six times a day or more. Loperamide 2 mg and glycopyrrolate at 0.5–1 mg can be prescribed to combat bothersome side effects. AChEIs should be used cautiously, if at all, in MUSK MG due to described lack of efficacy or even paradoxical worsening [27]. The exact mechanism remains unclear but it is hypothesized that as post-synaptic AChR clustering is mediated by the agrin-MUSK-LRP4-Dok7 complex and ACh has an antagonistic action on this AChR clustering, and as MUSK MG is characterized by impaired AChR clustering, an increased ACh level with AChEI treatment further accentuates breakdown of post-synaptic AChR clustering [28].

Besides pyridostigmine and neostigmine, another AChEI which continues to have clinical relevance is ambenonium. Developed in the 1950s, mainly to provide a longer acting alternative, ambenonium is a high-affinity reversible AChEI inhibitor [29, 30]. However, due to its broad AChE inhibition, there can be more frequent undesirable parasympathomimetic side effects. In our clinical practice, we reserve it for those patients who have rare intolerance to pyridostigmine due to bromide reactions. It is started at a low dose of 5 mg three times a day and then titrated up to a maximum of 25 mg three to four times a day. Monarsen is a novel antisense oligonucleotide that targets AChE mRNA and in effect reduces the action of AChE [31]. The initial randomized controlled trials showed that 10-, 20- and 30-mg doses as adjunctive therapy reduced QMG scores with a dose–response effect [32]. Further development has not been evident.

β-Agonists also have permissive action on neuromuscular transmission in MG. In fact, ephedrine was used to treat MG prior to AChEI [33]. Several open-label studies have found positive results with the use of ephedrine at doses ranging from 45 to 200 mg/day and salbutamol at 4–12 mg/day in congenital myasthenic syndromes [34–37]. The mechanism of action may be by maintaining stability of the post-synaptic AChR complex and clustering counteracting the destabilizing action of ACh [38]. The efficacy of β-agonists in autoimmune MG remains uncertain, and phase II and III studies of salbutamol at doses of 4 mg three times a day as adjuvant therapy for AChR-positive generalized MG are underway [39].

## 4 Current Immunosuppressive Treatment

Current immunosuppressant (IST) drugs used to treat MG are shown in Table 1.

### 4.1 Corticosteroids

The introduction of corticosteroids in the 1950s and 1960s was a major landmark in MG treatment that resulted in a dramatic drop in mortality. Corticosteroids continue to be the mainstay of treatment today [40, 41]. The mechanism of action in MG is surmised to be due to inhibition of T-cell

and monocyte-macrophage activation and not by reduction of antibody levels [42]. Initial clinical evidence of benefit in MG came from small case series and randomized controlled trials using prednisone 100 mg on alternate days, but the number of patients was small [43–45]. Subsequent, larger, long-term prospective studies showed 70–80% improvement in status at doses of 60–80 mg daily [46, 47]. The improvement with corticosteroids can start within 2 weeks and this rapid onset of action is one reason for its first-line status [48].

High-dose intravenous (IV) pulse corticosteroids were also found to be significantly better than placebo with the added benefit of a faster clinical response and fewer systemic side effects compared with daily regimens in the short term [49, 50]. However, initiation at high doses can cause clinical worsening in about a third of patients. The worsening is usually noticeable by 3–4 days, generally within the first 2 weeks, and can be sufficiently severe to necessitate ICU admission [41, 51, 52]. A recent systematic review noted older age, more severe disease, presence of bulbar symptoms, history of thymoma and thymectomy to be risk factors associated with worsening [53].

A lower dose initiation at 10–20 mg on alternate days with weekly up-titration to a higher dose is equally effective, circumvents the initial worsening and is preferrable in most situations [54]. Thus, the initial dose and the rate of titration can be adjusted on a patient-specific basis considering the clinical features and extent of symptoms, balanced to offset the risk of a 'steroid dip', especially in the elderly. Some patients respond well even with initial low doses and do not require uptitration. Higher doses and longer duration of treatment do not ensure a better outcome. If the response is suboptimal or if attempts to taper corticosteroid fail, alternate immunosuppressants must be initiated without delay [55]. Finally, if a patient has achieved clinical remission or a minimal manifestation status, corticosteroid tapering can be attempted. The rate of tapering has been controversial, but a recent study suggests that rapid tapering of corticosteroids is feasible and well tolerated [56].

Most of the evidence for corticosteroid use in MG comes from very early trials in which the quality of evidence is low by current standards and the trials have a high risk of bias. The patient numbers were low and outcome measures heterogeneous. But despite a lack of Class I evidence, corticosteroids remain the first-line drug for MG in most cases given widespread experience of major improvements in MG patients within weeks of starting corticosteroid therapy. The systemic side effects (weight gain, cataracts, hypertension, diabetes, osteoporosis, skin fragility, mood changes, hirsutism, cushingoid appearance, etc) are the major drawbacks,

**Table 1** Summary of conventional immunosuppressive agents used in myasthenia gravis

| Agent | Mechanism | Earliest time to clinical benefit | Dosing |
|---|---|---|---|
| Corticosteroids | Inhibition of T cells and monocyte-macrophage activation | 2–12 wk | Initiation at 10/20 mg daily and weekly uptitration to 50/60 mg daily |
| Azathioprine | Purine analogue inhibiting DNA and RNA replication | 12 mo | Initiation at 50 mg daily and increased weekly to 2–3 mg/kg/d |
| Mycophenolate mofetil | Inhibition of inositol monophosphate dehydrogenase | 6–12 mo | 1–2 g/day in divided doses |
| Cyclosporine | Inhibits calcineurin | 2–12 mo | Initiation at 3 mg/kg/d and increased to 6 mg/kg/d, titration based on clinical efficacy, therapeutic drug monitoring (400–600 ng/mL) and/or serum creatinine levels |
| Tacrolimus | Macrolide antibiotic that inhibits calcineurin | 2–12 mo | 3 mg/kg/d with further titration based on clinical efficacy or therapeutic drug monitoring (7–8 ng/mL) |
| Methotrexate | Folic acid antimetabolite | 3–6 mo | Initiation at 10 mg/wk single dose, increased weekly up to 20–25 mg/wk |
| Cyclophosphamide | Alkylating agent preventing DNA replication | 3–4 mo | Pulse of 1–1.5 mg/m$^2$ given over 5 d repeated monthly for 6 mo |
| IVIG | Multiple mechanism, predominantly FcRn saturation | 10–15 d | 2 g/kg divided over 2–5 d |
| SCIG | Same as IVIG but with lower peak and trough immunoglobulin levels and steadier state | 2 wk | Weekly dose calculated by multiplying the maintenance dose of IVIG in grams by 1.37 divided by the interval between IVIG doses |
| PLEX | Removal of pathogenic antibodies by 'apheresis' | 2–4 d | 30–40 mL/kg of plasma exchanged per day for 5 d |

*d* days, *DNA* deoxy ribonucleic acid, *FcRn* neonatal Fc receptor, *IVIG* intravenous immunoglobulin, *mo* month, *PLEX* therapeutic plasma exchange, *RNA* ribonucleic acid, *SCIG* subcutaneous immunoglobulin, *wk* week

limiting the use of corticosteroids for long-term maintenance and necessitating the use of steroid-sparing agents.

### 4.2 Azathioprine

Azathioprine is a purine analogue which is metabolized to its active components 6-mercaptopurine and 6-thioguanine triphosphate. Incorporation of the metabolites into DNA and RNA inhibits cellular synthesis and replication and thus limits lymphocyte proliferation [57]. Several other mechanisms including 6-thioguanine-mediated Rac1 inhibition and CD28-mediated T-cell apoptosis have been recognized as mechanisms of azathioprine-mediated immunosuppression [58]. Azathioprine was used successfully at doses of 150–200 mg daily for treatment of MG as early as 1969 [59]. The earliest study comparing azathioprine alone with a combination of azathioprine and corticosteroid observed that though equally efficacious, azathioprine monotherapy was better suited for patients with non-turbulent disease since the drug had a gradual onset of action [60]. The initial response can be observed at about 6 months and continues to improve up to 2 years [61]. In fact, monotherapy with azathioprine was found to have a lower failure rate than monotherapy with prednisone, but some studies showed poor patient tolerability due to idiosyncratic reactions in 10–20% of patients [62, 63]. A distinct advantage was observed in patients on combination prednisone plus azathioprine at a daily dose of 2.5 mg/kg compared with patients on prednisone alone in a multicentre randomized controlled trial of 34 patients. Although not different at 1 year, patients on the prednisone plus azathioprine combination had reduced doses of prednisone at years 2 and 3, longer remissions and fewer treatment failures, lower AChR levels and fewer adverse effects compared with prednisone plus placebo patients [64].

