

Novel Immunotherapies for Myasthenia Gravis

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Abstract: Myasthenia gravis (MG), a prototype autoimmune neurological disease, had its therapy centred on corticosteroids, non-steroidal broad-spectrum immunotherapy and cholinesterase inhibitors for several decades. Treatment-refractory MG and long-term toxicities of the medications have been major concerns with the conventional therapies. Advances in the immunology and pathogenesis of MG have ushered in an era of newer therapies which are more specific and efficacious. Complement inhibitors and neonatal Fc receptor blockers target disease-specific pathogenic mechanisms linked to myasthenia and have proven their efficacy in pivotal clinical studies. B cell-depleting agents, specifically rituximab, have also emerged as useful for the treatment of severe MG. Many more biologicals are in the pipeline and in diverse stages of development. This review discusses the evidence for the novel therapies and the specific issues related to their clinical use.

Keywords: myasthenia gravis, refractory myasthenia gravis, complement inhibitors, FcRn blocker, B cell depletion

Introduction and Background

Introduction

Myasthenia gravis (MG) is a chronic autoimmune disease of the neuromuscular junction (NMJ) clinically characterized by fatigable weakness of the ocular, limb and bulbar (speech, swallowing and respiratory) muscles. It is the most common acquired disease of the NMJ with an incidence of 0.3–2.8 per 100,000.¹ The burden of MG translates not only to disabling symptoms and increased hospitalizations, but also marked economic, social and emotional costs.²

In MG, well-characterized antibodies have been identified against specific targets in the post-synaptic membrane.³ Antibodies against acetylcholine receptor (AChR) are observed in a vast majority (nearly 85%) of generalized MG and antibodies against other components, namely muscle specific kinase (MuSK), lipoprotein related protein 4 (LRP4) and agrin have been reported in 5%, 2% and less than 1%, respectively in the remaining population. The remaining 5–8% with generalized disease have no currently attributable antigenic targets or antibodies and are referred to as seronegative MG.⁴

The clinical severity of MG can range from mild ocular symptoms to frequent respiratory and bulbar crisis. In general, one-fifth of MG patients manifest only ocular weakness and are referred to as ocular MG whereas the rest, with a more diffuse weakness, are referred to as generalized MG (gMG). Ocular MG is less likely (approximately 50%) to have antibodies compared with gMG.⁵ Distinctive clinical phenotypes have been recognized for each of the antibody subtypes of MG.³ AChR antibody positive MG are classified into three subtypes: early onset (<50 years of age), late onset (>50 years) and thymoma associated MG (TAMG). Early onset MG has a female preponderance and strong associations with human leukocyte antigen (HLA) DR3-D8 and thymic follicular hyperplasia. In contrast, late onset MG often occurs in males, has no HLA association and may display anti-striational antibodies despite harbouring atrophic thymus.⁴ Thymoma occurs in 15–30% of MG and is commonly associated with co-existing anti-ryanodine receptor and anti-titin antibodies.^{6,7} MuSK-MG tends to present with a bulbar-dominant phenotype and usually does not have any significant thymic abnormalities.⁸

Immunopathology of MG

The origin of the autoimmunity in MG has not been precisely elucidated, though genetic susceptibility and environmental triggers such as viral infections have been implicated. Pathological changes in the thymus are believed to play a pivotal role in the pathogenesis of AChR-MG.⁹ The most accepted hypothesis centres around the failure of self-tolerance which occurs intrathymically in AChR-MG. Self-tolerance is ensured by a balance between immune cell generation and the timely removal of auto-reactive lymphocytes. The thymus is the primary organ for the maturation and differentiation of T cells. During their maturation, T cells including the T regulatory cells (Tregs) are exposed to thymic myoid cells which express AChR and autoimmune regulatory (AIRE) medullary epithelial cells. The latter play an important role in the clonal deletion of T cells sensitized to auto-antigens during the development of central tolerance. The lymphocytes which display auto-reactivity are removed within the thymus whereas those that escape this culling are suppressed in the periphery by the Treg cells.¹⁰

Two important factors which contribute to immune breakdown in MG are thymic pathology and genetics which are vastly different in early and late onset MG. In early onset MG, the thymus shows structural changes in the form of thymic follicular hyperplasia. The germinal centres of the follicles are implicated as the site of origin of autoimmunity in them. The mechanisms include aberrant production of cytokines and imbalance in the function of T effector and Treg cells. There is increase in the pro-inflammatory Th17 and T follicular helper cells (Tfh) which promote B cell activation and generate autoantibodies.^{10,11} Regulatory B cells which suppress autoimmunity are also functionally abnormal in MG. In TAMG, pathological abnormalities consistent with immune proliferation in the areas adjacent to the tumour have been reported without any follicular hyperplasia. Thymomas express loss of AIRE making the cells susceptible for mounting autoimmune responses.⁴ Late onset MG is associated with involuted thymus with paucity of the myoid cells and regulatory thymic cells which prevent autoimmunity. No specific thymic pathology has been demonstrated in MuSK-MG.⁴

In the NMJ, nerve action potential provokes the activation of presynaptic voltage gated calcium channels which initiates a cascade of events culminating in the release of acetyl choline (ACh) into the synaptic cleft. Acetyl choline binds to the AChR in the synaptic folds of the postsynaptic membrane resulting in the opening of the central pore of the receptors and subsequently the voltage gated sodium channels, which then initiate the muscle action potential.¹² Normal NMJ function requires clustering of AChR in the crests of the synaptic folds which is achieved by a kinase enzyme, MuSK. Activation of MuSK occurs during the development of NMJ by the interaction of agrin released from the developing motor axons with a post-synaptic protein, LRP4. Binding of this complex is crucial for the dimerization and activation of MuSK. MuSK activation induces a series of phosphorylation reactions recruiting DOK7 and rapsyn and finally inducing clustering and stabilization of AChR.¹³

The postsynaptic neuromuscular dysfunction in MG is produced by IgG auto-antibodies which act by three mechanisms: (i) functional blockade of the receptors, (ii) receptor internalization and degradation and (iii) complement activation and destruction of the membrane.¹⁴ Antibodies against AChR are IgG1 and IgG3 subtypes which are capable of fixing complements. Complement fixation and generation of the membrane attack complex result in damage to AChR and voltage gated sodium channels in the post-synaptic membrane which reduces the safety factor and increases the threshold for excitation. MuSK antibodies which are the IgG4 isotype do not significantly activate the complement pathway. Both IgG4 MuSK and IgG1/G2 LRP4 antibodies prevent the clustering of AChR in the post-synaptic membrane which is essential for normal transmission.¹⁵

Current Management of MG

The treatment strategy in MG is guided by the clinical pattern (ocular versus generalized), autoantibody subtype and disease severity. Current therapy of MG revolves around symptomatic treatment (cholinesterase inhibitors), long-term immunomodulatory therapy including thymectomy and management of acute crisis.

Cholinesterase inhibitors such as pyridostigmine can produce rapid relief of symptoms in mild MG and are usually prescribed as the initial therapy. The majority of the patients, however, require suppression of autoantibody production with immunosuppressive treatment which remains the cornerstone of MG therapy. Oral corticosteroids are initially used to induce remission while long-term maintenance is achieved with either low dose

oral corticosteroids or non-steroidal immunosuppressants. Azathioprine, methotrexate, ciclosporin, tacrolimus and mycophenolate mofetil are the most frequently used non-steroidal agents. Agents such as cyclophosphamide are usually reserved for poorly responsive patients. In addition, rapidly acting, but short-lasting therapies such as intravenous immunoglobulin (IVIg) or therapeutic plasma exchange (PLEX) are used as rescue therapies in patients with imminent or incident respiratory crisis and severe MG.¹⁶ Therapeutic thymectomy is recommended for all thymomatous MG and a subset of non-thymomatous AChR antibody positive gMG patients with an age of onset less than 50 years.^{16–18} The role of thymectomy in older patients and antibody negative MG has not been convincingly established.¹⁶

Therapy of MuSK-MG with IgG4 antibodies differs from AChR-MG. MuSK-MG has limited response to IVIg and may occasionally show paradoxical worsening with cholinesterase inhibitors. No consistent thymic abnormalities have been demonstrated in MuSK MG and hence thymectomy is not recommended.¹⁹ The novel complement blocking therapies are also ineffective in MuSK-MG as MuSK antibodies do not usually activate the complement pathway.¹³

The standard management of MG produces beneficial response in more than 75% of patients.²⁰ Many require long-standing therapy, sometimes lifelong, entailing the high risk of side effects from steroids and the non-specific immunosuppressive treatment.²¹

Need for Novel Immunotherapeutic Agents

Despite being one of the best studied immune diseases, there are clear unmet needs in MG therapy. Conventional therapies in MG induce remission in 70–80%, but very few attain sustained stable remission off therapy.^{20,22} This imposes the risk of long-term exposure to immunotherapies with cumulative toxicities including opportunistic infections, malignancies and systemic organ dysfunction. A primary reason for such toxicity is the non-specificity of immune targets for the standard medications.

