TREATMENT OF MYASTHENIA GRAVIS: AN EVERCHANGING FIELD

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ABSTRACT
Myasthenia gravis (MG) is a chronic autoimmune disorder affecting the neuromuscular junction, characterised by fluctuating muscle weakness. It is primarily mediated by antibodies against acetylcholine receptor (AChR), muscle-specific kinase (MuSK) or low-density lipoprotein-related protein 4 (LRP4). However, seronegative patients may constitute 10-15% of all MG cases. Treatment of MG is traditionally based on corticosteroids and pyridostigmine, with the addition of steroid-sparing immunosuppressive agents such as azathioprine, mycophenolate mofetil or rituximab, depending on the characteristics and the severity of each case. However, these therapies have not been rigorously evaluated in randomised-controlled clinical trials specifically for MG. During the last years, neonatal Fc receptor (FcRn) inhibitors and complement inhibitors have demonstrated a favourable safety and efficacy profile in MG patients within the context of randomised-controlled clinical trials. Therefore, they have been incorporated into daily clinical practice. Emerging agents of these drug classes and other novel therapeutic options, such as anti-CD19 monoclonal antibodies, Bruton's Tyrosine Kinase inhibitors and Chimeric antigen receptor (CAR) T cells are currently being investigated as adjunctive therapies in MG patients. This narrative review aims to provide a comprehensive overview of current pharmacologic treatment strategies for MG, with particular focus on recently approved agents and investigational therapies under clinical development.

Keywords: Myasthenia Gravis, immunotherapy, novel drugs, randomised - controlled clinical trial, adverse events.

Η ΘΕΡΑΠΕΙΑ ΤΗΣ ΒΑΡΕΙΑΣ ΜΥΑΣΘΕΝΕΙΑΣ: ΕΝΑ ΣΥΝΕΧΩΣ ΜΕΤΑΒΑΛΛΟΜΕΝΟ ΠΕΔΙΟ

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Περίληψη
Η βαρεία Μυασθένεια (MG) αποτελεί μία χρόνια αυτοάνοση διαταραχή, η οποία προσβάλλει τη νευρομυική σύναψη και χαρακτηρίζεται από κυμαινόμενη μυϊκή αδυναμία. Προκαλείται από αντισώματα έναντι των υποδοχέων ακετυλοχολίνης (AChR), της ειδικής για τους μυς τυροσινικής κινάσης (MuSK) ή του υποδοχέα LRP4. Ωστόσο, οι οροαρνητικοί ασθενείς αποτελούν το 10-15% των συνολικών περιπτώσεων MG. Η θεραπεία της MG παραδοσιακά στηρίζεται στα κορτικοστεροειδή και την πυριδοστιγμίνη, ενώ συχνά προστίθενται ανοσοκατασταλτικοί παράγοντες, όπως η αζαθειοπρίνη, η μυκοφαινολάτη μοφετίλ ή η ριτουξιμάμπη, ανάλογα με τα χαρακτηριστικά και την σοβαρότητα της νόσου. Παρόλα αυτά, οι παράγοντες αυτοί δεν έχουν ελεγχθεί σε τυχαιοποιημένες-ελεγχόμενες κλινικές δοκιμές. Κατά τη διάρκεια των τελευταίων ετών, οι αναστολείς του νεογνικού υποδοχέα Fc (FcRn) και οι αναστολείς του συμπληρώματος έχουν παρουσιάσει ευνοϊκό προφίλ ασφάλειας και αποτελεσματικότητας στην MG σε τυχαιοποιημένες-ελεγχόμενες κλινικές δοκιμές. Για το λόγο αυτό, οι εν λόγω θεραπείες έχουν ενσωματωθεί στην καθημερινή κλινική πράξη. Νέα φάρμακα των οικογενειών αυτών, καθώς και καινοτόμες θεραπευτικές επιλογές, όπως τα μονοκλωνικά αντισώματα έναντι του CD19 αντιγόνου, οι αναστολείς της τυροσινικής κινάσης του Bruton (BTK) και τα Τ-κύτταρα με χιμαιρικό υπο-

δοχέα αντιγόνου (CAR T cells) δοκιμάζονται σε ασθενείς με MG, ως επιπρόσθετη θεραπεία. Η παρούσα αφηγηματική ανασκόπηση στοχεύει στην αναλυτική παρουσίαση της φαρμακευτικής αντιμετώπισης της MG, με έμφαση στις πρόσφατα εγκεκριμένες θεραπείες, καθώς και στις επιλογές που επί του παρόντος διερευνώνται.

Λέξεις κλειδιά: Βαρεία Μυασθένεια, ανοσοθεραπεία, νέα φάρμακα, τυχαιοποιημένη - ελεγχόμενη κλινική δοκιμή, ανεπιθύμητες ενέργειες.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease affecting the neuromuscular junction (NMJ). The clinical presentation is defined by weakness of the skeletal muscles. MG is considered a rare disease affecting approximately 10 – 20 per 100,000 people.[1] The incidence of this disorder may reach up to 30 cases per 1 million person-years.[2]

MG is caused by autoantibodies targeting receptors in the NMJ. Antibodies against acetylcholine receptor (AChR) are found in the serum of up to 80-90% of patients with MG.[3] AChR antibodies lead to NMJ dysfunction via direct binding to the AChRs, cross-linking and internalising AChRs, as well as inducing complement-mediated AChR destruction. The majority of these patients manifest thymic hyperplasia (60-70%), while 10-12% may be diagnosed with thymoma.[4]

Muscle-specific kinase (MuSK) and low-density lipoprotein receptor-related protein 4 (LRP4) are essential for clustering AChRs at the postsynaptic membrane. Antibodies against MuSK and LRP4 are responsible for 1-10% and 1-3% of all MG cases, respectively.[5-7] In contrast to AChR antibodies, MuSK antibodies mostly belong to the IgG4 subtype and thus do not activate complement.[8] Up to 15% of MG patients are seronegative.[4]

The weakness in MG may be generalised or localised, with more proximal than distal distribution.[9] Diplopia and ptosis are the most common symptoms. Apart from extraocular muscles, weakness in MG is usually symmetric. Exercise typically worsens symptoms. The weakness is profound during night hours and may vary from day to day.

