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REVIEW ARTICLE

Monoclonal Antibody-Based Therapies for Myasthenia Gravis

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Abstract

Myasthenia gravis (MG) is an autoimmune, neuromuscular disorder that produces disabling weakness through a compromise of neuromuscular transmission. The disease fulfills strict criteria of an antibody-mediated disease. Close to 90% of patients have antibodies directed towards the nicotinic acetylcholine receptor (AChR) on the post-synaptic surface of skeletal muscle and another 5% to the muscle-specific kinase, which is involved in concentrating the AChR to the muscle surface of the neuromuscular junction. Conventional treatments of intravenous immunoglobulin and plasma exchange reduce autoantibody levels to produce their therapeutic effect, while prednisone and immunosuppressives do so by moderating autoantibody production. None of these treatments were specifically developed for MG and have a range of adverse effects. The extensive advances in monoclonal antibody technology allowing specific modulation of biological pathways has led to a tremendous increase in the potential treatment options. For MG, monoclonal antibody therapeutics target the effector mechanism of complement inhibition and the reduction of antibody levels by FcRn inhibition. Antibodies directed against CD20 and signaling pathways, which support lymphocyte activity, have been used to reduce autoantibody production. Thus far, only eculizumab, an antibody against C5, has reached the clinic. We review the present status of monoclonal antibody-based treatments for MG that have entered human testing and offer the promise to transform treatment of MG.

Key Points

Myasthenia gravis (MG) is caused by antibodies directed towards neuromuscular junction proteins and leads to compromised synaptic transmission and disabling weakness. Ultimately, all therapeutics targeting the immune system are designed to moderate the severity of autoantibody injury.

Standard treatments for MG have been copied from other autoimmune diseases, and few have been carefully evaluated by modern-day standards.

Monoclonal antibody therapies under evaluation for MG all have a rationale based on understanding of the autoimmune pathology and have, or are undergoing, rigorously designed clinical trials. None of the agents are designed to reacquire tolerance to the autoantigen and do not specifically target the autoimmune reaction of MG.

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1 Introduction

Myasthenia gravis (MG) is an autoantibody-mediated disease and, because of its well understood pathophysiology, a therapeutic response in MG serves as a proof-of-principle for drugs designed to moderate antibody-driven disorders in general [1]. Monoclonal antibodies have proven to be highly successful therapeutic agents for a wide variety of diseases from cancer to inflammatory diseases to migraine. The last decade has seen a range of monoclonal antibody therapeutics being applied to MG (Table 1 and Fig. 1).

In MG, autoantibodies attack post-synaptic proteins leading to a reduction of acetylcholine receptors (AChR) and a subsequent impairment of neuromuscular transmission leading to disabling weakness. The majority of patients have antibodies against the AChR while upwards of 8% of patients have autoantibodies directed towards the muscle specific kinase (MuSK), a protein that signals clustering of AChR to the post-synaptic membrane. Other antigenic targets include low-density lipoprotein-related receptor-related 4 (LRP-4), agrin, cortactin, and others, but have not been unequivocally validated as pathogenic. Some patients, defined as seronegative, remain with an absence of detectable circulating autoantibodies. B cell synthesis of autoantibodies is driven by T cells. The inciting factors that lead to activation of the autoimmune process are poorly defined [2].

2 Diagnosis and Standard Treatment of Myasthenia Gravis

MG leads to weakness of skeletal muscle with a characteristic loss of force generation with continuous activity (muscle fatigability). The severity of the disease is highly variable among patients and within an individual with rare spontaneous remissions and exacerbations that may be so severe as to require hospitalization with intensive care and artificial respiratory support, so-called myasthenic crisis [3]. Upwards of twenty percent of patients have ocular myasthenia with weakness only of the eye muscles producing drooping eyelids, double vision, or both [4–6]. A subgroup of patients with generalized weakness may have a preponderance of weakness involving muscles of the face and throat with individuals with MuSK antibodies tending to more commonly have such bulbar manifestations [7].