Need for prolonged therapy with corticosteroids with their myriad metabolic and immunological side effects is necessitated by the delayed onset of action of many of the non-steroidal agents. Patients with serious co-morbidities are often unable to tolerate immunotherapy, steroids in particular.^{23,24}

A subset of MG, approximately 10–15%, may be classified as treatment-refractory, though this entity has been variably defined in different studies. Mantegazza et al defined refractory MG as at least one of inadequate response to standard immunotherapies, relapses or crisis on attempting dose reduction of immunosuppressive therapies, recurrent and frequent crisis on therapy, intolerable side effects of the medications or co-morbidities which limit the therapy.²⁰ Drug refractory patients have recurrent disease exacerbations and need for hospitalizations including ventilatory support, are prone for co-morbidities including end-organ dysfunction and have poor functional quality of life.^{25,26}

Newer Immunotherapies in MG

A plethora of medications have been launched in MG therapeutic trials over the last decade. These predominantly include targeted immunotherapies directed specifically against the various cells and immune pathways implicated in MG pathogenesis (Figure 1). Inhibition of complement pathway and neonatal Fc receptor (FcRn) targeting for hindering IgG recycling are two of the novel and most successful mechanisms identified among them. Inhibition of B and T cells by direct depletion or through cytokines have also been successful. A few of the drugs, namely, eculizumab, ravulizumab and efgartigimod, have obtained approval from regulatory agencies while the majority are in various phases of development.^{27,28} This review will summarize the new and emerging immunotherapies in MG with focus on the complement inhibitors, FcRn blockers, and B cell depleting therapies (Table 1).

Complement Inhibitors

Complement Pathway and Role in MG

The complement system is an integral part of immune surveillance. It is mediated by a set of proteins which are activated by three separate mechanisms: classical, lectin and alternative pathways.²⁹ The autoantibodies in MG (particularly IgG1 and IgG3 AChR antibodies, but not usually the IgG4 MuSK antibodies) activate the complement system through the classical pathway. The

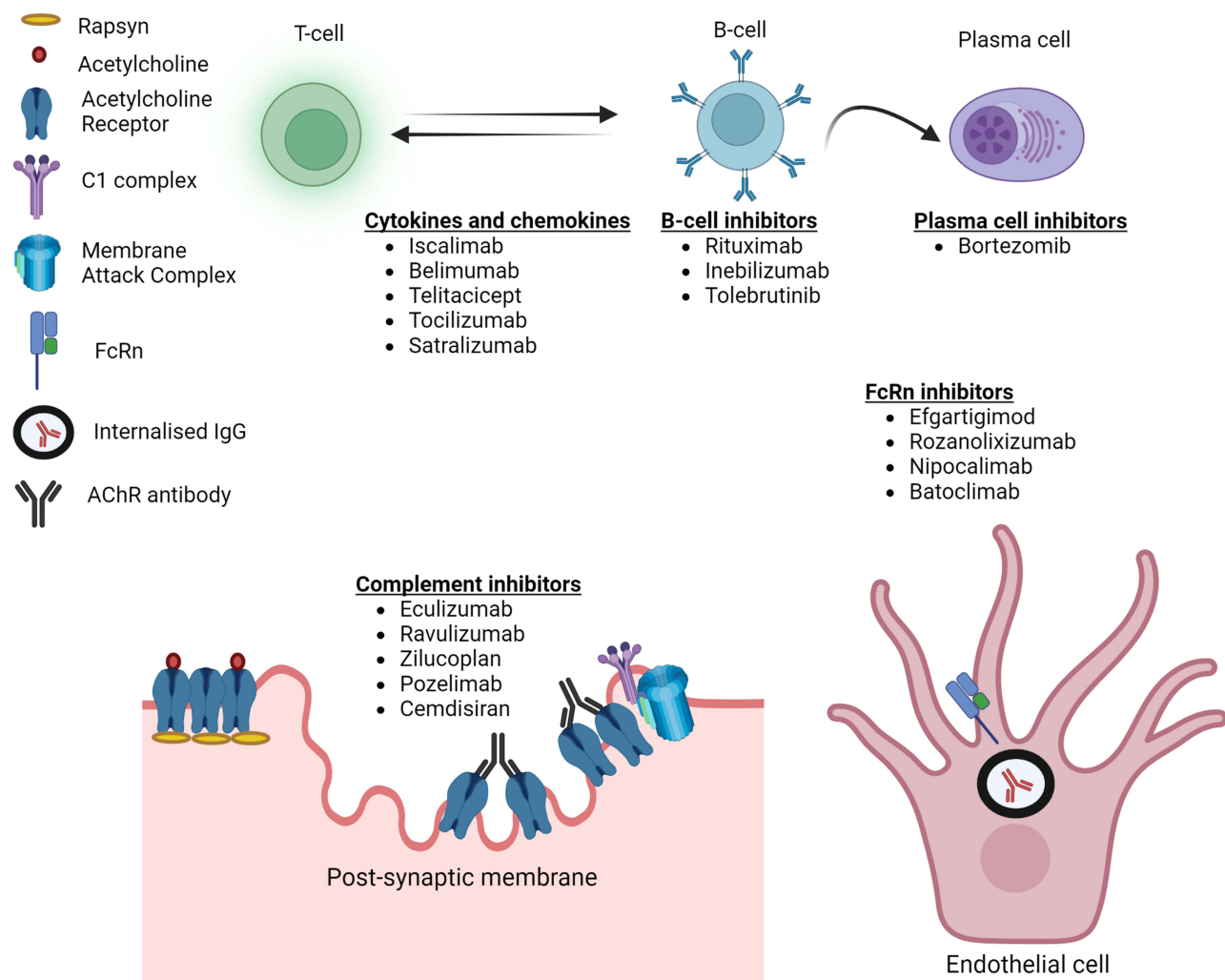


Figure 1 Targets of novel therapeutic agents in myasthenia gravis.

inciting antibody binds to C1q complement protein which sets off a cascade of enzymatic reactions that result in the production of C3 convertase, a key molecule of the complement system. C3 convertase generates and combines with C3b to form C5 convertase which then cleaves C5 into C5a and C5b. C5b further joins with C6, C7, C8 and C9 to form the main effector molecule C5b6789, also referred to as the “membrane attack complex” (MAC) or the “terminal complement component” (TCC). The lysis of the post-synaptic membrane by the MAC is an important pathogenetic mechanism in AChR-MG.³⁰

Animal and human studies have revealed the complement system as a viable and powerful target for therapy in AChR-MG.³⁰ Complement cascade can be disrupted by molecules which inhibit the key players in the cascade, the prime targets being C5, C3 and C1 components.³¹ Agents against C5, eculizumab, ravulizumab, and zilucoplan, have proven to be the most successful in human clinical trials while many more molecules are in the pipeline.

Eculizumab

Eculizumab is a humanized monoclonal antibody (mAb) directed against C5 complement protein. Binding of eculizumab to C5 prevents its cleavage to C5a and C5b and further prevents the C5a-induced chemotaxis of inflammatory cells and the formation of MAC. It was previously licensed for therapy of paroxysmal nocturnal hemoglobinuria (PNH) and atypical haemolytic uraemic syndrome (HUS)^{32,33} and more recently for aquaporin IgG positive neuromyelitis optica spectrum disorder (NMOSD).³⁴ It was approved for therapy of gMG in 2019.