The diagnosis is based on the detection of antibodies against AChR, MuSK, or LRP4 in patients with a compatible clinical picture.[10] Repetitive nerve stimulation and single-fibre electromyography may aid in the diagnosis, especially in seronegative cases.

The treatment strategy depends on the severity of the disease, antibody status, age and comorbidities, as it is mainly based on immunosuppression. During recent years, new promising therapeutic regimens have emerged in clinical practice. The aim of the current narrative review is the treatment of MG, with emphasis on substances still under investigation.

METHODS

This narrative review synthesises evidence from randomised-controlled clinical trials (RCTs), observational studies, real-world clinical data, and expert recommendations to provide an integrated overview of current and emerging pharmacologic strategies for the treatment of MG. The review presents both established immunotherapies and newly approved targeted agents, with a focus on their mechanisms of action, regulatory status, clinical efficacy, and safety profiles.

Therapeutic categories discussed include corticosteroids, steroid-sparing immunosuppressants, complement inhibitors, neonatal Fc receptor (FcRn) antagonists, and experimental therapies such as anti-CD19 monoclonal antibodies, Bruton's tyrosine kinase (BTK) inhibitors, telitacicept, and chimeric antigen receptor (CAR) T cells. In addition, the review highlights agents under clinical development and provides insight into the evolving treatment algorithm for MG across patient subgroups, including those with seronegative disease, MuSK or LRP4 antibodies, ocular MG, paediatric patients, and pregnant individuals.

By incorporating data from pivotal trials, ongoing studies, and expert consensus documents, this review aims to guide clinicians and researchers through the expanding therapeutic landscape of MG.

CURRENT TREATMENT OPTIONS

Symptomatic Treatment

Pyridostigmine is the preferred agent for the symptomatic treatment of MG.[11] Its mechanism of action is based on the increase of the acetylcholine amount in the synaptic cleft through inhibition of acetylcholinesterase. Ambenonium chloride is a less effective second-line acetylcholinesterase inhibitor.[12] This drug class is less effective in MuSK-associated MG, with frequent side effects.[5]

Gradual titration of pyridostigmine dosage is required. The typical adult dose is 30-60 mg every 4-6 hours.[13] Muscarinic adverse events may include vomiting, diarrhoea, nausea, muscle cramps, urinary urgency, hyperhidrosis, increased salivation and bronchial secretions, hypotension, and bradycardia. These side effects may be treated with atropine sulfate,

glycopyrronium bromide, or loperamide.[9]

Adjuvant symptomatic treatment with beta-2 adrenergic receptor agonists (salbutamol, tervutaline) may be also considered in selected cases of MG.[14,15]

Corticosteroids

Corticosteroids are the most commonly prescribed immunosuppressive drugs in MG. They exert their action by suppressing complement-mediated reactions at the endplates.[16] They also lead to CD4+ T-cells apoptosis and decrease in the AChR antibody levels, via reduction of B-cells' population.[17]

Prednisolone, rather than prednisone, is more frequently used in Greece.[15] The starting dose is 10-20 mg/day and may be titrated by 5 mg/week up to 60 mg/day. High-starting doses of prednisolone are contraindicated due to possible transient worsening of muscle weakness. The benefit from this treatment is manifested 2–6 weeks after its initiation.[9] Once therapeutic targets have been reached, a slow tapering is advised, due to a plethora of side effects, such as hyperglycaemia, cataract and osteoporosis. However, in most cases a low daily maintenance corticosteroid dose, instead of complete cessation, is advised.[18]

Azathioprine

Azathioprine is a purine synthesis inhibitor, leading to decreased B and T cell proliferation.[4] It is commonly used along with prednisolone as a first-choice treatment for generalised MG. Its effect is delayed and is usually seen after six months to two years.[19] Prednisolone dose may be reduced when the effect of Azathioprine has been reached.

Azathioprine may be started at a dose of 50 mg/day and increased by 50mg every two to four weeks, up to 2-3 mg/kg.[15] Testing for the activity of the enzyme thiopurine methyltransferase is advised before the initiation of azathioprine. Low or absent activity of this enzyme may lead to toxic accumulation of azathioprine. The most common adverse events include cytopenia, hepatotoxicity, and flu-like syndrome, especially during the first months of treatment.[9]

Mycophenolate Mofetil

Mycophenolate Mofetil (MMF) exerts its action by reducing both the T and B cells, via inhibition of the inosine monophosphate dehydrogenase.[20] This enzyme is crucial for the synthesis of guanosine nucleotides. The findings regarding its efficacy in MG are conflicting.[21,22] A slightly faster onset of effect may be shown with MMF compared to azathioprine. MMF, alongside cyclosporine, methotrexate and tacrolimus, are secondary alternatives to azathioprine.[9,14,15]

The starting dose of MMF is 500mg twice daily and may be titrated up to 1 – 1.5g twice daily. The most common side effects include gastrointestinal symptoms and cytopenia.

Methotrexate

Methotrexate suppresses the proliferation of immune cells via inhibition of dihydrofolate reductase, which is responsible for the conversion of dihydrofolate to tetrahydrofolate.[23] This reaction is vital for the synthesis of purines and pyrimidines. The efficacy and steroid-sparing properties of methotrexate in MG have not been proven in an RCT performed in 2016.[24]

Methotrexate is administered orally, once per week.[15] The initial dose is 7.5mg and may be increased by 2.5mg every one to two weeks, up to 20-25mg once weekly. Daily supplementation with folic acid is advised, except on the day of methotrexate administration.[25] The most important adverse events of methotrexate are suppression of the bone marrow, hepatotoxicity and pulmonary toxicity.

Cyclosporine

Cyclosporine is a calcineurin inhibitor and thus suppresses the synthesis of interleukins (IL), such as IL-2, which is crucial for the activation of T lymphocytes.[26] Cyclosporine's efficacy in MG as an add-on therapy to corticosteroids has been shown in a prospective RCT.[27] Its maximum therapeutic effect may be reached at approximately six to seven months.[28]

The starting dosage of cyclosporine is 2.5mg/kg per day in two divided doses.[15] It is typically increased by 0.5 mg/kg per day every four to eight weeks, up to 5 mg/kg per day. Close monitoring of cyclosporine's levels in the serum is advised due to serious side effects, including hypertension, nephrotoxicity, hepatotoxicity, tremor, and malignancies, such as lymphoma and squamous cell skin cancer.