Confirmation of the clinical diagnosis can be made by detection of AChR antibodies in the blood in close to 60% of patients with isolated ocular myasthenia and nearly 90% generalized patients [8], while MuSK antibodies are present in a third to half of patients without AChR antibodies. MuSK antibodies are rarely found in patients with purely ocular myasthenia. Extremely rarely, patients have been described with both antibodies. Identification of these autoantibodies is highly specific for MG. In those patients without serological evidence of MG, electrodiagnostic studies can confirm a disorder of neuromuscular transmission. Approximately 75% of patients will have a decremental response to repetitive nerve stimulation [9], and single-fiber electromyography has a higher sensitivity when performed by experts who publish reports of their experience rather than in common clinical practice [10]. Clinical tests, which involve observation for significant improvement in obviously weak muscles after administration of a cholinesterase inhibitor or application of an ice pack over ptotic eyelids, have been used as adjuncts to support a clinical diagnosis of MG [10].

Cholinesterase inhibitors continue to be the most commonly used treatment for MG since their first use in the 1930s. They enhance neuromuscular transmission and have no chronic adverse effects; however, they often are inadequate to reverse symptoms leading to the vast majority of patients moving to immunomodulating and immunosuppressive therapies. They also frequently have intolerable gastrointestinal adverse effects. Cholinergic-induced weakness is rarely, if ever, a concern. For patients with AChR antibody-positive MG younger than 65 years, thymectomy has been found to reduce the severity of the disease [11]. The most consistently effective treatment is prednisone used at high doses for months to years and tapered to the lowest effective dose. The best available data suggests that at least 20% of patients do not respond to prednisone [11], which prompts use of immunosuppressive treatments such as mycophenolate, azathioprine, and tacrolimus [12–14]. Each of these take many months to demonstrate clinical efficacy, have the potential for significant toxicity, and treatment response is unpredictable.

The deficiencies in care coupled with the generally understood biological mechanisms of MG make the application of monoclonal-based therapeutics, which specifically target disease mechanisms, particularly attractive approaches. This review summarizes the rationale and the present status of monoclonal antibody treatments for MG (Table 1, Fig. 1).

Table 1 Monoclonal antibody therapies for myasthenia gravis

Drug	Clinical testing	Target	Company	Standard administration
Rituximab	Phase II studies	CD20	Genentech	Treatment protocols vary 375 mg/m^2 IV weekly for 4 wk with repeat dosing in 6 mo Single IV infusion 500 mg
TAK-079	Phase II started	CD38	Takeda	Phase I study used IV and SC administration
Belilumab	Phase II completed	BAFF	GlaxoSmithKline	IV 10 mg/kg every other wk for 7 doses
Iscalimab	Phase II completed	CD40	Novartis	IV 10 mg/kg every 4 wk for 6 doses
Eculizumab	FDA-approved for MG	Complement 5	Alexion	IV 900 mg weekly for 4 wk then every other wk 1200 mg
Ravulizumab	Phase III started	Complement 5	Alexion	IV loading and maintenance dose based on weight
Efgartigimod	Phase III completed	FcRn	Argenx	IV 10 mg/kg weekly for 4 doses
Rozanolixizumab	Phase III started	FcRn	UCB	SC infusion 4 or 7 mg/kg for 3 weekly doses (phase II)
Nipocalimab	Phase II completed	FcRn	Momenta	IV multiple dosing arms
Batoclimab	Phase II completed	FcRn	Immunovant	SC 340 or 680 mg every 2 wk for 4 doses

BAFF B-cell activating factor of the TNF family, *FcRn* neonatal Fc receptor, *IV* intravenous, *MG* myasthenia gravis, *SC* subcutaneous