Table 1 Summary of the Newer Molecules for Myasthenia Gravis Therapy

Molecule	Mechanism of Action	Target Group	Route and Dose of Administration (if Available)	Current Evidence
Complement inhibitors				
Eculizumab	C5 complement inhibitor	AChR+ MG	IV induction of 900 mg weekly for 4 weeks followed by 1200 mg maintenance every 2 weeks	Approved for treatment of adults with AChR+ gMG
Ravulizumab	C5 complement inhibitor (long acting)	AChR+ MG	IV weight-based dose. Single loading dose of 2400–3000 mg and maintenance doses of 3000–3600 mg every 8 weeks	Approved for treatment of adults with AChR+ gMG
Zilucoplan	C5 and C5b complement inhibitor	AChR+ MG	SC, once daily dose of 0.3 mg/kg	Phase 3 study is completed (NCT04115293)
Pozelimab	C5 complement inhibitor	AChR+ or LRP4+ MG	IV loading dose followed by SC (usually in combination with cemdisiran)	Phase 3 study is ongoing (NCT05070858)
Cemdisiran	siRNA suppressing hepatic C5 synthesis	AChR+ or LRP4+ MG	200 mg SC 4-weekly (usually in combination with pozelimab)	Phase 3 study is ongoing (NCT05070858)
Gefurulimab (ALXN1720)	Anti-C5 antibody	AChR+ MG	SC weight-based dose once weekly	Phase 3 study is underway (NCT05556096)
Vemircopan (ALXN2050)	Complement pathway factor D inhibitor	AChR + MG	Oral, multiple dosages in trial	Phase 2 study is ongoing (NCT05218096)
FcRn blockers				
Efgartigimod	FcRn antagonist	All antibody subtypes of MG	IV, first cycle of 10 mg/kg/dose weekly for 4 weeks and repeat cycles at variable intervals based on symptom recurrence	Approved for treatment of AChR+ gMG in adults
Rozanolixizumab	Anti-FcRn monoclonal antibody	All antibody subtypes of MG	SC, in phase 2 study 7 mg/kg was given weekly for 3 weeks followed by weekly 7 mg/kg or 4 mg/kg injections for 3 more doses	Phase 3 study is completed (NCT03971422)
Nipocalimab (M281)	Anti-FcRn monoclonal antibody	All antibody subtypes of MG	IV infusion of 60 mg/kg every 2 weeks, multiple doses experimented in phase 2 trial	Phase 3 study is ongoing (NCT04951622)
Batoclimab (RVT 1401)	Anti-FcRn monoclonal antibody	All antibody subtypes of MG	SC 340 or 680 mg every week induction followed by maintenance of 340 mg every 1 or 2 weeks	Phase 3 study is ongoing (NCT05403541)
ABY-039	Bivalent antibody-mimetic against FcRn	-	-	Phase 1 study was prematurely terminated
B cell and plasma cell targeting therapies				
Rituximab	Anti CD20 monoclonal antibody	All antibody subtypes of MG	IV infusion. Various regimens are used, commonly two doses of 1 g 2 weeks apart or 375 mg/m ² infusions repeated weekly for 4 weeks	One phase 2 study was completed, extensive class IV data
Inebilizumab	Anti CD19 monoclonal antibody	AChR+ or MuSK+ MG	IV infusion, 300 mg 2 doses 2 weeks apart and maintenance after 6 months	Phase 3 study is underway (NCT04524273)

(Continued)

Table 1 (Continued).

Molecule	Mechanism of Action	Target Group	Route and Dose of Administration (if Available)	Current Evidence
Obinutuzumab	Anti CD20 monoclonal antibody	-	IV infusion as 6 treatment cycles, Dose of 100 mg in day 1, 900 mg on day 2, 1000 mg on days 8 and 15 of the first cycle followed by 1000 mg on the first day of the subsequent cycles	No ongoing study, anecdotal evidence emanates from a single case report
Bortezomib	26S proteasome inhibitor	All antibody subtypes of MG	SC, administered in 2 treatment cycles, each with 4 injections of 1.3 mg/m ² body surface per cycle	Phase 2 study was terminated due to recruitment difficulties
Tolebrutinib	Bruton's tyrosine kinase inhibitor	All antibody subtypes of MG	Oral once daily dose	Phase 3 study is underway (NCT05132569)
TAK-079	Anti CD38 monoclonal antibody	AChR+ or MuSK+ MG	SC injection weekly with one of 2 doses for 8 weeks	Recruitment has been completed for phase 2 study (NCT04159805)
Chemokine and cytokine pathway targeting therapies				
Belimumab	Monoclonal antibody against BAFF	AChR+ or MuSK+ MG	IV 10 mg/kg every 2 weeks for 4 weeks and then once every 4 weeks	Phase 2 study has been completed
Telitacicept (RC18)	Inhibition of BAFF and APRIL	AChR+ or MuSK+ MG	SC 160 mg or 240 mg weekly	Phase 2 study is ongoing (NCT04302103)
Iscalimab (CFZ533)	Anti CD40 monoclonal antibody	All antibody subtypes of MG	IV infusion 10 mg/kg, 2 to 4 weekly doses	Phase 2 study has been completed
Tocilizumab	IL-6 receptor antibody	AChR+ MG	IV infusion every 4 weeks	Phase 2 study is ongoing (NCT05067348)
Satralizumab	IL-6 receptor antibody	All antibody subtypes of MG	SC, 120 mg every 2 weeks for 4 weeks and every 4-weeks maintenance thereafter	Phase 3 study is ongoing (NCT04963270)
Tofacitinib	Intracellular signalling disruption by inhibition of Janus kinases	AChR+ or seronegative MG	Oral, 5 mg twice a day	Early phase 1 study is underway (NCT04431895)
Miscellaneous				
Subcutaneous immunoglobulin	Broad spectrum immunomodulator	AChR+, MUSK+ or LRP4+ MG	1–2 g/kg over 4 weeks, equivalent to IVIg doses	Prospective open label trial has been completed. Phase 2 study is underway (NCT04728425)
CAR T cell therapy	Targeted depletion of autoimmune cells with genetically modified T cells	All antibody subtypes of MG	IV infusion	Phase 2 study is ongoing (NCT04146051)
CAAR T cell therapy	Targeted depletion of autoantibody- expressing immune cell clones with genetically modified T cells	AChR+ or MuSK+ MG	IV infusion, multiple dosage regimens	Phase 1 open label study for MuSK MG is underway (NCT05451212)

(Continued)

Table 1 (Continued).

Molecule	Mechanism of Action	Target Group	Route and Dose of Administration (if Available)	Current Evidence
Autologous HSCT	Immune ablation and repopulation	All antibody subtypes of MG	-	No ongoing trials, class IV data

Abbreviations: APRIL, a proliferation-inducing ligand; AChR+, acetyl choline receptor antibody positive; BAFF, B-cell activating factor; CAAR, chimeric autoantibody receptor; CAR, Chimeric antigen receptor; FcRn neonatal Fc receptor; HSCT, haematopoietic stem cell transplantation; IL-6, interleukin 6; IV, intravenous; IVIg, intravenous immunoglobulin; LRP4+, low density lipoprotein receptor-related protein 4 antibody positive; MG, myasthenia gravis; MuSK+, muscle specific kinase antibody positive; SC, subcutaneous; siRNA, small interfering ribonucleic acid.