Tacrolimus

As cyclosporine, tacrolimus is another calcineurin inhibitor. Its efficacy in MG is mainly based on data from observational studies and therefore, is used as an off-label alternative to azathioprine.[29] The onset of clinical response to this treatment may be shown after 6 to 12 months.

The initial dosage of tacrolimus is 1 mg/day and may be titrated up to the usual maintenance dosage of 3 mg/day divided into two doses.[30] Tacrolimus shares common adverse events with cyclosporine, however, with a relatively safer profile.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that acts on DNA and inhibits the proliferation of T and B lymphocytes.[31] It is an off-label option for the treatment of refractory generalised MG, with a possible steroid-sparing effect.[32] Cyclophosphamide is typically administered in monthly pulses of 0.5 – 1.5g/m^2

of body surface area. It is not commonly used due to its unfavourable safety profile, as it may lead to teratogenicity, infertility, alopecia, cytopenia, cystitis and malignancy.[30]

Anti-CD20 monoclonal antibodies

Rituximab is a chimeric anti-CD20 monoclonal antibody which eliminates immature, naive and memory B-cells.[33] This way, rituximab leads to reduction of autoantibodies' levels and thus improvement of muscle strength in patients with MG.[34,35]

In the AChR seropositive MG, rituximab may be used as an alternative option when symptoms are refractory or other therapeutic regimens cannot be tolerated.[14] However, rituximab is considered a first-line treatment option for MuSK-positive MG patients.[36] Furthermore, it may be used in seronegative MG, although RCTs are currently lacking.[37]

Rituximab is administered intravenously, most commonly in two doses of 1g separated by two weeks or in four weekly doses of 375mg/m^2 body surface.[38] It may be administered again, usually after 4-6 months, depending on the disease progression or the CD20+ cell counts in the peripheral blood. Its therapeutic effect may be shown after 1-3 months.[30] The most important side effects include infusion-related reactions, serious infections, such as progressive multifocal encephalopathy (PML), cytopenia and hypogammaglobulinemia.[30]

Intravenous Immunoglobulin (IVIG)

IVIG is a mixture of donated human immunoglobulins, which contains all IgG subclasses. It has several anti-inflammatory and immunomodulatory effects. IVIG inhibits the complement activity and binds to autoantibodies, leading to deactivation of the latter.[39] Furthermore, IVIG blocks Fc receptors in the spleen and liver, leading to inhibition of autoantibodies recirculation in the serum.[40]

IVIG is mainly used in myasthenic crisis or impending crisis.[15,30] Myasthenic crisis is defined by severe weakness of bulbar and/or respiratory muscles with concurrent need for respiratory support. IVIG may be selected as a bridge treatment to corticosteroids or other slow-acting immunosuppressants. Furthermore, it may be rarely used as a maintenance treatment in refractory cases. Finally, IVIG may be administered preoperatively to selected MG cases with increased risk of postoperative deterioration. History of myasthenic crisis, bulbar or respiratory symptoms, and chronic pulmonary disease are risk factors for postoperative clinical worsening.

IVIG has a rapid therapeutic effect occurring approximately after 2-5 days, which may last up to six weeks.[41] The typical dosage of IVIG is 2 g/kg, divided in 2-5 daily doses. Anaphylactic reaction in IgA deficiency is a severe complication of IVIG administration, which may be prevented by routine testing of IgA levels in serum before starting treatment.[42] Other serious but uncommon adverse events include thrombotic events, autoimmune haemolytic anaemia, renal failure, aseptic meningitis and pulmonary oedema.[43]

Plasma exchange (PLEX)

PLEX is a procedure replacing plasma with albumin and saline. Its immunomodulatory function is mainly based on the removal of autoantibodies, immunocomplexes and cytokines, the shift of humoral to cell-mediated immunity and the increase of T-regulatory cells.[44]

The therapeutic benefit of PLEX is similar to IVIG, although PLEX may be more effective in MuSK-associated MG.[45] They share common indications, although PLEX, rather than IVIG, is considered the 1st line treatment option for myasthenic crisis, due to its predictable result.[46]

Three to seven PLEX sessions over 7-14 days are typically required in myasthenic crisis. It is contraindicated in sepsis and may lead to adverse events such as hypotension, hypocalcaemia, thrombosis in the catheter site, and infections.[15]

Immunoadsorption may be an alternative therapeutic option to PLEX for the treatment of severe MG relapses or myasthenic crises. This technique leads to the removal of specific autoantibodies, such as anti-AChR or anti-MuSK, via the use of specific ligands, such as protein A or synthetic peptides (e.g. fragments of AChR).[47] No RCTs regarding its efficacy in MG exist. However, small studies have shown similar benefits to PLEX or IVIG in MG exacerbations.[48,49] Immunoadsorption is not routinely used in clinical practice due to increased cost and limited availability.

Thymectomy

Thymomatous MG is a well-recognised paraneoplastic syndrome. AChR may be expressed in thymic activated epithelial cells and autoreactive T cells against AChR may in turn escape the thymus and activate B cells in the periphery to produce antibodies.[50]

All recently diagnosed MG patients should be examined with thoracic CT or MRI, to identify thymoma or thymic hyperplasia.[14] Patients with thymoma, irrespective of the MG status, should be operated due to oncological indications. In young patients (age < 50 years) with generalised non-thymomatous AChR-associated MG, thymectomy should be performed early on after the diagnosis and as soon as the patient is clinically stable.[14,15] Non-thymomatous thymectomy is currently not indicated for MuSK or LRP4-associated MG. Thymectomy may be a therapeutic option in seronegative MG or ocular AChR-associated MG, when other treatments have failed.[51]