In the long-term, azathioprine is safe and well tolerated with a low incidence of side effects including haematological, gastrointestinal, dermatological and infectious [65, 66]. Initiation at a dosage of 50 mg daily for 2 weeks followed by a further gradual increase to full doses of 2–3 mg/kg daily rarely results in idiosyncratic reactions but periodic monitoring of peripheral blood counts and liver enzymes is required. Although thiopurine methyltransferase (TMPT) and inosine triphosphate pyrophosphatase (ITPase) deficiencies are associated with increased marrow toxicity, routine screening for these enzyme levels before initiation of azathioprine is impractical and not recommended [67, 68]. Based on a case-control study using a Danish population-based registry, a very slight increased risk of lymphoma (odds ratio 1.2, 95% confidence interval 0.62–2.4) was seen in MG patients at high cumulative azathioprine doses and therapy duration of > 5 years [69]. In clinical practice, azathioprine is one of the first-choice steroid-sparing agents in patients who cannot be given corticosteroids, or who are on corticosteroids but are having intolerable side effects. Despite initial concerns, azathioprine is considered safe during pregnancy and has been one of the favoured ISTs for women with MG planning pregnancy [70, 71].

### 4.3 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid, which is a strong inhibitor of the inositol monophosphate dehydrogenase isoform expressed selectively in T and B lymphocytes (de novo pathway of purine synthesis). By its inhibition, MMF depletes guanosine monophosphate, thus having an antiproliferative effect on lymphocytes by consequent inhibition of DNA and RNA synthesis [72]. Initial case reports and case series suggested a beneficial effect for MMF in MG treatment-resistant cases. Retrospective analysis of MMF at 2 g/day as an adjunctive agent in MG showed improvement in functional grade and corticosteroid dose reduction [73]. Maximum benefit was observed at a mean duration of 13 months or more. MMF was well tolerated, and gastrointestinal symptoms were seen only in 3 of the 38 (7.8%) patients in the series and diarrhoea requiring dose reduction was seen only in one (2.6%). In IST-naïve patients with mild to moderate MG, MMF at doses of 2.5 g/day in combination with corticosteroid at 20 mg/day did not have any advantage over corticosteroid with placebo, in QMG score or prednisone dose reduction [74]. The study duration of 12 weeks was very brief and the dosage of prednisone 20 mg daily for 12 weeks was sufficient to produce a good treatment response in treatment-naïve patients with mild to moderate MG. The results of the only phase III trial of MMF in MG patients on corticosteroid ≥ 20 mg/day was also negative. At MMF 2 gm/day, the MGFA post-intervention status (PIS), steroid dose reduction, MG ADL and QMG were not different compared with placebo at 36 weeks of treatment and the study endpoints did not meet the prefixed treatment response [75]. Corticosteroid taper in this study was initiated as early as 2 weeks after achieving minimal manifestation (MM) status and this may have been premature. Also, the duration of 36 weeks may be insufficient to show a significant difference. Interestingly, gastrointestinal side effects were noted in the placebo group while patients on MMF had more serious infections.

Despite these negative trials, MMF continues to be used for MG based on real-world clinical experience, retrospective studies in MG and benefits in other autoimmune diseases, and its use is endorsed in several treatment guidelines [76–79]. In clinical practice, MMF is often used as the first, or more frequently the second-line IST after azathioprine [80]. Similar to azathioprine, monitoring protocols for blood counts and liver enzymes are followed, but unlike azathioprine, MMF is teratogenic and is not advisable during pregnancy or conception [76].

### 4.4 Cyclosporine

Cyclosporine A (CsA) is a fungal-derived lipophilic cyclic peptide that inhibits T-cell activation by blocking transcription of cytokine genes [81]. CsA inhibits calcineurin which regulates translocation and activation of transcription factors and cell signalling pathways inhibiting interleukin synthesis. Initially, CsA was employed in preventing allograft rejection in transplant patients. In one of the earliest drug trials in MG (1987), CsA was compared with placebo in twenty IST-naïve patients with moderate to severe MG not well controlled with AChEI [82]. Those who were post-thymectomy, on corticosteroids or other ISTs were excluded. Patients were initiated at CsA 6 mg/kg with further dose uptitration based on trough levels (400–600 ng/mL), creatinine (≤ 2 mg/dL) and treatment response. Both muscle strength and fall in AChR levels were significantly better in the CsA group. Improvement started as early as 2 weeks and maximum improvement was observed by 3.6 months (range 1–6 months).

Nephrotoxicity was the major adverse event seen in three of the ten patients on cyclosporine with the maximum creatinine level up to 2.1 mg/dL and this tended to normalize on drug withdrawal. Although considered minor, easily controlled hypertension, paraesthesia, gum sensitivity, altered taste, increased hair growth, headache, muscle cramps and diarrhoea were seen in 20% of patients on CsA. In a more recent study, CsA was used in patients refractory to thymectomy, high-dose CS, azathioprine, IVIG or PLEX [77]. Moderate to significant improvement in mean disability score based on muscle strength was observed in about 70% and complete remission in 15% [83]. As noted previously, improvement was noted as early as 3 weeks with maximum improvement observed by 6 months. The initial dosage range was 6–8 mg/kg daily in divided doses and was uptitrated based on serum levels and creatinine. Nephrotoxicity, hypertension, gingival hypertrophy, headache, flu-like syndrome and diarrhoea reversed on dose reduction. Further studies have shown that lower doses such as 3 mg/kg daily are also effective [84]. Alternate microemulsion preconcentrate formulation of CsA, which offers a better therapeutic index, was evaluated in MG and was found to be safe and effective over a 2-year period, with reduction in steroid requirement and disease activity [85]. Cyclosporine has a role in MG refractory to the standard first-line agents or in patients dependent on long-term IVIG or PLEX. Compared with the other ISTs, except corticosteroids, the clinical response with CsA can be fast, starting as early as 2–4 weeks. Monitoring should include drug trough levels, blood glucose levels, renal function, and liver function tests as well as screening for other systemic side effects.

### 4.5 Tacrolimus

Tacrolimus (FK 506) is a macrolide antibiotic which has a similar mode of action to CsA. By binding to immunophilin, tacrolimus inhibits calcineurin and in turn interleukin synthesis, nitric oxide synthase activation, cell degranulation and it also potentiates glucocorticoid action [81]. The majority of studies of tacrolimus in MG are from China and Japan. A systematic review of prospective clinical trials from 1947 to 2014 shows that tacrolimus reduces QMG score and corticosteroid burden both in refractory and new-onset MG [86]. There are two dosing strategies: initiating at 0.1 mg/kg or initiating at a fixed daily dose of 3 mg, with further uptitration to a drug trough level of 7–8 ng/mL. The fixed-dose approach followed in our practice provides a lower dose and less potential for side effects. Improvements are noted within 1–2 months, with most patients responding by 6 months.

The only randomized double-blind trial in the review failed to show a benefit compared with placebo, but the study included patients with MM and the mean baseline QMG was low [87]. A more recent RCT from China on tacrolimus in corticosteroid-unresponsive MG also failed to show a significant difference in the reduction from baseline of QMG between tacrolimus and placebo [88]. The authors performed a post-hoc analysis which seemed to suggest some benefit with tacrolimus, but that would need to be confirmed in an appropriate study [88]. Tacrolimus monotherapy has shown reduction in ptosis and bulbar symptoms in MG [89]. While comparative studies are not available in MG, in other disorders tacrolimus has significantly less cosmetic side effects such as gum hypertrophy and hypertrichosis compared with CsA [90].