The product carries a boxed warning on the risk of meningococcal infection.³⁵ The subjects for the clinical trials were included after mandatory vaccination against *Neisseria meningitidis* at least 2 weeks prior to the first infusion.²⁶ The other less serious side effects include headache and nasopharyngitis.²⁶

The pilot phase 2 study of eculizumab in AChR antibody positive refractory MG showed encouraging results with rapid and clinically meaningful improvement in the treatment group.³⁶ The phase 3 placebo-controlled randomized REGAIN study (Safety and Efficacy of Eculizumab in AChR positive Refractory Generalized Myasthenia Gravis; NCT01997229) enrolled 125 AChR antibody positive refractory gMG who were assigned to either eculizumab or placebo. The induction dose of eculizumab was 900 mg on day 1, weeks 1, 2 and 3 and 1200 mg in week 4, and thereafter maintenance dose of 1200 mg every second week for 26 weeks. Primary endpoint assigned was the change in Myasthenia Gravis Activity of Daily Living (MG-ADL) score from baseline to week 26 using worst-rank ANCOVA and the secondary endpoints assessed were the change from baseline in the total scores of Quantitative Myasthenia Gravis score (QMG), Myasthenia Gravis Composite (MGC) and Myasthenia Gravis Quality of Life 15 (MG-QOL-15), and the proportion of responders.²⁶

The study failed to attain significance for the primary endpoint (mean rank of 56.6 vs 68.3, $p=0.0698$). However, the secondary outcomes were significantly better in the intervention group including changes in QMG and MGQOL-15 scores and the responder analysis for MG-ADL and QMG. In the pre-specified sensitivity analysis, significant difference in all scores were noted between the two groups in favour of eculizumab, starting from week 1 and sustained through week 26. A major drawback detected in the trial design and possibly the reason for the negative result for the primary endpoint was the use of the worst rank analysis. This relegated all patients who discontinued therapy to the lowest rank irrespective of the reason for such discontinuation. This was notable in the eculizumab group where three patients who had good therapeutic responses discontinued due to side effects other than myasthenic worsening, namely *Moraxella lacunata* bacteremia, bowel perforation and prostatic carcinoma.²⁶ In a post-hoc analysis, 25% of refractory MG on eculizumab had attained minimal manifestations status at 26 weeks, which was double that of the placebo group.³⁷

The side effects were mild to moderate, and the most common ones were headache, upper respiratory infection and nasopharyngitis, reported equally in both the groups. Meningococcal infection was not noted. Fewer patients in the eculizumab group had MG exacerbations and need for rescue therapy.²⁶

The participants of the REGAIN trial were enrolled into an open label extension (OLE) phase for a maximum of 4 years. After a blinded induction phase (active drug provided as 1200 mg every 2 weeks for eculizumab group and 900 mg on day 1 and weekly for 3 weeks for the previous placebo group), all patients were continued on 1200 mg once in 2 weeks. A total of 117 participants (56 in eculizumab/eculizumab group and 61 in the placebo/ eculizumab group) entered the study. Primary endpoint was change in mean MG-ADL score over time. Interim analysis showed a reduction of 75% in the episodes of myasthenic worsening compared with the baseline. Infections of specific interest occurred in less than one-fifth of the study group and none had meningococcal meningitis. Improvements in myasthenia scores and quality of life scores were sustained with rapid improvements in the placebo/eculizumab group.³⁸

Various post hoc analyses of the REGAIN trial and OLE have underlined the efficacy and broad-spectrum responses with eculizumab. At the end of the OLE, 84.7% and 71.4% patients were classified as responders based on clinically

meaningful improvements in MG-ADL (≥ 3 points) or QMG scores (≥ 5 points). While the majority were early responders (response within 12 weeks), new responders continued to emerge with longer term therapy.³⁹ In the REGAIN trial, eculizumab-treated patients were two times more likely to have achieved minimal manifestation post intervention status compared with placebo at week 26, while in the OLE at 130 weeks, a substantial majority (88%) of the patients had attained improved status and 57.3% had reached minimal manifestation status.³⁷ Minimal symptom expression defined as MG-ADL score of 0–1 or MG-QOL-15 score of 0–3 was attained by a significantly higher proportion of eculizumab-treated patients at week 26 of REGAIN.⁴⁰

Eculizumab was shown to be uniformly beneficial in subgroups in REGAIN and OLE who presumably had the worst spectrum of refractory MG as defined by failed use of chronic IVIg therapy and rituximab. Eculizumab was administered in both these subsets after a sufficient washout period. The 17 patients on chronic IVIg who completed OLE (8 in eculizumab/eculizumab and 9 in placebo/eculizumab groups, respectively) had higher exacerbation rate in the year preceding randomization compared with the total REGAIN cohort. Eculizumab in REGAIN and OLE produced rapid and sustained improvement in the majority and reduced the exacerbation rate by more than two-thirds from 150 exacerbations per 100 patient-years in the pre-treatment year to 47 exacerbations per 100 patient-years during treatment.⁴¹ Another subgroup analysis on 14 patients who were previously exposed to rituximab did not show any difference from the unexposed group in terms of efficacy or safety of eculizumab.⁴²

Eculizumab could also produce rapid improvement in two of three ventilator-dependent AChR-MG patients who were previously resistant to other immunotherapies, IVIg and PLEX. While two achieved minimal manifestations status with 4–6 weeks of therapy, the third had partial amelioration of symptoms allowing transition to non-invasive ventilation.⁴³

The RCT and OLE, various subgroup studies and case reports have firmly established the role of eculizumab as a rescue therapy in resistant MG, but its role as a first-line agent and duration of therapy are undefined. The annual cost of therapy which exceeds half a million US dollars has been a major deterrent to the wider use of this drug.^{44,45}

Ravulizumab

Ravulizumab is a long-acting C5 complement inhibitor and has a mechanism of action similar to that of eculizumab. The long half-life of this molecule necessitates fewer intravenous infusions for maintenance. This drug was previously approved for treatment of PNH and is under investigation for atypical HUS and IgA nephropathy.⁴⁶ It was licensed by regulatory authorities for gMG in 2022.

In the phase 3 randomized placebo-controlled CHAMPION-MG study (NCT03920293), 175 adults with symptomatic AChR antibody positive gMG were recruited to receive ravulizumab infusion versus placebo. The participants were randomized 1:1 to the treatment and control arms. The dosage of ravulizumab was weight-based given as 2400–3000 mg single loading dose on day one followed by maintenance doses of 3000–3600 mg every 8 weeks starting from day 15. The primary efficacy endpoint of significant improvement in MG-ADL and for the secondary outcomes were achieved in the treatment group at 26 weeks. No marked difference in adverse effects was noted between the two groups.⁴⁷ The open-label extension phase of the study is ongoing.

Zilucoplan

Zilucoplan is a small macrocyclic peptide molecule which prevents the terminal activation of the complement cascade by two mechanisms. It binds to the C5 complement component and prevents its cleavage. It additionally binds to the existing C5b to prevent its attachment to C6. The molecule can be given as a subcutaneous injection. The advantages of this molecule include its small size which ensures good NMJ penetration, ability to concomitantly administer IVIg therapy as this is not an antibody and the potential for self-administration.⁴⁸

In the phase 2 clinical study in symptomatic adult AChR-MG patients, 44 patients were randomized and received one of the three interventions – once daily subcutaneous injection of zilucoplan at 0.3 mg/kg, once daily zilucoplan at 0.1 mg/kg or placebo. The main efficacy endpoints of changes in MG-ADL and QMG scores were assessed at the end of 12 weeks treatment. High-dose zilucoplan group showed a rapid and statistically significant improvement in the scores compared with placebo. They also had reduced need for rescue therapies. No serious treatment emergent adverse

reactions were reported with zilucoplan.⁴⁹ The phase 3 trial to study the efficacy and tolerability of 0.3 mg/kg zilucoplan versus placebo (RAISE; NCT04115293) has been completed.

Pozelimab with Cemdisiran

Pozelimab is a human mAb against C5 complement whereas cemdisiran is a small synthetic interfering ribonucleic acid (siRNA) which can suppress the hepatic production of C5. Both molecules are given as subcutaneous injection and are generally safe and well-tolerated at different doses. Loading dose of intravenous pozelimab 15 mg/kg followed by four repeat doses of pozelimab 400 mg administered subcutaneously once every week was found to inhibit complement activation in healthy volunteers.⁵⁰ In animal studies, combination of pozelimab with cemdisiran allowed lower doses and decreased dosing frequency compared with use of the individual agents separately.⁵¹ The phase 3 randomized controlled trial of the combination (intravenous pozelimab loading followed by 4-weekly subcutaneous injections along with cemdisiran 200 mg subcutaneous 4-weekly) versus placebo in gMG is ongoing (NCT05070858).