The maximum benefit from thymectomy may be

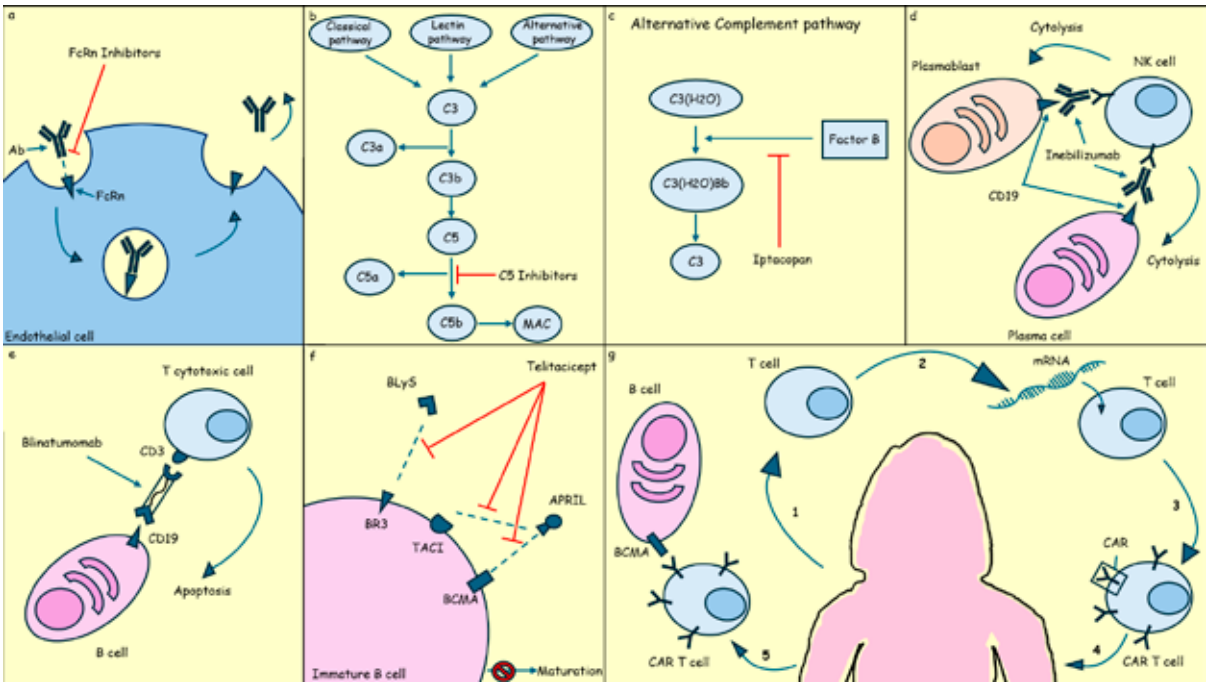

Figure 1. Mechanism of action of emerging therapies for Myasthenia Gravis. (**a**) FcRn Inhibitors. (**b**) Complement C5 Inhibitors. **(c)** Iptacopan - Complement Factor B Inhibitor). (**d**) Inebilizumab – anti-CD19 monoclonal antibody. (**e**) Blinatumomab - bispecific antibody binding to CD3 on T cells and CD19 on B cells. (**f**) Telitacicept - dual BLyS/APRIL inhibitor. (**g**) CAR T cells.

Ab: Antibody; AChR: Acetylcholine Receptor; APRIL: A-Proliferation-Inducing Ligand; BCMA: B Cell Maturation Antigen; BLyS: B-Lymphocyte Stimulator; BR3: BLyS Receptor 3; CAR: Chimeric Antigen Receptor; FcRn: Neonatal Fc receptors; MAC: Membrane Attack Complex; NK cell: Natural Killer cell; TACI: Transmembrane Activator and Calcium Modulator and Cyclophilin Ligand Interactor.

shown up to one year after the operation.[52] In thymomatous MG, thymectomy may lead to complete remission in up to 30% of patients.[53]

FcRn Inhibitors

Neonatal Fc receptors (FcRn) are expressed in multiple cell types, such as endothelial and epithelial cells.[54] FcRn binds to the Fc portion of IgGs and protects them from intracellular degradation, leading to their recirculation in serum and thus increasing their half-life. FcRn inhibitors are a new therapeutic drug class used in MG leading to a decreased half-life of autoantibodies (**Figure 1**).

Efgartigimod is an IgG1 Fc fragment which inhibits FcRn, approved by the U.S. Food and Drug Administration (FDA) in 2021 and by the European Medicines Agency (EMA) in 2022, as an add-on therapeutic option for generalised MG with positive antibodies against AChR. Its approval was based on the phase 3 RCT ADAPT which showed clinical improvement 7 to 14 days after the initiation of each therapeutic cycle.[55] ADAPT-SERON, a multi-centre, phase 3 RCT regarding Efgartigimod's efficacy in seronegative and MuSK-associated generalised MG is currently ongoing (**Table 1**).[56] Interestingly, a phase 3 RCT, called ADAPT oculus, is currently recruiting patients with ocular MG in order to test Efgartigimod's efficacy in this group.[57] ADAPT Jr is a phase 2/3 clinical trial aiming to the study of pharmacokinetics of Efgartigimod in paediatric patients with gMG.[58] Efgartigimod has been off-label used in cases of myasthenic crisis with promising results.[59]

Efgartigimod is administered in cycles of four weekly intravenous doses of 10mg/kg. Each therapeutic cycle must start at least 7 weeks apart from the start of the previous one. Subsequent cycles may be administered according to clinical judgement. A subcutaneous form of Efgartigimod has also been approved for the treatment of MG.

IgG class medicinal products, such as IVIG or monoclonal antibodies, should not be administered concurrently with Efgartigimod, as it may decrease their half-life. They should be administered at least two weeks after the last dose of Efgartigimod.[15] All vaccinations should be administered at least two weeks after the last dose or four weeks before the initiation of a therapeutic cycle. IgG levels in serum should be measured before initiation of this agent. The most common adverse events include headache and nasopharyngitis.[55]

Rozanolixizumab is a humanised IgG4 monoclonal

Table 1. Emerging treatment options for Myasthenia Gravis.