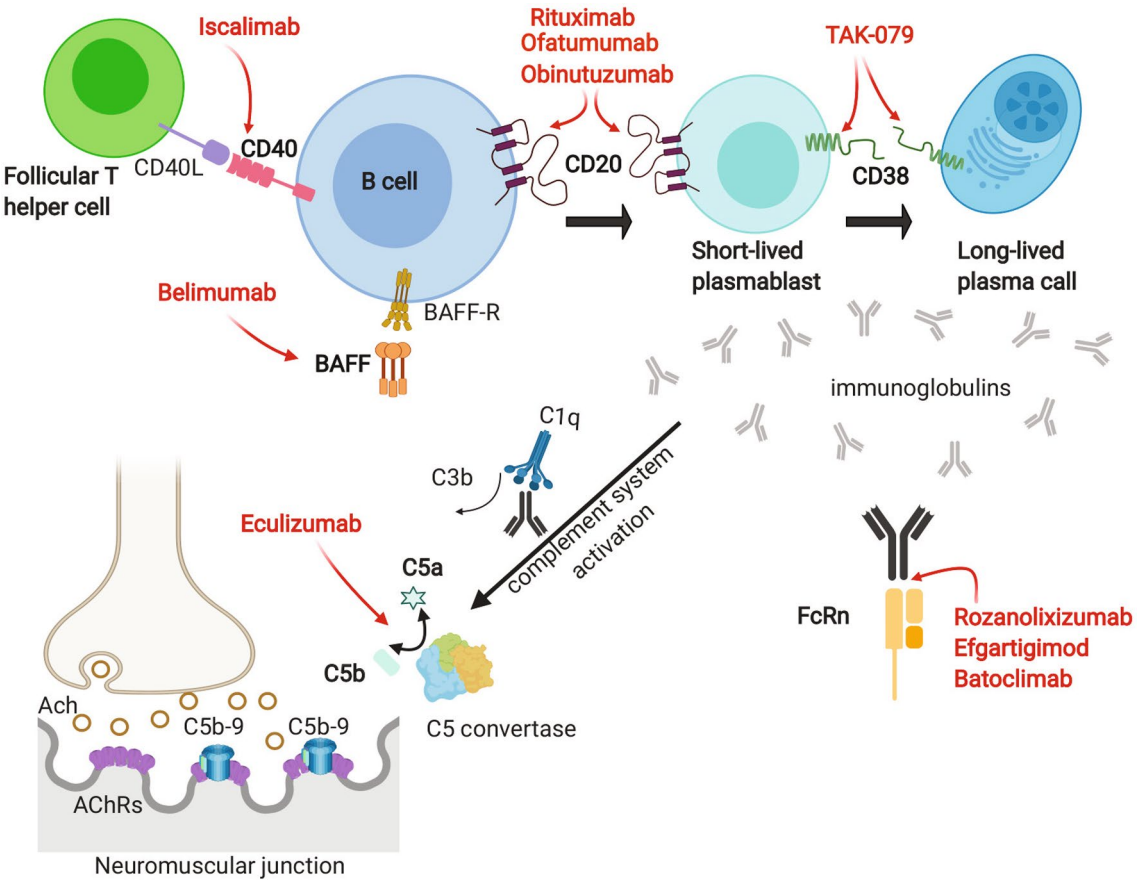

Fig. 1 Schematic summary of myasthenia gravis pathophysiology and targets of monoclonal antibody therapies. *ACh* acetylcholine, *AChR* acetylcholine receptor, *BAFF* B-cell activating factor of the TNF family, *C* Complement, *C5b9* represents terminal component of complement, *CD* Cluster of Differentiation, *FcRn* neonatal Fc receptor

3 Clinical Trials in Myasthenia Gravis

A discussion of clinical trials in MG cannot be provided in the absence of some understanding of clinical outcome measures. For a thorough discussion of outcome measures and trial design please see Kaminski and Kusner [3] and Kaminski et al. [15]. Common to all areas in medicine, the rigor of trial performance for MG has increased over the last two decades. For MG, a focused set of guidelines was proposed in 2000 with the publication of the MG Foundation of America Taskforce on Clinical Research Standards [16]. Here the deficiencies, including lack of standardization in outcome measures and statistical assessment, were reviewed and recommendations for future studies were set forth. Since this publication, the guidelines have been largely accepted and were updated in 2012 [17].

The quantitative MG score (QMG) was recommended as a primary outcome measure and has since been used in the pivotal study establishing thymectomy as efficacious for AChR antibody-positive early-onset MG [11] as well as several phase II investigations described below (Table 2). With the FDA interest in patient-reported outcome measures, there has been a shift to use the MG-ADL (Myasthenia Gravis–Activities of Daily Living) as a primary outcome measure as was done for the phase III trial demonstrating the effectiveness of eculizumab for AChR antibody-positive MG [18]. Other secondary outcome measures are presented in Table 2. For all the biologics discussed in this review, prospective trials have been performed or are underway with a hope for efficacy and safety appropriate to allow general clinical use. Such studies have not been performed for 'established' therapies for which FDA approval has not been attempted.