FcRn Blockers

FcRn Pathway in Health

Immunoglobulins are heterodimers made of two heavy and two light chains. Each immunoglobulin molecule has a variable region which houses the Fab (antigen-binding) fragment and a constant region with the complement-binding crystallizable fragment (Fc). The attachment of the Fc fragments to Fc receptors is crucial in regulating their interaction with the cellular immune mechanisms and enhancing the serum levels of IgG. The latter function is modulated by neonatal Fc receptors (FcRn) widely distributed in multiple cell types, particularly endothelial and myeloid cells. FcRn helps in the recycling of IgG and increases its longevity in circulation. The binding of FcRn to IgG is pH dependent and occurs only in an acidic pH. After the uptake of IgG by the cells, it is transported to the acidic environment of endosomes where FcRn binds to IgG and protects it from degradation by the lysosomal enzymes. FcRn transports IgG back to the surface and releases it in the neutral physiological pH.⁵² This pH-dependent binding is essential for prolonging the half-life of IgG antibodies which typically remain in circulation nearly 4 times longer than the other immunoglobulin subtypes (IgM and IgA). Serum albumin shares the long half-life and FcRn-mediated recycling by binding to a site distinct from that of IgG.⁵³ Serum proteins and IgG molecules which do not bind to FcRn are degraded within the lysosomes.⁵⁴

FcRn Blocking Agents in MG

Antibodies in MG are proven to be pathogenic and all the different antibody subtypes of seropositive MG belong to the IgG class. Blocking of FcRn can interfere with their recycling and thereby reduce the concentration of the pathogenic IgG autoantibodies.⁵⁴ Many authors consider this technique similar to a “medical plasma exchange”, given the rapid reduction in IgG levels. While reducing the autoreactive antibodies, these agents keep the concentrations of the other antibody subtypes (IgM and IgA) stable.⁵⁵ About 25% of the normal IgG response is also retained with these therapies and recovery of IgG levels occur faster compared with B-cell depleting therapies.⁵⁶ These factors may allow the body to mount an effective immune response on therapy and sustain a lower risk of infection.

Novel therapeutic agents which target FcRn to reduce IgG levels are classified under the umbrella term ‘antibodies which enhance the degradation of IgGs’ or ‘Abdegs’.⁵² The various molecules include engineered Fc fragments (efgartigimod), monoclonal antibodies against FcRn (rozanolixizumab, nipocalimab, batoclimab and orilanolimab), and peptide fragments. Efgartigimod was approved for therapy of gMG in 2021, while the others are in various phases of development. By reducing the pathogenic autoantibodies, they prevent all the terminal effects of the antibodies including complement activation, apoptosis by internalization and blocking.⁵⁴ An unintentional class effect noted in healthy volunteers and patients is a mild to moderate reduction of serum albumin levels, possibly resulting from a spill-over blockade of albumin turnover.⁵³ This can potentially influence the blood levels of highly albumin-bound medications including concomitant anti-myasthenic therapies and adversely affect the lipid levels.⁵³

Efgartigimod

Efgartigimod is an engineered Fc domain of human IgG1 with increased affinity for FcRn receptors than the endogenous IgG, thereby competitively inhibiting the latter's recycling. Unlike FcRn mAbs, efgartigimod retains the pH-dependent binding. The intact pH-dependent binding allows the recycling of efgartigimod, prolonging its half-life in circulation.⁵⁴

In the exploratory phase 2 study, 24 confirmed AChR antibody positive gMG patients were randomized to receive four 10 mg/kg weekly doses of efgartigimod or placebo. The primary endpoints were safety and tolerability. The treatment-related adverse effects were mild and generally comparable between the two groups. Headache and reduction in lymphocyte and monocyte counts were more commonly noted in the intervention arm. One patient in the efgartigimod group developed herpes zoster in the infusion arm. A clear positive therapeutic effect was discerned in the treatment group as early as 1 week after the first infusion with about three-fourths of the treatment group showing rapid improvement. The study was not powered to assess efficacy.⁵⁷

The phase 3 multicentric randomized controlled ADAPT trial of efgartigimod proved its efficacy against placebo as an add-on therapy for AChR antibody positive gMG. This study included adults with gMG irrespective of the antibody status on a stable dose of anti-myasthenic medicines and an MG-ADL score of ≥ 5 . Efgartigimod 10 mg/kg/dose was administered as a weekly infusion for 4 weeks and the cycle was repeated after a variable interval of 8 weeks or more depending on the re-emergence of symptoms and tolerability. The total follow-up period was 26 weeks. Among the 167 patients (84 efgartigimod and 83 placebo) enrolled, 77% were AChR antibody positive. Compared with placebo, efgartigimod-treated AChR-MG had significant improvement in MG-ADL score at 4 weeks (primary outcome). The other efficacy scores (QMG, MGC and MGQoL15 revised) showed a similar pattern with the maximum improvement noted by 4–5 weeks and sustained for 7 weeks. The drug was tolerated well and adverse effects including serious ones were no more common than in placebo. Headache was similar in the two groups whereas mild to moderate infections were more common in the intervention group compared with placebo (46% vs 37%).⁵⁸

Efgartigimod produced about 60–70% reduction in the levels of total IgG and all IgG subtypes commencing in the first week of the initial dose, the levels inversely corresponding with clinical improvement.^{57,58} Levels of anti-AChR antibody also fell by 40–70% in most of the patients with recovery by 12 weeks after the first infusion. The resurgence in antibody and IgG levels occurred prior to or paralleled symptomatic worsening.^{54,57,58}

Nipocalimab

Nipocalimab is a fully human aglycosylated IgG1 monoclonal Ab against FcRn which strongly binds to FcRn independent of pH. Multiple intravenous doses of nipocalimab in 50 healthy volunteers produced a marked reduction of serum IgG levels by 85%, and the low levels were maintained for 24 days. The drug exhibited a satisfactory safety and tolerability profile.⁵⁶

In the phase 2 study (NCT03772587), 68 patients with gMG were divided into five treatment arms to receive either of 4 dosages of nipocalimab or placebo as intravenous infusions over 8 weeks. A dose-dependent reduction in IgG and anti-AChR antibody levels was noted which correlated well with clinical improvement.⁵⁹ Results are awaited from the ongoing phase 3 randomized controlled study in adults (NCT04951622) and phase 2/3 open-label study in children (NCT05265273).

Rozanolixizumab

Rozanolixizumab is a high affinity humanized IgG4 mAb against FcRn which is administered subcutaneously. This drug completed a phase 2 trial in 43 patients with moderate to severe gMG who were positive for either of AChR or MuSK antibodies. The study was conducted in 2 periods separated by 2 weeks. In period 1, patients were randomized to receive either rozanolixizumab subcutaneous infusions 7 mg/kg once a week for 3 weeks or placebo and then re-randomized in period 2 to receive 3 doses of either 7 mg/kg or 4 mg/kg rozanolixizumab. This model enabled the investigators to assess the sustainability of the drug effect, adverse effects on longer use, and efficacy of a lower dose. The drug was generally well-tolerated with headache being the most frequent side effect, more common in the treatment arm. The primary efficacy outcome of improvement in QMG score from day 1 to 29 was not significant but overall data including antibody

measurements suggested potential efficacy for the drug in moderate to severe gMG.⁶⁰ The phase 3 study (NCT03971422) to confirm efficacy is ongoing.

B Cell Depleting Therapies

Role of B Cells in MG Pathogenesis

The pathogenesis of MG is believed to be initiated by T cell dysregulation, but autoreactive B cells play a major role in driving and propagating the dysfunction. In the presence of follicular dendritic cells, pro-inflammatory T helper cells and cytokines, there is proliferation of the autoreactive B cells within the germinal centres and in the periphery. The final differentiation into the plasma cells which secrete the pathogenic antibodies is crucial in the pathogenesis.^{61,62}

Targeting B Cells in MG Therapy

B cells can be targeted directly by depleting or inhibiting cells of the B cell lineage or indirectly by targeting their facilitators such as cytokines or other immune cells.⁶³ B cell-based therapies are an attractive option as the pathogenic antibodies are derived from plasma cells. The distinct subtype of plasma cells which produce the antibodies may influence the therapeutic response. MuSK antibodies are secreted by short-living plasma cells which are highly susceptible to depletion by anti CD19/20 agents whereas the IgG1 and IgG3-secreting long-living plasma cells lack these surface markers.^{64,65} In this section, we will discuss the direct B cell and plasma cell depleting therapies.