Drug Class	Therapeutic agent	Clinical Trial	Phase	MG Subtypes	Number of patients	Time frame	Status	Primary Outcomes
FcRn inhibitors	Nipocalimab	Vivacity-MG3[64]	3	Adult / gMG	196	6 months	Completed	Decrease in MG-ADL
	Efgartigimod IV	ADAPT SERON[56]	3	Adult / gMG, MuSK+, seronegative	119	29 days	Active	MG-ADL
	Efgartigimod SC	ADAPT oculus[57]	3	Adult / ocular MG	124	29 days	Recruiting	MGII
	Efgartigimod SC / IV	ADAPT Jr SC[58] / ADAPT Jr[124]	2/3	2 – 17y / gMG, AChR+	12	24-26 months	Recruiting	Pharmacokinetics, IgG levels, AChR-Ab levels
	Batoclimab	FLEX[81]	3	Adult / gMG	240	3 months	Active	MG-ADL (AChR+)
	Rozanolixizumab	roMyG[62]	2/3	2-17y / gMG, AChR+, MuSK+	12	18 weeks	Recruiting	Adverse events
	IMVT-1402	NCT07039916[82]	3	Adult / gMG	231	3 months	Recruiting	MG-ADL
Complement C5 inhibitors	Zilucoplan	ziMyG[79]	2/3	2-17y / gMG, AChR+	8	29 days	Recruiting	Pharmacokinetics, C5 serum levels
	Pozelimab + Cemdisiran	NIMBLE[85]	3	Adult / MG, AChR+, LRP4+	335	6 months	Recruiting	MG-ADL
	Gefurulimab	PREVAIL[88]	3	Adult / gMG, AChR+	260	26 weeks	Active	MG-ADL
Factor B Complement inhibitor	Iptacopan	NCT06517758[91]	3	Adult / gMG, AChR+	146	6 months	Recruiting	MG-ADL
Anti-CD20 monoclonal Ab	B007	NCT06447597[92]	2/3	Adult / gMG, AChR+, MuSK+	104	16 weeks	Recruiting	MG-ADL
Anti-CD19 monoclonal Ab	Inebilizumab	MINT[97]	3	Adult / AChR+, MuSK+	238	26 weeks	Active	MG-ADL
Anti-CD19 BiTE	Blinatumomab	NCT06836973[98]	2/3	Adult / Refractory, AChR+, MuSK+, LRP4+	2	6 months	Not yet recruiting	Efficacy, Safety, Autoantibodies status
IL-6 receptor inhibitor	Satralizumab	LUMINESCE[102]	3	Over 12 y / gMG, AChR+, MuSK+, LRP4+	188	6 months	Completed	Decrease in MG-ADL

BlyS / APRIL inhibitor	Telitacicept	NCT05737160[106,107]	3	Adult / gMG, AChR+, MuSK+	114	24 weeks	Completed	Decrease in both MG-ADL + QMG / IgG, IgA, IgM decrease
BTK inhibitor	Remibrutinib	RELIEVE[110]	3	Adult / gMG, AChR+, MuSK+, seronegative	180	6 months	Recruiting	MG-ADL
Purine analog	Cladribine	MyClad[112]	3	Adult / gMG, AChR+, MuSK+, LRP4+, seronegative	240	6 months	Recruiting	MG-ADL
mRNA anti-BCMA CAR T cell therapy	Descartes-08	AURORA[119]	3	Adult / Generalized AChR+	100	4 months	Recruiting	MG-ADL

Ab: Antibody; APRIL: A-proliferation – inducing ligand; BCMA: B Cell Maturation Antigen; BiTE: Bispecific T-cell engager; BlyS: B-lymphocyte stimulator; BTK: Bruton's tyrosine kinase; CAR: Chimeric Antigen Receptor; FcRn: Neonatal Fc receptors; gMG: generalized Myasthenia Gravis; IL-6: Interleukin-6 IV: intravenous; LRP4: Lipoprotein Receptor-related Protein 4; MG-ADL: Myasthenia Gravis Activities of Daily Living scale; MGII: Myasthenia gravis impairment index; MuSK: Muscle-specific Tyrosine Kinase; QMG: Quantitative Myasthenia Gravis scale; SC: subcutaneous.

antibody targeting and inhibiting the FcRn. It was approved by the FDA in 2023 and by the EMA in 2024, as an add-on treatment for generalised MG with positive antibodies against AChR or MuSK, based on the multi-centre, phase 3 RCT Mycarin G.[60] Its therapeutic benefit may be apparent as soon as day 8 after its administration.[61] Rozanolixizumab is given via subcutaneous infusion in six weekly doses. Further therapeutic cycles may be initiated based on clinical assessment. A phase 2/3 clinical trial is currently recruiting paediatric patients with AchR or MuSK-positive generalised MG, in order to assess the efficacy and potential adverse effects of rozanolixizumab in this patient group (**Table 1**).[62]

The most common adverse events include headache, diarrhoea, and fever.[61] Rozanolixizumab should not be offered to patients with hyperprolinaemia, as it contains 29mg of proline per ml. Further precautions regarding vaccinations, IgG class medications and hyperglobulinemia resemble those of Efgartigimod alfa.

Nipocalimab is another monoclonal antibody which inhibits FcRn.[63] It has been approved by the FDA on April 2025 for the treatment of AChR or MuSK-associated generalised MG in adult and paediatric patients ≥12 years of age and has been submitted for approval to the EMA. The phase 3 RCT Vivacity-MG3 showed a statistically significant reduction of MG-ADL in the nipocalimab group against the placebo group (**Table 1**).[64] A statistically significant decrease of quantitative Myasthenia Gravis scale (QMG) score was observed in the nipocalimab group, compared to the placebo group, within 8 weeks of treatment initiation.[65] The most commonly observed adverse events were infections and headache. Nipocalimab is administered intravenously every two weeks based on the patient's body weight.