### 4.6 Methotrexate

Beyond being a folic acid antimetabolite, a number of mechanisms including inhibition of purine and pyrimidine synthesis, suppression of transmethylation reactions and reduction of antigen-dependent T-cell proliferation and adenosine-mediated suppression of inflammation have been proposed as the immunomodulatory actions of methotrexate [91]. There have been relatively few studies looking into the efficacy of methotrexate in MG. A single blinded trial evaluating the steroid-sparing effect of methotrexate at 17.5 mg weekly compared with azathioprine 2.5 mg/kg/day showed that QMG scores, remissions and relapses were comparable and in addition the dose of steroid per kg bodyweight was reduced by half in the methotrexate group [92]. In contrast, the randomized controlled trial of methotrexate in MG patients on stable doses of steroid treated with methotrexate initially at doses of 10 mg weekly and increased to 15 mg/

week at 2 weeks and 20 mg/week at 5 weeks if needed, failed to show any steroid-sparing effect for methotrexate at 1 year compared with placebo and there were no differences in secondary outcome measures including QMG, MGC, MG QOL and MG-ADL [93]. However, patients on placebo had a greater dropout rate due to MG worsening and a post-hoc analysis per protocol analysis showed that patients on methotrexate had lower MG scores.

The most common adverse event was nonspecific pain. Elevated liver enzymes and increased infections in methotrexate patients were noted but not severe. Despite a lack of evidence from RCTs, methotrexate may be considered as a corticosteroid-sparing agent in those who are not tolerating other ISTs. methotrexate is also a relatively inexpensive treatment option in resource-limitsed settings [41]. It is initiated at a dose of 10 mg per week and uptitrated every 2 weeks gradually to 20 or 25 mg per week. Monitoring includes full blood counts, serum transaminase and creatinine. Methotrexate is absolutely contraindicated in pregnancy. Folic acid supplementation with a minimum of 5 mg once a week separated as much as possible from the methotrexate dose is recommended [94].

### 4.7 Cyclophosphamide

Cyclophosphamide is one of the many alkylating agents that was initially utilized in cancer chemotherapy and has since found wide application in organ-threatening severe autoimmune disorders. Its active metabolite, phosphoramide mustard, interacts with DNA bases and forms inter-strand cross-links inhibiting DNA replication [95]. At doses lower than those used in cancer chemotherapy, cyclophosphamide has good immunosuppressive and immunomodulatory actions by inhibiting T-cell, B-cell and antibody-mediated immune damage. Initial evidence in the early 1980s showed cyclophosphamide to be effective in MG with improvement seen as early as 1 month after starting treatment [96]. A randomized controlled trial in 2002 employed low-dose pulses of IV cyclophosphamide at 500 mg/m$^2$ monthly for 6 months and then every other month for three more doses in corticosteroid-dependent severe MG [97]. Both muscle strength and steroid dose reduction were significantly better in the cyclophosphamide group at the end of 12 months and cyclophosphamide was well tolerated in these patients, perhaps because of the low-dose regimen and limited total exposure to the drug.

The most frequently encountered side effects in this study were nausea, vomiting, abdominal pain, diarrhoea, akathisia and fasciculations, but these side effects were not different in the placebo group. There were no dropouts due to toxicity and no increased incidence of haematological or infection events. Long-term efficacy was also examined in a retrospective analysis of patients with refractory MG. It was observed that in patients who received monthly pulses of IV cyclophosphamide at 1–1.5 mg/m$^2$, 10 of 12 patients who completed a 6-month course of treatment were asymptomatic at 6 months [98]. Unfortunately, the effect was not sustained, starting to wane by 1 year and all except one patient relapsed by 4.5 years. Three of the 22 patients who received cyclophosphamide had severe adverse effects which included severe vomiting, pancytopenia, sepsis, multiorgan dysfunction and congestive heart failure.

A recent similar retrospective study using high-dose cyclophosphamide (30–50 mg/kg monthly) for 6 months showed a median relapse-free survival of 9 months and subsequent relapse within 12 months [99]. The adverse events included leukopenia and gastrointestinal symptoms, which were encountered in two out of eight patients, but required monitoring only. Thus, pulse IV monthly cyclophosphamide offers a treatment option in severe refractory MG. Like methotrexate, cyclophosphamide is a relatively inexpensive and rapid-acting, remission-inducing treatment option [20, 100]. The main disadvantage is the adverse toxicity profile, the need for elaborate premedication and monitoring protocols, and the high likelihood of relapse. Experience with cyclophosphamide in other autoimmune and renal disorders has made evident the bone marrow, bladder and gonadal toxicities and the long-term risk of malignancies including leukaemia and bladder cancer. Close monitoring of cumulative dosage is also necessary. Gonadal toxicity is seen at cumulative doses > 168 mg/kg and malignancies at doses higher than a total of 36 g [101]. Hence, cyclophosphamide may be best limited to severe refractory MG unresponsive to other agents and as a short-term measure for remission induction. While oral cyclophosphamide is also utilized in other autoimmune disorders, there is a lack of evidence for its use in MG.

### 4.8 Intravenous Immunoglobulins (IVIG)

IVIG is routinely employed for the treatment of acute worsening of MG or as maintenance treatment of MG; however, the mechanisms of action are complex and not completely understood, although effects on the Fc receptor may be paramount [98]. Commercially available IVIG is prepared from pooled donor plasma and consists predominantly of IgG. Several mechanisms including T-cell inactivation and B-cell and antibody downregulation by competing with Fc receptors, restoring the balance of anti-inflammatory cytokines and indirect inhibition of the complement cascade have all been suggested as immunomodulatory actions [102]. The initial study of IVIG in MG was in 1984. Four of five patients with severe MG given IVIG in doses of either 1 g/kg or 2 g/kg showed significant improvement in status by 10–15 days [103]. In 2007, a randomized placebo-controlled trial

using IVIG at 2 g/kg or placebo in patients with worsening MG showed meaningful improvement in QMG scores at 14 days, which persisted to 28 days in those receiving IVIG, and provided class I evidence for the use of IVIG in worsening MG [104]. A subsequent randomized and single-blinded study in 2011 compared the efficacy of IVIG at a dose of 1 g/kg per day for 2 days with PLEX in patients with moderate to severe MG. The results showed that the same proportion of patients improved with both treatments, 69% with IVIG and 65% with PLEX, with the same dropout rates in both arms and similar time to improvement [105]. This study provided Class I evidence on the comparable efficacy and tolerability of IVIG and PLEX in moderate to severe MG.

A Cochrane review in 2012 confirmed that in acute exacerbations, patients on IVIG showed a favourable response compared with placebo and no difference in outcomes when compared with PLEX [106]. Later, phase III studies have also observed IVIG to be safe and effective in acute exacerbations of MG [107]. In comparison with corticosteroids, the review concluded that there was not enough evidence to favour IVIG. The dose of 2 g/kg was not superior to 1 g/kg in terms of change in myasthenia muscle score at 15 days. For maintenance therapy, the studies in the Cochrane review were underpowered and no evidence on functional improvement or corticosteroid-sparing effect of IVIG could be determined. A subsequent retrospective study comparing PLEX with IVIG for maintenance therapy in juvenile MG revealed both PLEX and IVIG had high response rates, although PLEX was found to be more consistent [108]. Evidence for IVIG as a chronic maintenance therapy is less robust but several case series over the years have demonstrated its efficacy, especially in patients with refractory MG and IVIG is recommended for this indication [20, 109, 110].

In comparison with PLEX, IVIG has some safety advantages such as ease of IV access, lack of vasospasm or vasovagal reactions and a lesser chance of serious cardiac adverse events. IVIG has well-known side effects such as flu-like symptoms (80% of adverse effects) [101]. Generally, IVIG is well tolerated, but dermatological reactions can prevent or limit use. Other rare reactions that have been described include arrhythmia, hypotension, transfusion-related lung injury and, very rarely (< 1%), delayed thrombotic, renal, haematological disorders, although this experience is atypical [111]. There is a wide variation in observed side effects from 2.5 to 87.5%, but in clinical experience, IVIG is well tolerated [111]. The vast majority of the side effects are mild and consist of fever, headache, nausea, diarrhoea, blood pressure changes and tachycardia [112]. The choice of IVIG or PLEX is based mainly on access issues as PLEX is not widely available in certain geographic areas. Also, cost issues limit access for both treatments. Both treatments are associated with fluid volume shifts and need to be used carefully in patients with underlying cardiac disease.