Rituximab

Rituximab is a chimeric mouse/human antiCD20 mAb which has gained wide acceptance as a therapy for severe and refractory MG in the last few years. Rituximab rapidly depletes the mature and memory B cells in the peripheral blood while largely sparing the pre-B cells and plasma cells located in the bone marrow and secondary lymphoid organs. This depletion is achieved by antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis of the target cells. The effects persist for about 6 months before the circulating B cells are repopulated from the bone marrow.⁶⁶

The pathogenic antibodies in MG are produced by plasma cells which reside in the bone marrow. Rituximab spares the long-lived plasma cells which do not express CD20 while it does diminish the short-lived plasma cells and B regulatory cells (interleukin-10 producing cells) which have CD20 expression.⁶⁵ In general, the suppression of antibody production is transient in MG.¹⁵ Anti-AChR antibodies are produced by the long-lived plasma cells whereas the MuSK antibodies are thought to be secreted from the short-living plasma cell blasts.⁶⁴ Theoretically, this suggests that MuSK-MG may be more responsive to rituximab therapy.

To date, there has been a single phase 2 randomized controlled trial for rituximab in MG.⁶⁷ The bulk of the efficacy and safety information for this drug exists as case series and reports and systematic reviews (Table 2).⁶⁷⁻⁷⁸ The most commonly used rituximab regimens include 2 doses of 1 g 2 weeks apart or 375 mg/m² infusions repeated weekly for 4 weeks. Some authors have used low dose regimens of 375 mg/m² or 500 mg twice given 2 weeks apart or 600 mg single dose inductions. Reinfusions are usually guided by clinical symptoms or B cell repopulation.⁶⁹

The phase 2 B-cell Targeted Treatment in MG (BeatMG) study published in 2021 was a placebo controlled randomized study in adults with mild to moderate gMG with positive AChR antibody. The study required the patients to be on a minimum dose of 15 mg of prednisolone per day. Fifty-two patients were recruited to receive either two cycles of rituximab at 6-month intervals with 4 doses of 375 mg/m² in each cycle, or matched placebo. A futility design was employed, and the primary endpoint was a reduced requirement for steroid 4 weeks prior to week 52. The study failed to attain significance in the primary steroid sparing outcome (60% with rituximab versus 56% with placebo). Secondary efficacy and other exploratory outcomes were also not different between the two groups though the placebo group had thrice the requirement for rescue therapy for myasthenia exacerbations compared with the study group. No specific safety concerns were recorded with rituximab. The inclusion of patients with a low disease activity (as suggested by good placebo response) and the prerequisite of high prednisolone dose were probable contributors to the negative results.⁶⁷

Table 2 Summary of Systematic Reviews, Randomized Trials, and Prospective Studies of Rituximab in Myasthenia Gravis

Authors	Type of Evidence	Study Population	Dosage Schedule	Outcomes
Nowak et al, 2021 (BEAT-MG study) ⁶⁷	Phase 2 randomized controlled study	52 AChR+ mild to moderate MG on a minimum of 15 mg/day prednisolone (25 received rituximab and 27 placebo)	2 cycles of weekly 375 mg/m ² for 4 weeks at 6-month intervals versus placebo for 52 weeks	No significant steroid sparing effect (primary outcome) was noted in the treatment group compared to placebo (60% vs 56%). Requirement for rescue therapy for exacerbations was lower in the intervention group.
Iorio et al, 2015 ⁶⁸	Systematic review and meta-analysis of studies with 2 or more patients from 2000–2014	168 patients (91 AChR+, 70 MuSK+, 7 seronegative) from 37 studies	Variable dosage regimens	Positive response was reported in 83.9% with no significant difference between the antibody subtypes
Tandan et al, 2017 ⁶⁹	Systematic review and meta-analysis of case reports and series from 2000–2015	169 patients (99 AChR+, 57 MuSK+) from 47 publications	Variable dosage regimens	MM or better was achieved in 44% and remission in 27%. MuSK+ MG had better outcomes than AChR+ MG (MM in 72% and 30% respectively, and remission in 47% and 16% respectively)
Di Stefano et al, 2020 ⁷⁰	Systematic review of observational studies with ≥5 patients from 1999–2019	165 AChR+ MG from 13 studies	Variable dosage regimens	Marked clinical improvement in 68% and remission was maintained > 1 year
Li et al, 2021 ⁷¹	Systematic review and meta-analysis of observational studies from 2008–2020	260 refractory AChR+ MG from 21 studies	171 were treated with routine dose and 89 with lower dose regimens	Clinical improvement was documented in 77% patients with no significant difference between the two dosage groups
Zhao et al, 2021 ⁷²	Systematic review and meta-analysis of case series and observational studies from 2000–2021	417 refractory MG from 24 studies (242 AChR+, 155 MuSK+, 20 seronegative)	Variable dosage regimens	64% achieved MM or better and 81% could withdraw oral immunosuppressant therapy. MuSK+ MG and mild to moderate severity group had better response to therapy
Anderson et al, 2016 ⁷³	Prospective, open label study	14 refractory MG (6 MuSK+, 5 AChR+, 3 seronegative)	375 mg/m ² weekly for 4 weeks and then monthly for 2 months or 750 mg/m ² every 2 weeks for 1 month	All patients showed marked improvement at the end of follow up of 22.6 months
Hehir et al, 2017 ⁷⁴	Prospective review, multicentric	55 MuSK+ MG; 24 treated with Rituximab and 31 with no exposure to rituximab	4 weekly doses of 375 mg/m ² with retreatment as clinically indicated	Rituximab therapy was significantly associated with improved outcome (58% vs 16%) and reduced prednisolone requirement after >3.5 years follow up
Jing et al, 2017 ⁷⁵	Prospective study	8 AChR+ refractory MG	Low dose 600 mg induction and 600 mg maintenance after 6 months based on clinical status	All patients had clinical improvement at median 6 months follow up. B cell depletion for 6 months was achieved with low dose

(Continued)

Table 2 (Continued).

Authors	Type of Evidence	Study Population	Dosage Schedule	Outcomes
Beecher et al, 2018 ⁷⁶	Prospective open label study	22 refractory MG (10 AChR+, 9 MuSK+, 3 seronegative)	Induction (either 4 doses of 375 mg/m ² or 2 doses of 750 mg/m ²) followed by maintenance doses during clinical worsening	Significant improvement of manual muscle test scores, reduction in prednisolone dose and increased time to relapse with rituximab; mean 28.8 months follow up
Landon-Cardinal et al, 2018 ⁷⁷	Prospective study	12 severe (MGFA IV or V) and refractory AChR+ MG	1 g on days 0 and 14 and after 6 months	Post-intervention improved status was noted in 55% at 12 month evaluation, only 1 patient achieved primary outcome of 20-point improvement in MMS
Du et al, 2022 ⁷⁸	Prospective single arm study	13 new onset AChR+ MG	Low dose rituximab of 100 mg repeated weekly for a maximum of 3 times, with maintenance of 100 mg; individualized based on clinical status and CD19 counts	All patients achieved MM or better with a low cumulative dose of rituximab over a median follow up period of 19 months

Abbreviations: AChR+, acetyl choline receptor antibody positive; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MM, Minimal manifestations status; MMS, Myasthenic Muscle Score; MuSK+, muscle specific kinase antibody positive.

Among the two early systematic reviews which compared the efficacy of rituximab in the different antibody subgroups of MG, divergent outcomes were recorded. While both reviews recorded a positive therapeutic outcome with rituximab, only one study showed a significant difference between AChR-MG and MuSK-MG.^{68,69} Tandan et al, recorded a higher frequency of positive response with MuSK-MG than AChR-MG patients. Minimal manifestation status was attained in 72% and 30%, respectively and pharmacological or complete stable remission in 47% and 16%, respectively for MuSK-MG and AChR-MG in this analysis. A more recent study of rituximab in refractory MG reiterated this observation.⁷² A multicentric prospective study which compared rituximab therapy with conventional immunotherapy in MuSK-MG found marked clinical improvement and lower corticosteroid requirement in the rituximab-treated group.⁷⁴

Therapeutic efficacy of rituximab in AChR-MG was specifically examined in two systematic reviews where unequivocal clinical improvement was noted in 68–77% of the subjects.^{70,71} One of these reviews compared routine and low dose rituximab (171 and 89 subjects, respectively) in refractory AChR-MG and failed to record any significant difference in the therapeutic outcomes or side effects. Low dose rituximab protocol as monotherapy or add-on immunotherapy was also shown to have excellent efficacy and safety profile in new-onset and early MG in a few retrospective series.^{78–80} However, none of these studies had a comparison arm with routine immunotherapy.