Complement Inhibitors

Complement activation is one of the main pathophysiologic mechanisms of AChR-associated MG. Complement inhibitors have been recently approved by the FDA and the EMA for generalised anti-AChR MG cases, including eculizumab, ravulizumab and zilucoplan.[14,15,30]

Eculizumab is a humanised monoclonal antibody that binds to the complement protein C5 and thus inhibits the formation of the membrane attack complex (**Figure 1**).[66] It was the first complement inhibitor to be approved for MG by the FDA and EMA in 2017.[30] In Greece, it is indicated as an add-on therapy for refractory cases. It has also been approved for children ≥ 6 years of age in 2025.[67]

Eculizumab is administered intravenously at a starting weekly dose of 900mg for the first four weeks, followed by 1200mg for the fifth dose one week later and thereafter 1200mg every two weeks.[67] Clinical improvement is usually shown within two weeks after the first infusion, while the maximal effect is reached after three months.[68] Eculizumab has been used off-label in a handful of cases of myasthenic crisis with good results.[69-71]

Complement inhibition poses an increased risk of meningococcal infections.[30] Therefore, before initiating complement inhibitors, patients should be vaccinated with both the quadrivalent and group B Neisseria meningitidis vaccines. Other infections, including respiratory or urinary tract infections may be seen as well. In case of urgent need for initiation of this class of drugs without vaccination completion, chemoprophylaxis with antibiotics is advised.[15]

Ravulizumab is a modified version of eculizumab with a longer half-life.[30] It is indicated as an add-on treatment in AChR-associated generalised MG. Ravulizumab is administered intravenously, once per eight weeks, starting 2 weeks after the loading dose. Its efficacy in MG has been proven in a multi-centre, phase 3 RCT leading to its approval by the FDA and EMA in 2022.[72] The median time to clinical improvement is similar to eculizumab.[73] Ravulizumab has also been used effectively in case reports of myasthenic crisis.[74,75] However, further research is needed for the establishment of complement inhibitors' efficacy in this clinical scenario.

Zilucoplan is a synthetic peptide which binds to the C5 complement protein, preventing its cleavage to C5a and C5b by C5 convertase.[76] It also inhibits the binding between C5b and C6. The binding site of zilucoplan in C5 is different from eculizumab, thereby rendering it as a possible alternative if eculizumab or ravulizumab fail.[77]

Zilucoplan was approved as an add-on therapy in AChR-positive generalised MG, by the FDA and the EMA in 2023. As shown in the RCT RAISE, zilucoplan may benefit patients from the first week of its administration.[78] The maximum effect is seen during the fourth week and may remain at least until the 12th week. Zilucoplan is given as a subcutaneous injection once daily. It shares a common safety profile with other complement inhibitors, and thus vaccination against Neisseria meningitidis is necessary. A phase 2/3 clinical trial regarding the pharmacokinetics of zilucoplan in paediatric patients with AChR-positive generalised MG is currently recruiting participants (**Table 1**).[79]

EMERGING TREATMENT OPTIONS

Novel FcRn Inhibitors

Other FcRn inhibitors are currently being tested in MG. Batoclimab is a fully human monoclonal antibody targeting the IgG-binding site on FcRn.[80] It has been tested in thyroid eye disease, with favourable results.[80] However, this study was terminated due to cholesterol increase. The efficacy of batoclimab in generalised MG is currently being investigated in a phase 3 RCT called FLEX (Table).[81] No restrictions regarding the antibody status apply in this study. However, the primary outcome concerns patients with positive antibodies against AChR. Finally, IMVT-1402, a monoclonal antibody which blocks the FcRn, is under investigation for the treatment of generalised MG in a phase 3 RCT (**Table 1**).[82] The main outcome refers to the potential decrease in MG-ADL. This study is currently recruiting patients.

Novel Complement Inhibitors

Emerging complement inhibitors are currently being investigated for the treatment of MG. Pozelimab is a human IgG4 human monoclonal antibody which binds to C5 and prevents its cleavage to C5a and C5b.[83] It is currently approved for the treatment of CD55-deficient protein-losing enteropathy. Cemdisiran is an N-acetylgalactosamine conjugated siRNA which suppresses liver production of C5 protein.[84] Pozelimab and cemdisiran are currently being investigated as monotherapies and as a combination for the treatment of AChR or LRP4-postive MG in the multi-centre, phase 3 RCT NIMBLE trial (**Table 1**).[85] Approximately 335 patients are estimated to participate in this study. These agents are administered subcutaneously. Besides infections, adverse events of pozelimab may include hypertension, alopecia, bone fractures, increased uric acid and liver enzymes.[86]

Gefurulimab is a bispecific antibody which inhibits the cleavage of C5 to C5a and C5b. It also binds to albumin which may prolong its circulatory half-life and thereby lead to extended intervals between each dose.[87] A multi-centre, phase 3 RCT, called PREVAIL, regarding the efficacy of the subcutaneous form of Gefurulimab in adult patients with AChR-positive generalised MG is currently ongoing (**Table 1**).[88]

Iptacopan is a complement factor B inhibitor which has been approved for the treatment of paroxysmal nocturnal haemoglobinuria, complement 3 glomerulopathy, and immunoglobulin A nephropathy. Iptacopan is a small molecule which inhibits the alternative complement pathway, leaving the classical and lectin pathways intact (Figure).[89] This may lead to adequate immune responses against pathogens. Another benefit of this agent is the oral form. The most common side effects include headache, diarrhoea, nasopharyngitis, and nausea.[90] A phase 3 RCT is currently recruiting adult patients with AChR-positive generalised MG, in order to test the efficacy of iptacopan in this group (**Table 1**).[91]

A novel anti-CD20 monoclonal antibody

B007 is an experimental recombinant anti-CD20 humanised monoclonal antibody currently tested for the treatment of adult patients with AChR or MuSK-associated generalised MG (Table).[92] This study is a multi-centre phase 2/3 RCT with a primary outcome of Myasthenia Gravis – Activities of Daily Living (MG-ADL) scale reduction by two or more points. B007 is

administered subcutaneously. This agent is currently being investigated in other autoimmune disorders such as primary membranous nephropathy and pemphigus.[93,94]

Anti-CD19 agents

Plasmablasts and plasma cells contribute immensely to the pathophysiology of MG and other autoimmune diseases by the production of autoantibodies. The majority of these cells do not express CD20, but rather CD19 on their surface.[95] Anti-CD20 therapies may not effectively deplete these cell populations. Therefore, anti-CD19 agents have been designed and are currently being investigated in MG and other autoantibody-related diseases (**Figure 1**).