### 4.9 Subcutaneous Immunoglobulins (SCIG)

Most of the side effects of IVIG are inherent to the route of administration wherein there is a rapid rise in serum immunoglobulins and increase in serum viscosity as well as component products, resulting in immediate adverse effects [111, 113]. Subcutaneous immunoglobulin (16%, 20% immunoglobulin for subcutaneous infusion; SCIG) provides a lower rate of rise, reduced peak levels and a steady state and can be self-administered, offering the patient significant flexibility and a better QOL [114, 115]. Patients requiring chronic IVIG can frequently be transitioned to SCIG and this therapy is gaining popularity in autoimmune neuromuscular disorders. A recent systematic review on the efficacy and safety of SCIG in chronic MG identified five studies that showed improvement across several MG measures including MG QOL, MG ADL, stability of MRC sum score and reduction in PLEX requirement [116]. A recent retrospective study showed significant reduction in the MG impairment index (MGII) in patients on SCIG, as well as reduced doses of corticosteroid and AChEI [117]. The mean duration of SCIG was 19.5 months in this series and the treatment was well tolerated. SCIG has also been tested in a prospective trial in patients with mild to moderate exacerbations of MG. SCIG treatment led to clinically significant improvement in QMG, MMT, MG ADL and MGC scores and good patient satisfaction [118]. The most common adverse events are headache (approximately 70–80%) and injection-site reactions such as tenderness, pruritus and ecchymoses. The weekly dose of SCIG is calculated by multiplying the maintenance dose of IVIG in grams by a dose adjustment factor of 1.37 divided by the interval between IVIG doses [119]. SCIG can be given in divided doses over 2–3 days in a week. This treatment is ideally suited for patients who are on chronic IVIG treatment but having intolerable side effects, wearing-off symptoms or are eager for treatment autonomy. Limiting factors are manual dexterity impairment, dependent for self-care and the use of anticoagulant medication [119]. A prospective trial comparing IVIG and SCIG as maintenance therapy in MG is currently recruiting patients [120].

### 4.10 Therapeutic Plasma Exchange (PLEX)

PLEX refers to the process of 'apheresis' whereby blood drawn through a central or peripheral venous access is passed through a device that filters out the plasma (which is usually discarded) and reinfuses cellular components [121]. One cycle or volume of PLEX is 30–40 mL/kg body weight and removes about 1–1.5 times the patient's plasma volume [122]. This is usually repeated every other day for a total of five cycles. Removal of each volume of patient's plasma results in sequential reduction of autoantibodies such that, by the final cycle, theoretically the levels will be reduced to

< 5% of the pre-treatment levels. However, a recent study of antibody levels after PLEX showed that the reduction is about 70% of baseline values [123]. Other mechanisms of action of PLEX in MG include removal of cytokines and adhesion molecules, removal of immune complexes and sensitization of T and B cells to immunosuppressants or chemotherapeutic agents [121]. The depleted plasma volume is replaced either by donor plasma or 5% albumin infusion. Early evidence for the benefits of PLEX in MG was obtained in 1976. Patients refractory to corticosteroid and pyridostigmine were treated with PLEX for at least 5 days at 2 L per session and improved in 2–4 days [124]. Subsequently, several studies have evaluated PLEX in MG for acute and maintenance therapy.

A recent systematic review and meta-analysis looked into the evidence for PLEX in MG [125]. In the acute setting, meta-analysis indicated PLEX to be no different from IVIG in QOL scores, response times, electrophysiology or antibody titres. PLEX appeared to have faster recovery in early extubation and better respiratory status, but a shorter hospital stay was observed for IVIG patients. Another indication where PLEX is used is as pre-thymectomy treatment, but PLEX is not superior to IVIG [126]. In fact, a recent RCT comparing PLEX and IVIG found a significantly shorter duration of hospitalization, ICU length of stay after surgery, intubation period and duration of surgery with IVIG than with PLEX [127]. The evidence for PLEX in chronic MG in adults is limited but a crossover trial showed significant improvement in QMG with PLEX observed at 1 week and maintained for 8 weeks, while with IVIG the improvement was noted by 4 weeks and was not apparent at 8 weeks [128]. PLEX has been found to be better than IVIG in the treatment of acute MUSK MG [115]. In a retrospective analysis of 110 patients with MUSK MG, 93% of patients on PLEX had improvement in MGFA PIS, compared with 61% on IVIG [129]. However, a good number of MUSK MG patients did improve with IVIG, so this could be tried if PLEX were not available. Cardiovascular adverse events such as hypotension, fluid overload, arrhythmias, myocardial infarction and cardiac arrest can be seen with IVIG, but are encountered more frequently with PLEX. Systemic infections, acute renal failure and citrate reactions are also seen more commonly with PLEX. PLEX is recommended for the treatment of moderate to severe acute MG when rapid benefit is required, for maintenance treatment in refractory MG and for women during pregnancy [125].

## 5 Newer Biological Treatments

The newer biological therapies for MG are shown in Fig. 1 and outlined in Table 2.

### 5.1 Complement Inhibitors

Reduced circulating complement levels, deposition of complement and membrane attack complexes (MAC) at the NMJ and mitigation of experimental MG by complement-inhibiting cobra venom all indicate the importance of complement activity in AChR-positive MG [130, 131]. Therefore, development of complement inhibitors as a novel treatment for MG was logical.

#### 5.1.1 Eculizumab

Eculizumab was the first complement inhibitor to receive regulatory approval for clinical use. This is a humanized monoclonal antibody directed against C5 complement. It inhibits cleavage of C5 complement into its terminal active components, C5a and C5b, and the formation and deposition of MAC C5b-9. This was approved for treatment of paroxysmal nocturnal haemoglobinuria (PNH), a complement mediated disorder, in 2007 [132, 133].

In MG, an initial phase II study on 14 patients with severe refractory AChR antibody-positive disease employed an induction dose of 600 mg IV once weekly for 4 weeks, followed by a maintenance dose of 900 mg IV every 2 weeks for another 12 weeks [134]. The trial had a cross-over design but the washout period of 5 weeks proved to be too short. All patients were vaccinated against Neisseria meningitidis at least 14 days prior to the first dose of eculizumab, were on stable doses of conventional IST, and were not on IVIG, PLEX or rituximab. The primary efficacy endpoint of a 3-point reduction in QMG score was achieved by all except one patient (86%) and the frequency of severe adverse events was equal in both placebo and eculizumab-treated patients. In this study, 57% of patients on placebo treatment attained the prespecified outcome despite having severe MG prior to starting the study.

In a subsequent phase III multicentre trial (REGAIN), the same selection criteria were used. Sixty-two patients on eculizumab received an induction with 900 mg IV weekly for 4 weeks followed by 1200 mg IV on week 5, and then 1200 mg every second week or IV placebo at the same time points in 63 patients, with a total treatment duration of 26 weeks. In this trial, the primary efficacy outcome was change in MG-ADL, which did not achieve a significant difference [135], possibly due to the statistical analysis employed. This was a worst rank analysis which classified any patient who had a poor outcome, even if presumably unrelated to MG, as a negative outcome. The sample size might have been too small for this analytic approach. However, in analyses of the other endpoints in the study (MG-ADL, QMG and MG QOL15, MGC), a significant clinical improvement was noted in the patients who received eculizumab. No increase