4 B-Cell Targeting

MG is an antibody-mediated pathology and therefore dependent on B cells that generate pathogenic antibodies, which has made B cells an attractive target for developing

treatments. The vast majority of B cells express the cell surface marker, CD20, with the exceptions of early development pre-B cells as well as late-stage and long-lived plasma cells, which produce antibodies [19]. The first CD20 cell-specific biologic was the chimeric IgG1 monoclonal antibody rituximab. After binding to CD20-positive cells, rituximab eliminates the cells primarily by complement-mediated cytotoxicity, with antibody-dependent cellular cytotoxicity and phagocytosis being additional mechanisms. Long-lived plasma cells generally no longer express CD20 and therefore would not be removed by anti-CD20 therapies; however, aberrant expression of CD20 may occur in MG [20], perhaps offering a highly specific approach to elimination of cells driving autoimmunity [21]. Rituximab has a good safety profile with most adverse events related to infusion reactions at initiation. Rituximab use carries the risk of reactivation of hepatitis B, and patients should undergo serological testing for previous hepatitis B exposure. Progressive multifocal leukoencephalopathy (PML) has been observed but is profoundly rare. The risk of malignancy may be increased. A caveat to this good safety profile is that long-term risk has not been characterized.

Rituximab was first used in treatment of non-Hodgkin's lymphoma and leukemia in the 1990s but has been used off label for many autoimmune diseases including rheumatoid arthritis, neuromyelitis optica, and multiple sclerosis. A systematic review evaluating 169 patients in case reports and series of AChR and MuSK antibody-positive patients suggested therapeutic benefit and drop in autoantibody titer [22]. Patients with MuSK antibodies showed a greater clinical response and drop in autoantibody titer. Hehir and colleagues performed a prospective review of 54 MuSK antibody-positive patients across ten centers and found the 24 rituximab-treated patients on much lower doses of prednisone had lower use of immunosuppressives, and had improved clinical status [23]. In contrast, the BeatMG phase II trial, thus far published only in abstract form, did not identify efficacy in its primary outcome measure of prednisone dose reduction for treatment-resistant AChR antibody-positive MG (ClinicalTrials.gov identifier NCT02110706) [24].

Taken together, the data suggest that there may be a differential response to CD20 ablation between AChR and MuSK antibody-positive patients. In other autoimmune diseases, rituximab therapy reduces serum antibody levels generally and appears to lower autoantibodies to a greater extent [19]. The greater efficacy of rituximab in MuSK MG suggests that pathogenic antibody synthesis is primarily by short-lived plasma cells [25], in contrast to AChR antibody synthesis, which appears to be reliant on long-lived plasma cells, which do not express CD20. However, investigations thus far have been on treatment-resistant patients, leading to the question of whether earlier use of rituximab in the course of AChR antibody-positive MG could be more effective. Long-lived plasma cells would be expected to be particularly resistant to rituximab given the absence of CD20. In addition, the assessment of CD20 depletion of circulating cells is straightforward, but determination of efficacy of rituximab, or any other agent targeting lymphocytes in tissue, such as bone marrow or lymph nodes where long-lived antibody producing cells live, is difficult [19].

Newer agents specific for B-cell targeting have been developed. Obinutuzumab provides a distinct mechanism of action from rituximab through primarily direct cell death, rather than complement-mediated cytotoxicity. Whether this difference

Table 2 Major clinical outcome measures for myasthenia gravis trials

Outcome	Description	Score
MG-ADL	8-item patient-completed assessment of common symptoms with severity rated 0–3	0–24 2-point improvement considered meaningful
QMG	13-item scoring system performed by trained rater of ocular, bulbar, extremity, axial, and respiratory muscles involved in MG with severity rated 0–3 based on objective criteria	0–39 3-point change considered meaningful
MG Composite	10-item MGC contains mix of examiner- and patient-based assessments of ocular, bulbar/facial/neck, respiratory, limb domains with more critical domains weighed more heavily	0–51 3-point change considered meaningful
MGFA Clinical Classification*	Ordinal scale of 5 categories of clinical severity ranging from ocular (1) to myasthenic crisis (5) and subdivisions of bulbar predominance	Class 1: ocular Class 2: mild Class 3: moderate
MG-QOL15r	15-item patient-reported assessment with rating of 'not at all', 'somewhat', and 'very much'	0–45 not at all: 0 somewhat: 1 very much: 2