Rituximab has also been reported to be efficacious in juvenile MG. A retrospective multicentre study from France included 27 paediatric MG patients treated with rituximab as first-line agent and 37 on standard therapy. Rituximab therapy was associated with superior outcomes in terms of clinical improvement, tapering of glucocorticoid dose and cessation of oral immunosuppressant therapy compared with conventional first-line therapies. This study did not report any adverse effects in the rituximab group.⁸¹ Similar observations were noted with smaller series of refractory juvenile MG patients.^{82,83}

Adverse effects have been documented in 4.2–26.1% of patients,^{68,69,72,80} the most important ones being infusion reactions, cytopenias, infections including opportunistic infections and prolonged hypogammaglobulinaemia.^{69,72} Although most of the infections have been mild to moderate, serious infections and sepsis have resulted in deaths in many series and merit meticulous follow up. Increasing age is a risk factor for serious infections.⁸⁴ Two confirmed cases of progressive multifocal leukoencephalopathy in rituximab-treated MG patients who were on concomitant therapy with multiple immunosuppressants have been reported.^{84,85}

Inebilizumab

Inebilizumab is a humanized mAb targeting CD19 expressed in the B lineage cells. The expression of CD19 marker covers a broader group of cells than CD20. CD20 marker is restricted to pre-B cells in the bone marrow and the circulating naïve, mature and memory B cells whereas CD19 is additionally expressed on the early pro-B cells and the majority of plasma cells in blood and secondary lymphoid organs and about half of the plasma cells in the bone marrow.⁸⁶ The predominant mechanism of B cell depletion is through antibody dependent cell-mediated cytotoxicity. The drug was approved for treatment of aquaporin-4 IgG positive NMOSD in June 2020 and is under evaluation for immunotherapy for kidney transplant recipients and IgG4 disease.^{34,87} In the trials for NMOSD, the drug was well-tolerated with mild to moderate side effects in line with other B cell depleting agents.⁸⁷

Inebilizumab is currently undergoing phase 3 clinical studies in MG (NCT04524273). The Myasthenia gravis Inebilizumab Trial (MINT) study is a randomized placebo-controlled trial of intravenous inebilizumab (300 mg given on Day 1, 15 and 183) in antibody positive (either anti AChR or MuSK antibody) gMG as an add-on therapy.

Bortezomib

Bortezomib, a potent and reversible proteasome inhibitor, produces immune effects by targeting the plasma cells. Proteasomes are ubiquitous intracellular protein complexes which regulate the cell turnover and mediate the degradation of pro-apoptotic factors, thereby playing a central role in protein homeostasis. Misfolded and dysfunctional proteins are tagged by the proteasomes and marked as substrates for enzyme-mediated proteolysis. Bortezomib binds and induces apoptosis of the 26S proteasome, a cardinal player in nuclear and cytosolic protein degradation pathways. This results in the build-up of non-functional proteins including pro-apoptotic factors within the cells.⁸⁸

Plasma cells are non-dividing cells which secrete antibodies, including the pathogenic autoantibodies in MG. Broadly, there are two groups of plasma cells designated as short and long living plasma cells, the latter being particularly important in chronic dysimmune diseases. As they are terminally differentiated and non-dividing, they are usually resistant to radiotherapy, glucocorticoids, standard oral immunosuppressants, and CD19/20 inhibitors. However, the rapid intracellular synthesis of antibodies in these cells renders them highly susceptible to mechanisms which deter the protein degradation pathways such as proteasome inhibitors. In addition, bortezomib also targets the nuclear factor κ B (NF- κ B) signalling pathway which has important anti-apoptotic functions and is often upregulated in inflammatory diseases.⁸⁸

Bortezomib was primarily approved for use in multiple myeloma and mantle-cell lymphoma, but is a potential therapeutic option in a variety of autoimmune conditions resistant to standard therapy including gMG.⁸⁹ Its utility in MG was supported by experimental data in culture of thymic cells from patients with early onset MG where bortezomib demonstrably depleted the resident autoreactive long-lived plasma cells with in vitro reduction in anti-AChR antibody production from them.⁹⁰

A single case report has suggested clinical benefit for bortezomib in MG. One MuSK-MG patient who was poorly responsive to glucocorticoids, IVIg, PLEX, immunoadsorption and rituximab was treated with bortezomib and achieved a speedy and sustained improvement in symptoms.⁹¹ The drug was administered subcutaneously at a dose of 1.3 mg/m² body surface, four doses given within 2 weeks. A single-centre open-label study of bortezomib in antibody-mediated autoimmune diseases (TAVAB, NCT02102594) including MG was terminated due to recruitment difficulties.⁸⁹

The main limiting side effect is bortezomib-induced polyneuropathy. This neurotoxicity is dose-dependent and perpetuated by repeated cycles. The propensity for neuropathy is diminished by restricting the dose to a single cycle of bortezomib which appears sufficient to induce remission in immunological diseases and by adopting subcutaneous rather than intravenous route of administration.⁹²

Tolebrutinib

Tolebrutinib belongs a class of molecules referred to as Bruton's Tyrosine Kinase (BTK) inhibitors. The facilitatory role of BTK in innate and adaptive immunity, in particular, its influence on the proliferation and maturation of B cells, has made BTK inhibitors an attractive therapeutic option for autoimmune diseases. BTK belongs to the protein kinase family

and is important in the signalling pathways involved in B cell proliferation and function including production of antibodies and cytokines, and antigen presentation. It is also expressed in myeloid cells (components of innate immunity) and influences the production of inflammatory cytokines and adhesion molecules which promote inflammation.⁹³ The suppression of these functions by BTK inhibitors results in their efficacy in autoimmune diseases and B cell malignancies. Tolebrutinib, an orally administered irreversible covalent BTK inhibitor, is currently being evaluated in a phase 3 placebo-controlled randomized trial in gMG (NCT05132569).

Cytokine and Chemokine Targeting Therapies

Cytokines and Chemokines in MG

Cytokines are small signalling molecules which help in the coordination of immune system function and communication between the various immune and inflammatory cells. These are secreted by stimulated cells (chiefly T helper cells and macrophages) and act on a variety of target cells which harbour their specific receptors. Chemokines are a specific subgroup of cytokines with chemoattractant properties that attract leukocytes to sites of inflammation.⁹⁴

The targeting of cytokines can impact either or both of B and T cell mediated mechanisms of pathogenesis. The viable targets include the following.⁶³

- (i) CD40-CD154 pathway: This is important for the activation of B cells and differentiation of plasma cells through other immune cells.
- (ii) B cell activating factor (BAFF) pathway: The pathway has a key role in B cell maturation and survival.
- (iii) CXCL13 signalling: CXCL13 chemokine and its receptor CXCR5, expressed on B cells and Tfh cells play a major role in the migration of B cells to secondary lymphoid organs and for the development of germinal centres.
- (iv) Interleukin 17 (IL-17) pathway: IL-17 is a cytokine secreted by the pro-inflammatory Th17 cells and is overexpressed in MG.
- (v) Interferon-I pathway: This pathway is overactivated in TAMG and Early onset MG and could be responsible for the chronic inflammatory changes.
- (vi) Interleukin 6 (IL-6) pathway: IL-6 has pro-inflammatory activity and influences both T and B cells. It induces the conversion of T helper to Th17 proinflammatory cells and promotes the maturation and survival of plasma cells.