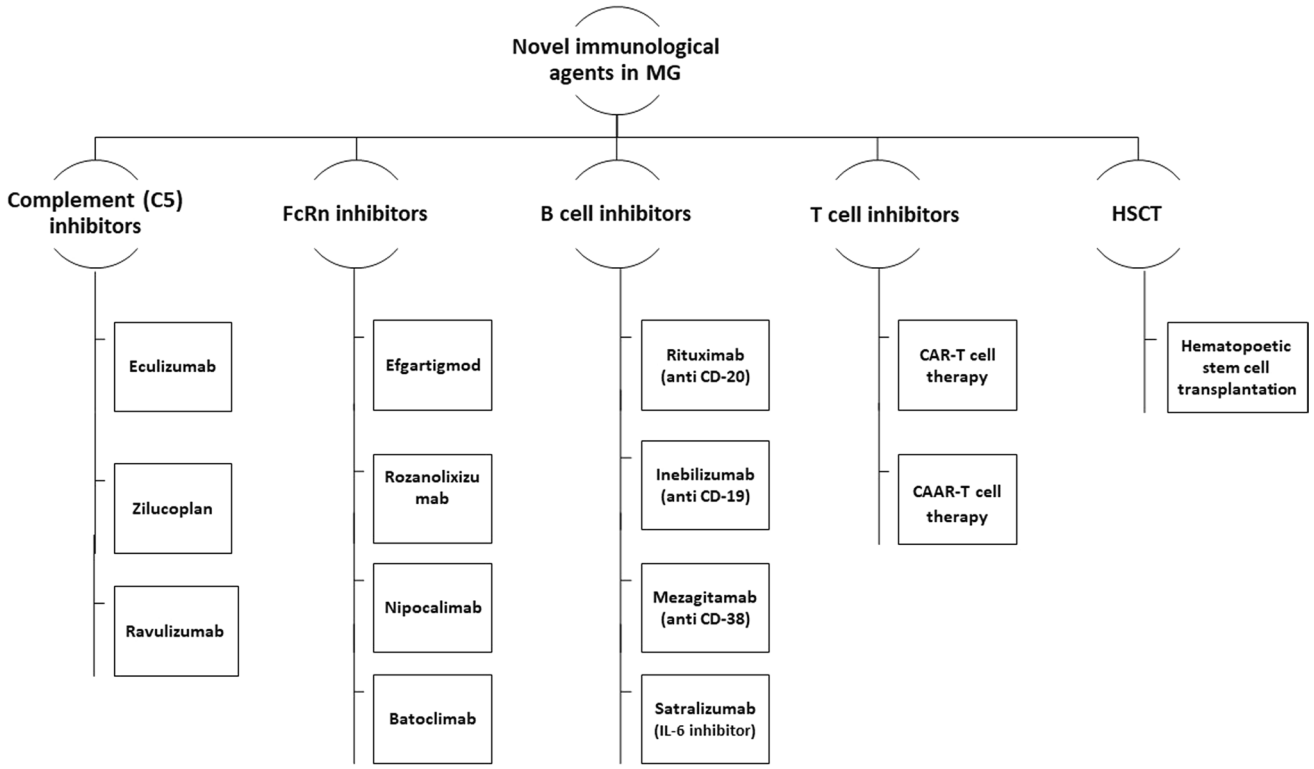


**Fig. 1** Novel immunological agents in myasthenia gravis (MG). *CAAR-T* chimeric auto-antibody receptor T cells, *CAR-T* chimeric antigen receptor T cells, *FcRN* neonatal Fc receptor, *HSCT* hematopoietic stem cell transplantation, *IL* interleukin

in serious infections or safety concerns were observed. Infection with encapsulated organisms, in particular Neisseria meningitides, is a feared complication expected with complement inhibitor therapies, but all patients in the trial had been vaccinated and none had meningococcal infection. The most common adverse events were mild and included headache, upper respiratory tract infection, and nasopharyngitis. The most frequently reported serious adverse events were infections but these were not more frequent in the active treatment arm (3% in eculizumab vs 10% in placebo). There was one death in the eculizumab arm, due to myasthenic crisis, and death was 90 days after the last eculizumab infusion.

In the post-hoc analysis of the REGAIN trial and its open-label extension, the MGFA post-intervention status improved for patients on eculizumab at all time points assessed. After 130 weeks in the studies, nearly 90% of patients improved and 60% achieved MM status. Also, the mean daily doses of conventional IST could be reduced even before achieving MM. Eculizumab was well tolerated with headache and nasopharyngitis being the most common side effects. Worsening MG was observed in 15% and myasthenic crisis in 3% of patients. Two deaths that occurred during the extension phase were due to comorbid illnesses and there was one case of non-fatal meningitis. Eculizumab has been approved for treatment of refractory AChR-positive generalized MG, but the cost is prohibitive and there has been a delay in roll-out of biosimilars [41].

### 5.1.2 Zilucoplan

Zilucoplan is a synthetic macrolide that has a greater affinity for inhibiting cleavage of C5 complement and also binds to preformed C5b, blocking its interaction with C6 complement [136]. Initially developed as an alternative to eculizumab resistance in PNH, it has the advantage of offering self-administered, rapid, subcutaneous (SC) dosing. The phase II study in MG evaluated two doses of SC zilucoplan at 0.1 mg/kg and 0.3 mg/kg daily or placebo for 12 weeks [137]. The patient selection criteria were similar to those in the eculizumab studies, but entry was not restricted to refractory or severe MG, and 45 patients were randomized to the three arms. The study met its primary efficacy endpoint of meaningful difference in QMG score for the 0.3mg/kg dosing, with a mean difference of − 2.8 compared with placebo and an onset of action as early as 1 week. The 0.1mg/kg dosing showed less robust change. The secondary outcome measures such as MG-ADL, MGC and MG QoL15r all showed a clinically meaningful response. None of the participants in the 0.3mg/kg dosing arm required rescue therapies.

**Table 2** Summary of the newer biological agents under evaluation in myasthenia gravis

| Agent (pharmaceutical company) | Mechanism | Dosing | Adverse effects in trials | Current status |
|---|---|---|---|---|
| Eculizumab (Alexion)* | C5 complement inhibitor | 900 mg IV qwk × 4, then 1200 mg IV q2wk | Risk of Neisseria meningitidis | Approved for AChR-positive GMG |
| Efgartigimod (Argenx)* | FcRn inhibitor | 10 mg/kg IV qwk | Mild; headache, reduced monocyte count, rhinorrhoea, myalgia, pruritis, injection-site pain, herpes zoster | Approved for AChR-positive GMG by FDA in December 2021 |
| Zilucoplan (UCB) | C5 and C5b complement inhibitor | 0.3mg/kg SC qd | Mild; injection-site reactions, headache | Orphan drug status for moderate to severe AChR-positive MG; ongoing phase III trial |
| Ravulizumab (Alexion) | C5 complement inhibitor with extended half-life | Weight based (<60 kg: 2400 mg, 60–100kg: 2700 mg, >100 kg: 3000 mg) IV; 2nd dose 15 d after 1st dose, then q8wk maintenance | Risk of Neisseria meningitidis | Ongoing phase III trial |
| Rozanolixizumab (UCB) | High affinity FcRn blocker | 7 mg/kg and 10 mg/kg qwk SC | Mild to moderate headache | Positive phase III trial results |
| Nipocalimab (Johnson & Johnson) | High affinity FcRn blocker | 60 mg/kg IV q2wk | Well tolerated | Ongoing phase III trial |
| Batoclimab (Immunovant) | FcRn blocker | 340 mg or 680 mg SC qwk × 4, then 340 mg q2wk | Influenza-like illness | Ongoing phase II trial |
| Rituximab (Genetech, Roche) | Anti-CD20 antibody | Induction with 375 mg/m$^2$ IV qwk × 4 or 1 g q2wk × 1 and repeat in 6 mo | Infusion reactions, minor risk of infections | MUSK MG and as a second-line agent for refractory AChR MG |
| Inebilizumab (Vielo Bio) | Anti-CD19 antibody | 300 mg IV q2wk × 1, then 300 mg IV in 6 mo | Fever, urinary infection | Ongoing phase II trial |
| Mezagitamab (Takeda) | Anti-CD38 antibody | 600 mg SC qwk | Fever, headache, postural hypotension | Ongoing phase II trial |
| Satralizumab (Hoffman-La Roche) | Anti-interleukin-6 antibody | 120 mg SC q2wk (0, 2 and 4 wk) followed by q4wk | Headache, arthralgia, injection-related reaction | Ongoing phase III trial |
| CAR-T and CAAR-T cell therapies | Chimeric autoantibody receptor expressing T cells directed against autoreactive B cells | | Serious cytokine-release syndrome | Ongoing phase I trial |
| Haematopoietic stem cell therapy | Eradication of all autoreactive T and B cells | | Toxicity related to conditioning regimen | Ongoing phase I trial |