MG myasthenia gravis, *MG-ADL* Myasthenia Gravis Activities of Daily Living, *MGFA* MG Foundation of America, *MG-QOL15r* MG-Quality of Life–revised, *QMG* Quantitative Myasthenia Gravis

*MGFA Classification is no longer considered an outcome measure, but was used in some studies in this manner prior to 2000

would be superior for treatment of MG cannot be predicted. There is a single case report of obinutuzumab being used in a patient with treatment-resistant MG and chronic lymphocytic leukemia with success [26]. Ofatumumab and ocrelizumab are human monoclonal antibodies to CD20 and may have greater cytotoxic potential with fewer adverse effects than rituximab. Each have demonstrated efficacy in randomized trials of multiple sclerosis [27, 28]; whether they may demonstrate superiority in treatment of MG is speculative.

A limitation of all CD20-targeted approaches is that they do not eliminate the non-CD20 expressing, long-lived plasma cells, which has led to the consideration of antibody targeting of antigens specific to these cells. CD38 is expressed on plasma cells, but also T and NK cells as well as a range of non-immune cells [29]. TAK-079 is a high-affinity antibody directed against CD38 [30] and is under evaluation in a planned phase II trial for MuSK and AChR antibody-positive MG. Inebilizumab [31] is an anti-CD19 monoclonal antibody approved for the antibody-mediated disease, neuromyelitis optica. One might expect it to have greater efficacy for MG compared with CD20-depleting treatments, but no studies have been performed yet.

5 B-Cell Activating Factor Inhibition

B-cell activating factor of the TNF family (BAFF), also referred to as Blys, would be considered a reasonable therapeutic target for MG. BAFF is a cytokine that plays a role in a broad array of B-cell functions from early development to maintenance in normal and autoreactive cells. BAFF is elevated in serum of patients with MG [32] and in the hyperplastic thymus [33]. Polymorphisms of the *BAFF* gene are associated with MG susceptibility [34].

Belimumab is a humanized immunoglobulin G1λ antibody that binds and blocks the activity of BAFF leading to a reduction of B-cell differentiation. This ultimately results in reduced levels of circulating CD19 B cells, CD20 + B cells, CD27− naive B cells, CD20 +/CD69 + activated B cells, and CD20 +/CD138 + plasmacytoid B cells [35]. Belimumab is approved for the treatment of systemic lupus erythematosus (SLE) [36] and is being assessed for other autoimmune disorders. Despite the strong biological rationale and efficacy in SLE, a phase II trial of 40 AChR and MuSK antibody-positive patients with generalized MG on various standard therapies treated for 24 weeks found no improvement in any clinical endpoints, including the primary outcome using the QMG [37]. No specific adverse events were associated with belimumab treatment.

6 CD40–CD40L Inhibition

CD40 is expressed on a range of immune cells including dendritic cells, B cells, and macrophages, while the CD40 ligand (CD40L) is expressed on activated T cells. The interaction of the two proteins promotes proinflammatory cytokine secretion, dendritic cell activation, and overall increased immune response [38–40]. An impaired CD40 activation can compromise development of tolerance by allowing auto-reactive T lymphocytes to avoid negative selection and subsequent autoimmune disease induction. Over expression of CD40 can contribute to activation of autoreactive T cells and proinflammatory cytokines. Aberrant expression of CD40 in certain tissues will lead to localized inflammation. However, CD40–CD40L also plays a role in increasing Treg expression. Antibodies to CD40L moderate severity of experimental autoimmune MG with an associated drop in pro-inflammatory cytokines [41].

Iscalimab is an anti-CD40 monoclonal antibody [42] that does not reduce CD40-expressing B cells but blocks primary and recall T cell-dependent antibody responses and reduces germinal cell formation. A double-blind, placebo-controlled, phase II study involving 44 patients with generalized MG and AChR or MuSK antibodies demonstrated good safety but no difference in QMG scores between groups. Results have only been published on the ClinicalTrials.gov website as of August 2020 (NCT02565576).