Belimumab

Belimumab is a human recombinant neutralizing mAb against a cytokine of the tumour necrosis factor (TNF) family called the B-cell activating factor (BAFF), also known as B Lymphocyte Stimulator (BLyS). Receptors for BAFF are located in all circulating B cells and BAFF plays key roles in B cell survival, maturation and immune function.⁹⁵ Overexpression of BAFF promotes the survival of autoreactive B cells and is correlated with autoimmune diseases including MG. Suppression of BAFF by belimumab causes the depletion of the B cell lineage cells dependent on it for survival and homeostasis.⁹⁶

Clinical efficacy of belimumab was shown in systemic lupus erythematosus for which it is an approved therapy. However, the drug's performance in MG has been disappointing, notwithstanding the fact that some of the commonly used MG therapies indirectly affect BAFF activity. A 24-week phase 2 study of intravenous belimumab in MG did not find any benefit for the therapy over placebo.⁹⁷

Iscalimab

Iscalimab is a fully human non-depleting antiCD40 mAb which targets the activation and signalling pathways mediated by CD40. CD40 is a co-stimulatory molecule expressed in B cells and other antigen presenting cells which interacts with its ligand CD154 (CD40L) located on activated T cells. The CD40-CD154 co-stimulatory pathway is essential for the T cell dependent antibody responses, and the differentiation, survival and activation of

memory B cells, dendritic cells and macrophages.⁹⁸ A phase 2 placebo-controlled randomized trial of iscalimab (CFZ533) as an add-on therapy in moderate to severe MG (NCT02565576) is currently underway.

Interleukin 6 Antagonists

Interleukin 6 (IL-6) is a soluble cytokine which mediates a wide variety of functions including inflammation, immune response and haematological functions. In the acute phase of inflammation, IL-6 facilitates the production of a subgroup of acute phase reactants and augments the immune function by stimulating haematopoiesis. However, it plays a major role in the transition of acute neutrophilic inflammation to chronic mononuclear infiltrates paving the way for potentially harmful chronic inflammatory response.⁹⁹ Its role in AChR-MG was illustrated by the presence of elevated IL-6 in treatment-naïve patients and the subsequent suppression of the levels with immunotherapy.¹⁰⁰ Antibodies against IL-6 could downregulate the pro-inflammatory Th-17 response and suppress the symptoms in experimental autoimmune MG models.¹⁰¹

Tocilizumab and satralizumab are mAbs against IL-6 receptors which have been approved for other chronic autoimmune diseases. Subcutaneously administered satralizumab was effective in reducing relapses of NMOSD both as monotherapy and add-on immunotherapy and has been recently approved for this indication.^{102,103} Jonsson et al, described two patients with refractory MG who responded to intravenous tocilizumab after failure of classical immunotherapy, thymectomy and repeated doses of IVIg and rituximab.¹⁰⁴ Both the drugs are under development as therapy for gMG (NCT05067348 and NCT04963270).

Subcutaneous Immunoglobulin

Chronic IVIg administration is a therapeutic option in refractory gMG. Subcutaneously administered immunoglobulin is an attractive alternative for IVIg as it avoids hospital admission, reduces utilization of health resources, preserves patient autonomy and portends better quality of life. Subcutaneous immunoglobulin (SCIg) was also associated with more persistent blood levels of the drug and fewer systemic adverse effects.^{105,106}

In a prospective open-label study, SCIg (2 g/kg) was administered over 4 weeks in 23 adults with worsening mild or moderate MG. The primary outcome of significant reduction in QMG scores at 6 weeks was achieved compared with baseline at weeks 2, 4 and 6. Headache and infusion reactions were the common side effects which occurred in 74% and 61% of patients, respectively.¹⁰⁷ The magnitude of improvement in the QMG scores in this study was comparable to the pivotal study with IVIg.¹⁰⁸ This study provided class IV data for the non-inferiority of SCIg over IVIg.¹⁰⁷ However, with a global shortage of immunoglobulin products, it is unlikely that this will be useful in large number of MG patients.

Chimeric Antigen Receptor (CAR) and Chimeric Autoantibody Receptor (CAAR) T Cell Therapy

Chimeric antigen receptor (CAR) T cell therapy is a cell-based therapy which has shown marked success in the treatment of B cell malignancies over the last 6 years. The technique involves harvesting of T cells from the patient and genetically modifying them by attaching an artificially engineered receptor referred to as a chimeric antigen receptor (CAR). When the CAR T cells are infused into the circulation, the modified receptors bind to a specific antigen on the target cells (e.g., cancerous cells in B cell malignancies) and destroy them. The effect of CAR T cells is sustained long-term by their *in vivo* multiplication.^{109,110}

More recently, the application of CAR T cell therapy have been extended beyond cancer treatment to autoimmune diseases, fibrosis, degenerative diseases and infections. In autoimmune diseases where a specific pathogenic antibody is identified, the preferred approach is using an engineered T cell which can bind the specific autoreactive B-cell. This technique is referred to as Chimeric autoantibody receptor (CAAR) T cell therapy and by specifically targeting B cells which express the autoantibody, a general depletion of the B cell lineage cells is avoided. In most of the autoimmune diseases, however, the pathogenic antibody is not well-delineated. Here, using a CAR T-cell model targeting the specific B cell antigen (e.g., CD 19-specific CAR) ensures a more

thorough suppression of the abnormal cell clones compared with mAbs aiming at the same antigens.¹¹⁰ The limiting side effects include cytokine release syndrome, neurological side effects, infusion reactions and cytopenias.¹⁰⁹

The ongoing studies in MG include engineered T cells directed against B cell Maturation Antigen (BCMA) (NCT04146051) and MuSK antibody (NCT05451212).

Haematopoietic Stem Cell Transplantation

Autologous haematopoietic stem cell transplantation (HSCT) has emerged as a technique to attenuate or even completely terminate disease activity in many autoimmune neurological diseases including MG. The procedure involves stimulating the production of haematopoietic cells, harvesting them from circulation, ablating and resetting the immune system and then re-infusing the treated cells from the patient. The evidence for HSCT in MG is limited to a handful of patients. Bryant et al, conducted a retrospective analysis of 7 patients with severe MG who had received autologous HSCT (one for co-existent follicular lymphoma). All had attained stable remission off therapy after a median follow up of 40 months.¹¹¹ Similar outcomes were reported in other single case reports.^{112,113} The high propensity for early and late debilitating side effects including infections, secondary autoimmune diseases, and neoplasms have relegated HSCT to a lower position among the treatment options. Myasthenia gravis has been reported rarely as a chronic graft-versus-host reaction in recipients of HSCT.¹¹⁴

Limitations and Challenges of the Novel Agents

The novel therapies have brought with them some formidable challenges which limit their liberal use. The primary and immediate concern is the exorbitantly high cost, particularly for the recently approved eculizumab and efgartigimod. A cost-effectiveness analysis demonstrated that the addition of these drugs to conventional therapy increased the expenses 7- to 9-fold and discouraged the use of these medicines as benchmarks for costing decisions for emerging drugs.⁴⁵ While acknowledging their undeniable benefits in refractory MG, the report of the analysis also suggested restricting the use of these medicines to a limited subset of AChR-positive MG patients.⁴⁵

The use of these medicines is also limited by many unanswered questions. There is little understanding of their role in early MG and impact on reduction of doses of other immunosuppressant therapy in refractory MG. The optimal redosing schedule for efgartigimod and duration of therapy for all the novel therapies are not well-understood. Of particular concern is the unquantified risk of long-term toxicities including opportunistic infections and neoplasms which may emerge with extended use.

Conclusions

The newer biologicals herald an era where MG therapies are targeted to the specific pathomechanisms of the disease. Complement inhibitors, FcRn blockers and B cell depleters have established their position in MG management protocols. These medicines come with concerns pertaining to long-term safety, optimal usage and prohibitive cost. This necessitates the judicious use of these drugs in the correct clinical scenario for the correct patient. With the current evidence, they are maximally useful in patients with refractory MG, though cautious use in early severe disease may bring down the disease burden for the patient. Accumulation of real-world data will help in the logical placing of the drugs in treatment protocols. Research directed towards safer therapies and curative treatment for MG are essential additions to this rapidly expanding spectrum.

Disclosure

Prof. Dr. Saiju Jacob reports personal fees from and is part of the Advisory Board for ArgenX Ltd and UCB Pharma; speaker fees from Terumo BCT; personal fees from Regeneron and Immunovant, outside the submitted work. The authors report no other conflicts of interest in this work.

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