*AChR* acetylcholine receptor, *C5* complement 5, *CAAR* chimeric autoantigen receptor, *CAR* chimeric antigen receptor, *d* day, *FcRn* neonatal Fc receptor, *FDA* Food and Drug Administration, *GMG* generalized myasthenia gravis, *IV* intravenous, *q* every, *SC* subcutaneous, *wk* week

*Approved agents

Despite these very promising results in a small number of patients, nearly 30% did not achieve the clinically important difference of 3 points in QMG. Clearly, there are other underlying immunological mechanisms (blocking, cross-linking with accelerated degradation) besides the complement pathway and there are likely specific patient-related factors that play a role in MG pathogenesis, although these are currently obscure [1]. The side effects were mild, unrelated to the study drug and did not require treatment modification. One patient on 0.3 mg/kg had exacerbation of pre-existing diverticulitis with a paracolic abscess. There were no other life-threatening adverse effects, meningococcal infections, or deaths. Zilucoplan has received FDA orphan drug status in moderate to severe AChR-positive generalized MG and a phase III trial is currently underway [138, 139].

#### 5.1.3 Ravulizumab

Ravulizumab was developed with the intention of eliminating the two-weekly IV dosing schedule of eculizumab, and the interim trough levels leading to breakthrough haemolysis in PNH. By incorporating four histidine substitutions into eculizumab, the modified pharmacokinetics and augmented endosomal recycling significantly extended the plasma half-life of the new molecule, transforming maintenance dosing to an interval of 8 weeks [140, 141]. The completed phase II and III non-inferiority trials in PNH showed headache as the most common adverse effect [142]. There were rare, serious but non-fatal infections, including Neisseria meningitis, in the ravulizumab arm. Early results from the ongoing multicentre phase III trial in MG are promising with a 5-point reduction in QMG scores of 30% in the treatment arm compared with 11% in placebo [143]. So far, the secondary outcome measures do not differ. The most common side effects were headache, nausea and diarrhoea. MG crisis was seen in 1.2% in the treatment arm versus 3.4% in the placebo arm. There have been four deaths so far in the treatment arm, three related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. The trial has a 26-week duration followed by the open-label extension phase, and is ongoing. The results are not yet published [144].

### 5.2 FcRn Inhibitors

The neonatal Fc receptor (FcRn) is a β2 microglobulin that plays a crucial role in maintaining IgG levels by prolonging the half-life [145]. By binding at the Fc region, the FcRn rescues IgG from acidic lysosomal degradation and this promotes recycling. One mechanism by which IVIG exerts its therapeutic effect is by saturating this FcRn binding and diverting the autoantibodies into the degradation pathway [146]. An alternate strategy of accelerating IgG degradation is by blocking the FcRn receptors, preventing recycling and leading to a reduced IgG half-life that outpaces the rate of synthesis, thus decreasing circulating IgG levels [147]. The FcRn inhibitors are a highly selective, IgG specific, chemical 'plasma exchange', sparing other off-target blood components.

#### 5.2.1 Efgartigimod

Efgartigimod is a modified human IgG1-derived Fc fragment that has high affinity blocking for FcRn at physiological and acidic pH and was the first FcRn inhibitor to be clinically evaluated for MG [148]. Phase I studies in healthy volunteers showed that a single dose of efgartigimod resulted in a decrease in IgG levels by day 2 with a maximum drop between days 6 and 21. After multiple doses, the serum IgG levels dropped by 75–85% [149]. The adverse events noted were headache, chills, dizziness, fatigue, altered WBC counts and increased CRP levels. The phase II exploratory study in AChR-positive generalized MG patients utilizing an IV dose of 10 mg/kg weekly for four doses, showed a rapid reduction in IgG starting from the first dose and reaching a maximum reduction of up to 70% one week after the fourth dose [150]. Although the study was not powered to test efficacy, a meaningful improvement was seen in QMG, MG-ADL and MGC scores. The clinical improvement persisted even after IgG levels returned to normal.

While the most frequently reported adverse effects were headache and reduced monocyte count, both of which were mild, other side effects included rhinorrhoea, myalgia, pruritis, injection-site pain and herpes zoster in the infusion-site arm. The recently published results of the phase III multicentre ADAPT trial employed the same dosing, but a repeat cycle of four weekly treatments was permitted after a minimum period of 8 weeks off treatment [151]. Retreatment criteria required a 2-point reduction of MG-ADL from baseline. The primary endpoint was the proportion of MG-ADL responders (2-point reduction at each of 4 weeks starting from 1 week after the fourth dose) and was achieved by 68% on efgartigimod compared with 30% on placebo. The primary endpoint was based on the first infusion cycle in AChR-positive patients. Other outcome measures including MG-ADL, QMG, MCG, and MG-QOL15 all showed a significant improvement in cycle 1. During the retreatment cycle, 71% of patients who received efgartigimod were responders. Amongst patients who did not respond after the initial treatment cycle, 37% responded after the second treatment cycle. Although more patients in the efgartigimod group had undergone thymectomy, the proportion of responders was lower in those who had surgery, so thymectomy was not considered to be the reason for improvement. All patients with MUSK MG responded in the first cycle, including those on placebo. The inclusion criteria permitted entry of seronegative patients, but the number was small,

limiting efficacy assessments in this population although some improvements were seen. Upper respiratory tract infections and urinary infections were more common in patients who received efgartigimod, while headache was the same in both groups.

The results of this trial led to the recent US FDA approval (December, 2021) of IV efgartigimod for the treatment of MG and it has also been approved in Japan (January 2022) [152, 153]. A SC preparation of efgartigimod combined with recombinant human hyaluronidase was also found to have comparable pharmacological properties and tolerance in a phase I study [154]. A phase III trial comparing SC and IV formulations in MG was recently completed and topline results report IgG reductions with the SC formulation to be non-inferior to the IV formulation; it is planned to be submitted for US FDA approval [155]. Treatment initiation with IV and maintenance with the SC formulation may offer better tolerability and efficacy and needs further exploration.

#### 5.2.2 Rozanolixizumab

Rozanolixizumab is a human IgG4 antibody that acts by binding and blocking FcRn receptors, bringing about a fall in circulating IgG levels [156]. Animal studies revealed a 90% reduction in IgG levels without any safety concern and a phase I study in healthy subjects used both IV and SC doses of 1, 4, and 7 mg/kg. Headache was the most common adverse event followed by nausea, vomiting and pyrexia and was observed with IV dosing more frequently than SC and at the 7 mg/kg dose. Significant dose-dependent IgG reduction was seen with both routes of administration. The phase II trial of rozanoxilizumab in MG included both AChR- and MUSK-positive patients. The study initially randomized 69 patients to a weekly dose of SC 7 mg/kg for 3 weeks or placebo [157]. After a 2-week drug-free period, all patients were re-randomized to either 7 mg/kg or 4 mg/kg weekly SC doses of rozanolixizumab for 3 weeks. The primary endpoint of change in QMG, assessed only after the first period, showed a decrease that did not reach statistical significance, perhaps because the duration of SC treatment was too short. In period 2, patients who remained on 7 mg/kg SC weekly showed significant improvement in QMG, MG-ADL and MGC scores, suggesting a 6-week course of 7 mg/kg SC would be the most effective treatment regimen. Patients switched from placebo to 4 mg/kg and from 7 to 4 mg/kg also showed some benefit. Headaches remained the most common adverse event, but were mild to moderate, responding to standard therapy. A large multicentric phase III trial of 7 mg/kg or 10 mg/kg rozanolixizumab or placebo given SC weekly for 6 weeks in AChR/MUSK-positive MG was recently concluded and positive topline results were announced in December 2021 [158].