Inebilizumab is a humanised anti-CD19 monoclonal antibody, approved for the treatment of IgG4-related disease and neuromyelitis optica spectrum disorder (NMOSD). It is administered intravenously every 6 months besides the first month, at which time two doses are given with a gap of two weeks between them. Premedication with antihistamine, acetaminophen, and corticosteroids is advised.[96]

The most common adverse events include urinary tract infection, lymphopenia and arthralgia. Patients should be screened for hepatitis B and tuberculosis before the initiation of inebilizumab. Although no confirmed cases of PML have been observed in clinical trials, treating physicians should be aware of this risk, as PML has been described during treatment with other B-cell depleting therapies. MINT study is an active multi-centre, phase 3 RCT, investigating the efficacy of inebilizumab in adult patients with AChR or MuSK-positive MG (**Table 1**).[97]

Another anti-CD19 therapeutic option, currently being tested in MG is blinatumomab (**Table 1**).[98] This is a bispecific antibody which binds simultaneously to CD3 on T cells and CD19 on B cells (**Figure 1**). This concurrent binding leads to the release of cytotoxic substances, such as perforins and granzymes, directly into the B cells, triggering apoptosis of the latter.[99] Blinatumomab has been approved for the treatment of relapsed or refractory B cell precursor acute lymphoblastic leukaemia. It is administered intravenously. The most common side effects of blinatumomab include infections, headache, pyrexia, infusion-related reactions, and cytopenia. Cytokine release syndrome (CRS), which may be life-threatening or fatal, has been reported in patients receiving blinatumomab.

Interleukin-6 (IL-6) receptor inhibitors

IL-6 is a proinflammatory cytokine that is implicated in immunologic responses during inflammatory disease, infection, haematopoiesis, and oncogenesis.[100] IL-6 coordinates the proliferation and the differentiation of T cells, as well as the terminal differentiation of B cells. IL-6 may also be implicated in antibody production. IL-6 receptor inhibitors have been used in many autoimmune diseases such as rheumatoid arthritis (RA), giant cell arteritis and scleroderma. Serum IL-6 levels are higher in MG patients compared to healthy controls.[101]

Satralizumab is a humanised monoclonal antibody which inhibits IL-6 receptors. It is approved for the treatment of NMOSD. This agent has been tested in seropositive (AChR, MuSK, LRP4) generalised MG, in a multi-centre, placebo-controlled, phase 3 RCT, called LUMINESCE (**Table 1**).[102] Eligible patients were over 12 years old, with MG-ADL score of 5 or more and use of stable background therapy. The primary outcome was a change in MG-ADL scale at 6 months of treatment with satralizumab. One-hundred and eighty-eight patients participated in this study. A statistically significant, yet small, reduction of MG-ADL score was noticed between satralizumab and placebo groups with positive anti-AChR antibodies. Three patients showed a serious adverse event in the satralizumab group, including pneumonia, pyelonephritis and increased lipase. The open-label extension of this study was terminated early, due to the halt of further development of satralizumab for the treatment of MG by the sponsor.

Telitacicept

Telitacicept is a fusion protein which binds to and neutralises the activity of B-lymphocyte stimulator (BLyS) and A-proliferation-inducing ligand (APRIL) (**Figure 1**).[103] BLyS is an important molecule for the differentiation, maturation, function and survival of B cells. Increased serum levels of BLyS have been reported in patients with autoimmune disorders, such as systematic lupus erythematosus (SLE).[104] APRIL, as well, regulates the differentiation and maturation of B lymphocytes.[105]

Telitacicept is currently being tested in multiple autoimmune diseases, such as RA, ANCA-associated vasculitis, SLE, and multiple sclerosis (MS). It has also been tested recently in 114 adult patients with AChR or MuSK-positive generalised MG, in a multi-center placebo-controlled phase 3 RCT (Table).[106,107] The treatment group received weekly subcutaneous doses of telitacicept for 6 months. MG-ADL and QMG scores were significantly decreased in the treatment group compared to the placebo group. This also applied to the IgG, IgA and IgM serum levels of the patients treated with telitacicept compared to placebo. The most frequently reported side effect was IgM decrease.

Bruton's Tyrosine Kinase (BTK) inhibitors

BTK inhibitors have been used in multiple hematologic disorders for almost 15 years. Among numerous functions, BTK is a crucial component of the B cell receptor (BCR) signalling pathway, which is activated

when a B cell encounters an antigen.[108] This leads to B cell proliferation, differentiation, and antibody production. BTK inhibitors may block these processes and thus lead to potential remission of autoimmune diseases.

Remibrutinib is a new oral, highly selective BTK inhibitor which has been tested in chronic spontaneous urticaria with success and a favourable safety profile.[109] RELIEVE is a multi-centre, placebo-controlled phase 3 RCT, currently investigating the efficacy of remibrutinib in 180 adult patients with AChR or MuSK-associated or seronegative generalised MG (**Table 1**).[110] The primary outcome of this study is a potential reduction of MG-ADL score at 6 months. Researchers are currently recruiting patients.

Cladribine

Cladribine is a chlorinated deoxyadenosine analog. It induces B and T lymphocyte apoptosis, via increasing the expression of deoxycytidine kinase, disrupting intracellular processes and inhibiting DNA synthesis / repair.[111] It has been approved for the treatment of various haematologic cancers and MS as well. It is administered orally. The adverse events of cladribine may include anaemia, thrombocytopenia, lymphopenia, headache, serious infections, fever, and neurotoxicity. Cases of PML have been reported in patients receiving cladribine. Screening for human immunodeficiency virus, tuberculosis, hepatitis B, and hepatitis C is advised before each treatment cycle. Varicella zoster virus antibody status should be evaluated as well.

Cladribine is currently being investigated in adult patients with generalised MG, in a multi-centre, placebo-controlled, phase 3 RCT, called MyClad (**Table 1**).[112] Two-hundred and forty patients are estimated to participate in this study. Patients will be divided into three groups. Participants of the first group will receive placebo in two courses separated by four weeks. A low dose of oral cladribine will be administered to the patients of the second group, in two courses separated by four weeks. Participants of the third group will receive a high dose of oral cladribine, following the same schedule as the previous groups. The primary outcome is a change of MG-ADL score at 6 months.