#### 5.2.3 Nipocalimab

Nipocalimab is a human IgG1 antibody that saturates with high affinity and blocks the IgG Fc binding site on FcRn, at both endosomal and extracellular pH [159]. In a phase I study in 50 healthy volunteers, nipocalimab produced a dose-dependent rapid and sustained reduction in IgG levels comparable to PLEX with no increased risk of infections [159]. A mild reduction of albumin was observed at the highest doses. The phase II Vivacity-MG trial, which evaluated four different IV dosages (5 mg every 4 weeks, 30 mg every 4 weeks, 60 mg every 2 weeks and 60-mg single dose) of nipocalimab in patients with moderate to severe generalized MG, showed a favourable safety profile with no significant adverse effects, increased risk of infections or headaches compared with placebo [160]. Across all dosages there was significant reduction in serum antibody levels which paralleled improvement in MG-ADL scores. A phase III trial examining drug or placebo IV every 2 weeks for 24 weeks followed by an open-label extension phase is currently underway [161]. One notable pharmacokinetic property of nipocalimab is that with a transfer rate of 0.002%, it is practically impervious to placental transfer and does not reach the foetal circulation [162]. Since the risk of teratogenicity and foetal health are a major concern in the treatment of women of reproductive age, the low rate of placental transfer may prove to be an advantage of nipocalimab and this agent is currently being explored in pregnant women at risk of autoimmune haemolytic disease of the newborn [163].

#### 5.2.4 Batoclimab

Batoclimab is another human IgG1 directed against FcRn. Two separate phase I trials have evaluated batoclimab by IV and SC routes in single and multiple ascending doses [164, 165]. The drug was well tolerated at all doses and both routes of administration. An influenza-like illness was the most common adverse event. As with other FcR inhibitors, a dose-dependent reduction in IgG levels was observed with the maximum drop at day 10. Unpublished results of the phase II study which employed doses at 340 mg and 680 mg SC in seropositive MG showed positive results [166, 167]. Another phase II trial with an open-label extension using SC 340 mg every 2 weeks is ongoing [168].

### 5.3 B-Cell Inhibitors

#### 5.3.1 Rituximab

Rituximab is a chimeric murine/human monoclonal antibody that binds specifically with CD20 transmembrane protein. CD20 is selectively expressed by certain B cells but not

expressed by B-cell precursors, mature, memory B cells or long-lived plasma cells [169]. Rituximab produces selective B-cell depletion through complement and antibody-mediated mechanisms and by apoptosis. Initially developed for treatment of B-cell lymphomas, utility in treatment of diverse autoimmune diseases has been recognized over the years [170]. Given the role of B cells in MG pathogenesis, rituximab has also been explored in MG since 2008 [171].

In 2017, a systematic review investigated the role of rituximab in MG based on data from 168 patients from case reports and case series [172]. The most common induction treatment was 375 mg/m$^2$ IV weekly for 4 weeks. The response was significantly better for MUSK MG with nearly 70% of patients attaining MM or better as opposed to 30% of AChR-positive patients who responded. Besides MUSK MG, age < 45 years and mild to moderate MGFA severity grades predicted a favourable response. Rituximab was well tolerated and of 105 patients with available data, 15 had some adverse effects including agranulocytosis, pneumonia, reactivation of herpes zoster and spondylodiscitis. The side effects were seldom severe.

The only phase II clinical trial of rituximab in AChR-positive generalized MG did not show benefits on the endpoints assessed. The study was completed in 2018 and the results recently published in December 2021. The outcome measures included steroid-sparing, and improvement in MGC or QMG scores [173]. Although most of the patients in the trial were only mildly symptomatic and this could have led to a ceiling effect in improvement, a subgroup analysis of patients with more severe disease also failed to show any benefit with rituximab.

Efficacy of rituximab in longstanding refractory MG seems to be limited. In a prospective trial of 12 patients with refractory AChR-positive MG and a median disease duration of 12 years, rituximab in a total dose of 3 g (1 g given 2 weeks apart followed by 1 g at 6 months), only a single patient achieved the primary endpoint of a 20-point reduction in myasthenia muscle score at 12 months [174]. However, a limitation of using muscle scores as the outcome metric in chronic refractory MG cases may be that the initial reversible neuromuscular weakness gradually progresses to a fixed myopathy with lesser chance of meaningful improvement in strength due to structural changes at the post-synaptic membrane [175]. Nevertheless, nearly half of the patients achieved a significant reduction in QMG and an improved MGFA PIS, so that the study showed an overall favourable outcome. The potential benefit of initiating rituximab early in the disease course was examined in a cohort of 72 patients with non-MUSK generalized myasthenia. Of the 72 patients, the initial dose of RTX was 1000 mg in only three patients while the majority (57) received 500 mg and 12 received doses as low as 100 mg. The maintenance dose was 500 mg in all except three who received 100 mg. When rituximab was initiated within 12 months of disease onset, the primary outcome of time to remission was significantly shorter. Also, patients on early therapy required fewer rescue treatments and had lower rates of treatment discontinuation compared with conventional therapies [176]. However, this was a retrospective study with a non-randomized design so the evidence is limited.

A subsequent systematic analysis reviewed articles from 1999 to 2019 which included at least five patients [177]. Some used a dosing regimen of 1 g given at baseline and repeated after 2 weeks, but the most common induction dosage was 375 mg/m$^2$ weekly for 4 weeks. The outcome measures were heterogenous but overall, improvements were evident in manual strength testing, time to remission or MM and reduction in standard IST.

The antibody titres may be a predictor of treatment response for MUSK but not in AChR MG [172, 177]. In MUSK MG, sustained remission after rituximab paralleled sustained low levels of IgG4 antibodies. In those patients who did not respond, the IgG4 levels remained high [178]. Hence, CD19/20 B-cell counts might be a better measure to guide rituximab maintenance treatment, especially in MUSK MG.

Unlike other recent biologicals, long-term safety data for rituximab is available. In the final report of the rheumatoid arthritis global clinical trial programme over 11 years, the rate of all adverse events was highest during the first 6 months, mostly due to infusion-related events, and subsequently decreased and remained stable [179]. Infusion reactions include a warm sensation or paraesthesia, flu-like syndrome, headache, chest discomfort, flushing, etc. and could be mitigated with premedication with corticosteroids and antihistamines. Serious opportunistic infections were rare at 0.05/100 patient-years in the active treatment arm versus 0.09/100 patient-years with placebo, with a single report of progressive multifocal leukoencephalopathy (PML). In MG trials, there has been a single case of PML in a patient who had previously received azathioprine and MMF [177]. Other infections include respiratory tract infections, gastroenteritis, erysipelas, herpes zoster reactivation and giardiasis [177]. There was no increased risk for cardiac events or malignancies compared with placebo-treated patients with rheumatoid arthritis.

The 2016 and 2021 international consensus guidelines on management of MG list rituximab as a second-line option in treatment failure or intolerance to conventional agents [41]. While there is sufficient evidence to support the use of rituximab early in MUSK MG, questions remain on its role as an initial agent in AChR MG, and the preferred induction and maintenance regimens, especially given the current environment of SARS-CoV-2 infections and vaccinations. A SC preparation of rituximab is under investigation for oncological therapy [180]. Recently, after expiration of the

rituximab patents, biosimilars (Riximyo® and Ruxience®) have been approved for clinical use and have the advantage of being considerably less expensive [181]. Rituximab is being used more frequently in several autoimmune diseases and in several centres across the world and is the first- or second-line disease-modifying agent in autoimmune disorders. Besides the favourable safety profile and the relative ease of administration and maintenance, rituximab is comparatively cheaper in several parts of the world, including Asia and Scandinavian countries. Further cost-effective analyses in comparison with other ISTs may be pertinent as a single course of rituximab is almost equal to the 6-monthly cost of MMF [182].