Chimeric antigen receptor (CAR) T cells

CAR T cells are genetically engineered immune cells designed to recognise and destroy specific cells in the body. The CAR molecule combines the extracellular target binding domain of an antibody directed toward the desired target with the intracellular T-cell activation protein domains.[113] This treatment has been used in cancer and, more recently, in autoimmune diseases, such as SLE.[114]

CAR T cell therapy has been tested in refractory generalised MG in a prospective, non-randomised phase 1b/2a study.[115] In this study, the researchers used autologous RNA CAR T cells, targeting B-cell maturation antigen (BCMA), which is expressed on the surface of mature plasma cells. Eleven patients with anti-AChR antibodies, two with anti-MuSK antibodies and one seronegative patient participated in this study. The main outcome of this study was safety and tolerability, whereas the secondary outcomes concerned efficacy. The adverse events were mild, with the most common ones being headache, nausea and vomiting. Significant clinical improvement was shown in a follow-up period of up to 9 months.

Case reports regarding the treatment of refractory generalised MG with CAR T cells have been published as well. Haghikia et al. have treated one patient with anti-AChR-positive refractory generalised MG with an anti-CD19 CAR T construct, with minimal side effects, subsequent elimination of anti-CD19 B cells and a significant decrease of autoantibodies up until day 62 after the infusion.[116] Significant improvement of muscle strength was noted as well. Similar results were reported by two other studies using anti-BCMA CAR T cells and bispecific anti-CD19/BCMA CAR T cells respectively, in anti-AChR and anti-MuSK-positive refractory generalised MG patients.[117,118] The AURORA study, which is a double-blind, placebo-controlled phase 3 RCT evaluating the tolerability, safety and efficacy of anti-BCMA CAR T cell therapy in generalised MG with positive antibodies against AChR, is currently recruiting patients (**Table 1**, **Figure 1**).[119]

Potentially dangerous side effects of CAR T cell therapy include CRS and immune effector cell-associated neurotoxicity syndrome (ICANS).[120] CRS is characterised by fever, hypotension, hypoxia and multiorgan system toxicities. It usually occurs during the first week after CAR T cells infusion, whereas ICANS occurs during the second week. ICANS is characterised by headache, encephalopathy, focal neurological deficits, seizures and brain oedema. Both adverse events may be life-threatening. However, none of these have been reported in studies regarding MG treatment with CAR T cells.[115-118] Nevertheless, further research regarding the efficacy and safety of this treatment in MG is required.

Special Myasthenia Gravis populations

The therapeutic landscape of MG has widened through the last decade, especially due to the approval of FcRn inhibitors and complement inhibitors. However, the treatment options in specific populations, such as non-AChR-associated MG, ophthalmic MG and pregnant patients remain limited.

Anti-MuSK MG is currently treated with corticosteroids and rituximab, although the latter is an off-label treatment. If rituximab is not available, aza-

thioprine or MMF may be used.[15] Rozanolixizumab and nipocalimab, two FcRn inhibitors, have been approved as add-on therapies for anti-MuSK MG. Real world data regarding their efficacy and safety profile in this population is awaited. Multiple active RCTs are currently recruiting anti-MuSK-associated MG patients.[56,81,82] However, they are commonly outnumbered by the anti-AChR-associated MG subgroup.

Anti-LRP4 MG patients are even more underrepresented in clinical trials compared to the anti-MuSK subgroup. Their treatment is currently based on corticosteroids and older off-label immunotherapies.[15] Refractory cases may benefit by the off-label addition of a complement inhibitor or an FcRn inhibitor. Studies focused on this population are needed.

Seronegative MG is not rare as it may constitute up to 15% of all MG patients.[4] Nevertheless, treatment options resemble those of Anti-LRP4 MG patients. Seronegative MG patients are not usually included in RCTs. However, ADAPT SERON is currently investigating the efficacy of efgartigimod in seronegative patients.[56] Furthermore, seronegative patients are included in the RCTs currently testing remibrutinib and cladribine, respectively.[110,112]

Ocular MG is treated with corticosteroids. Other immunomodulatory agents, such as azathioprine and MMF may be used in refractory cases or patients who do not tolerate corticosteroids. Efgartigimod may be an additional option for ocular MG, depending on the results of the currently active RCT ADAPT oculus (**Table 1**).[57]

Pregnant MG patients pose a therapeutic challenge. Pyridostigmine and daily doses of prednisolone under 20mg are considered safe during pregnancy and lactation.[15] However, corticosteroids increase the risk of gestational diabetes mellitus, hypertension and infections. Alternative options to steroids are azathioprine and cyclosporine. Rituximab may be administered at least 3 months before pregnancy.[121] MMF, methotrexate and cyclophosphamide should not be administered to women of reproductive age, due to their teratogenic effects. IVIG and PLEX may be used to treat exacerbations of MG during pregnancy. Data regarding safety and efficacy of new MG therapeutic options, such as FcRn inhibitors and complement inhibitors, are currently lacking. However, eculizumab has been used in case reports of pregnant MG patients without safety-concerning issues.[122]

The first-line therapeutic option for paediatric MG is pyridostigmine. Steroids are avoided in children if symptoms are well-controlled, due to their side effects. Azathioprine, MMF and cyclosporine have been used effectively in juvenile MG.[123] New therapeutic agents, such as eculizumab (over 5 years of age) and nipocalimab (over 11 years of age) have been approved for the treatment of paediatric MG. Phase 2/3 studies regarding the safety and efficacy of efgartigimod, rozanolixizumab and zilucoplan in children suffering from MG are currently active (**Table 1**).[58,62,79]

CONCLUSION

The treatment of MG has reached an unprecedented level of variety with the addition of FcRn inhibitors and complement inhibitors. These drug classes have shown their safety and efficacy through well-designed RCTs, in contrast to older regimens, most of which have never been tested in such studies. Furthermore, new members of these classes are currently being tested and may be soon added to the therapeutic arsenal against MG. Novel drug families, such as anti-CD19 monoclonal antibodies, BlyS / APRIL inhibitors and BTK inhibitors are currently being investigated. Finally, personalised treatment with CAR T cell therapy is quite promising in multiple diseases, such as MG, and may change the whole therapeutic strategy of these patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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