#### 5.3.2 Other Direct and Indirect B-Cell Inhibitors

Second-generation anti-CD20 agents such as ocrelizumab, ofatumumab, obinutuzumab and veltuzumab have the advantage of being fully humanized and thus may be better tolerated and more efficacious than rituximab, although currently evidence is not available and clinical trials in MG are not underway [183]. Ofatumumab showed sustained remission in a patient with refractory MG who lost responsiveness to rituximab [184]. The anti-CD19 agent, inebilizumab, is a humanized IgG1κ that binds and depletes CD19 expressing pre-B and mature B cells [185]. A phase III trial (MINT trial) is recruiting patients with moderate to severe AChR or MUSK antibody-positive MG to receive inebilizumab on days 1, 15 and 183 [186]. Iscalimab is another fully human IgG antibody directed against CD40 antigen that was evaluated in a phase II trial in moderate to severe AChR- or MUSK-positive MG, and while the results are not yet published, initial reports are disappointing [187, 188]. Mezagitamab is a fully humanized anti-CD38 monoclonal antibody administered subcutaneously which has received orphan drug status in refractory multiple myeloma and is being evaluated in MG [189]. Belimumab, a monoclonal antibody against BAFF (B lymphocyte activating factor belonging to the tumour necrosis factor [TNF] family; aka BlyS [B lymphocyte stimulator]) was evaluated in a phase II trial in AChR-positive MG, but failed to show any significant difference in QMG scores [190].

There are several other proinflammatory mediators such as cytokines and interleukins which are involved in MG pathogenesis [191]. Monoclonal antibodies that target these chemokines and downstream effectors such as tocilizumab (inhibits IL6) and secukinumab (inhibits IL17A) might be promising adjuvants and may be evaluated in future trials [8]. Satralizumab is another agent that has recently generated much interest. It is a humanized monoclonal IgG2 antibody that binds with IL6 receptor and inhibits the downstream signalling pathway responsible for T-cell and B-cell activation and B-cell differentiation [192]. It has the unique property of dissociating from IL6 in the acidic endosomal pH and getting recycled by the FcRn pathway, thus prolonging its half-life. Satralizumab was approved for the treatment of seropositive neuromyelitis optica (NMO) and a phase III trial is currently recruiting patients with MG with an initial 2-weekly dosing regimen followed by 4-weekly SC schedules [193].

Another attractive target for immunomodulation is the cytoplasmic Bruton's tyrosine kinase (BTK), which on phosphorylation leads to increased B-cell proliferation, differentiation and survival and is expressed in several immune cell types with the exception of T cells and plasma cells [194]. BTK inhibitors (BTKi) are revolutionizing the treatment of B-cell malignancies and the next-generation agents offer excellent avenues in treatment of autoimmune disorders [195]. Tolebrutinib, an oral BTKi, has already been found to be efficacious and well tolerated in multiple sclerosis in phase IIb trials and a phase III trial is currently recruiting patients with generalized MG [196, 197].

### 5.4 CAR-T Cell Therapy

The concept of adoptive T-cell transfer has been a breakthrough in the field of haemato-oncology. In essence, this therapy consists of priming a patient's own T cells with antitumour activity, expanding them and reinfusing the modified T cells into the patient [198]. The target specificity of these T cells and their selective target elimination is enabled by expression of chimeric antigen receptors (CARs), which are synthetic receptors containing a T-cell activating domain and extracellular target-recognizing domain. The newer generations of CAR allows proliferation and persistence of these CAR-T cells in the circulation, thus earning the epithet of 'living drugs' [199, 200]. Anti-CD19 CAR-T cells have been approved for the treatment of refractory leukaemia and lymphomas as they have shown remarkable efficacy [201, 202]. Given the proof of principle from oncology, the benefits of CAR-T cell therapy in autoimmune disorders are also being explored. By redirecting T cells against autoantibody-secreting B cells in mouse models of type 1 diabetes and systemic lupus erythematosus (SLE), selective B-cell elimination and a favourable disease response was observed [203]. Currently, there are a number of trials recruiting patients for CAR-T cell therapy in refractory autoimmune disorders including SLE, Sjogren's syndrome, scleroderma and lupus nephritis, most from China [204]. CAR-T cells directed against B-cell maturation antigen (BCMA) is the cutting-edge treatment for refractory multiple myeloma. Descartes-08, which is a CD8-positive investigational CAR-T cell therapy that targets BCMA but engineered to have a limited and predictable half-life, is being evaluated in a phase I/II trial in severe MG with early results that appear to be encouraging [205, 206].

However, life-threatening side effects have been noted in patients with haematological malignancies treated with the CAR-T cell therapy and are a major concern. Cytokine release syndrome (CRS) has been the most serious and is triggered by the CAR-T cell activation with other immune cells redirected to target engagement [202]. The symptoms can range from mild fever, malaise and anorexia to severe, life-threatening hypotension and hypoxemia due to capillary leakage [207]. Elevated interleukin-6 (IL6) is the main mediator of CRS and agents such as tocilizumab and corticosteroids may be beneficial for treatment of this complication.

### 5.5 CAAR-T Cell Therapy

CAAR-T cells differ from CAR-T cells by their expression of chimeric autoantibody receptors to the antibodies expressed by antibody-secreting autoreactive B cells. The binding of the CAAR-T cell antigen to the corresponding autoantibody expressing B cells results in their target elimination [208]. CAAR-T cells theoretically can be developed against any autoimmune condition in which the autoantibodies are pathogenic and the molecular structure of the epitope is well defined; both of which are evidently true for MUSK MG. Preclinical studies in the mouse model showed that CAAR-T cells selectively suppress B cells that express anti-MUSK antibodies without major safety concerns [209]. The same treatment may be limited for AChR MG given the variation in the antibody epitopes. A phase I trial is currently recruiting patients with pemphigus vulgaris for CAAR-T cell-based treatment [210].

### 5.6 Haematopoietic Stem Cell Transplantation

The role of memory B cells and long-lived plasma cells in sustaining autoimmune pathogenesis has now been recognized [211]. Surviving in bone marrow niches, the long-lived plasma cells, in particular, are not targeted by standard immunomodulatory treatments. Their continued activation in MG has been postulated to be the reason for the sustained antibody levels, despite treatment including thymectomy [212]. In addition, these cells do not express CD20 and are not targeted by existing anti–B-cell therapies. Hematopoietic stem cell transplantation (HSCT) is the only modality of treatment that eradicates all autoreactive T and B cells, allows immune resetting, and offers potential life-long sustained remission equivalent to a cure. HSCT is being utilized increasingly in severe refractory autoimmune disorders [213]. Evidence has been accumulating in favour of HSCT in cases of refractory MG with all patients achieving complete stable remission, although the benefits may not be permanent as evident in some autoimmune disorders such as chronic inflammatory demyelinating polyneuropathy [214–218]. Unfortunately, the phase I study of HSCT in refractory MG was terminated prematurely because of failure of recruitment and no observations have been published. The main concerns with HSCT are the aggressive conditioning regimen, the resultant systemic toxicity, infertility and increased risk of infections. Individualized conditioning regimens might address some of these concerns. A phase II study of HSCT is currently recruiting patients with various neurological autoimmune disorders, including refractory MG [219].

## 6 Conclusion

The evolution of MG pharmacotherapy from AChEI and β-agonists, to the recent advent of novel biological agents, closely reflects advances in the fields of immunopathology, molecular and translation medicine. Improved clinical trial designs have facilitated the gathering of high-level evidence to support the use of these novel therapies. The focus of MG therapy has shifted towards patient-determined, target-specific and selective immunological agents such as complement and FcRn inhibitors, direct and indirect B-cell depletors and CAR-T cell therapies and away from older, broad-spectrum immunosuppressant therapies. The benign safety profiles of these novel agents have supported their use. Despite these advances, many challenging questions remain such as the long-term safety, efficacy in seronegative MG, potential use as first-line agents in treatment-naïve patients and the method and timing of switching from one agent to another [13].

In addition, given the different mechanisms of action, combination therapies might be considered for some refractory patients. In contrast, experience regarding the clinical use of conventional IST has accumulated over many decades, and in fact, all the newer agents have been tested in patients on stable immunomodulatory treatment with conventional agents and not as standalone therapies. These considerations coupled with the decidedly high cost of novel agents are likely to prevent access for many patients, especially those in resource-limited countries. Factors such as patent protection, orphan drug status, relatively small numbers of patients and the high cost of research and development all play a role in escalating prices that are likely to remain high until biosimilar agents are available [13]. Hence, despite many positive advances, it is probable that conventional agents will remain in use in many parts of the world.

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