7 Complement Inhibition

AChR antibodies are polyclonal and compromise neuromuscular transmission by (i) blockade of ion channel function, (ii) antigenic modulation, which reduces AChR surface half-life, and (iii) activation of complement [43, 44]. In animal models of experimental autoimmune MG, complement activation is the predominant mechanism that drives pathology, while in humans there are likely differential contributions of each of these mechanisms across patients and over the course of the disease.

AChR antibodies activate the classical complement pathway through binding the antigen and its Fc receptor is bound by C1q triggering a multistep enzymatic process leading to formation of the terminal complement component (TCC). The pore formed by the TCC leads to focal lysis of the post-synaptic surface, which produces loss of AChR, sodium channels, and post-synaptic folds. A critical step includes the activation of the C5 convertase.

Eculizumab is a humanized, chimeric monoclonal antibody that targets complement protein 5 (C5) [45]. Eculizumab inhibits the C5 convertase and thereby limits the formation of the TCC [46].

Eculizumab was first found to be effective for paroxysmal nocturnal hemoglobinuria (PNH). PNH is an ultra-rare disease caused by a deficiency in glycosylphosphatidylinositol (GPI)-anchored proteins on cell surfaces. The red blood cells of these patients are at risk for spontaneous lysis by low levels of complement activation, which is normally blunted by GPI-anchored intrinsic complement inhibitors. Patients have severe anemia, and the release of hemoglobin from the red cells leads to dark urine with risk of kidney injury. The primary treatment for PNH was repeated blood transfusions. The application of eculizumab was phenomenally successful with the majority of patients no longer requiring transfusion [47]. Treatment resistance has been identified in patients with a genetic variant of C5, which compromises binding of eculizumab [48]. Atypical hemolytic uremic syndrome is another rare disease, which is caused by uncontrolled activation of complement with deposition of the TCC on endothelial cells. Based on uncontrolled and retrospective analyses, eculizumab is now first-line treatment for atypical hemolytic uremic syndrome [49]. Recently, eculizumab was demonstrated effective for the antibody-mediated disease neuromyelitis optica by reducing exacerbation rates from 43 to 3% in the treated group [50]. A phase II, randomized, placebo-controlled masked trial of eculizumab in 34 subjects with Guillain–Barré syndrome suggested safety but did not achieve a clinical measure of efficacy [51].

In 2013, a pilot crossover study evaluated safety and efficacy of eculizumab in AChR antibody-positive treatment-refractory generalized MG [52]. Subjects demonstrated clinically significant improvement in the treatment group with no significant adverse effects. The study had a crossover design with a washout period long enough for serum complement activity to return to normal, but surprisingly subjects did not return to their baseline level of weakness, suggesting the potential for non-complement mechanisms for efficacy. In the REGAIN study, 125 subjects with treatment-resistant MG were randomized to eculizumab and placebo groups for the 26-week study [18]. Although the study marginally missed its primary endpoint of efficacy, which was a 3-point reduction in MG-ADL (p value of 0.07), the trial met several secondary endpoints including a reduction in MG-QOL15. In treatment responders, onset of improvement was within 1 week for two-thirds of patients with many having a 5-point reduction in the QMG score, with 3 points considered clinically meaningful. At the end of the study, 85% of eculizumab-treated patients reached a priori-determined significant improvement. An open-label extension study has demonstrated sustained benefit with good safety profile [53]. In 2017, eculizumab was approved by the FDA for generalized AChR antibody-positive MG.

The safety profile of eculizumab in MG patients is similar to that reported in other disorders. Headache and upper respiratory tract infection are more common with eculizumab treatment followed by nasopharyngitis and nausea compared with placebo. Life-threatening meningococcal infection is the most significant potential complication as occurs among patients with genetic disorders of complement deficiency. Before starting complement inhibitors, meningococcal vaccine is recommended using Center of Disease Control guidelines. From 2008 to 2016, prior to approval of eculizumab for MG, 16 cases of meningococcal meningitis in the United States were reported with 11 caused by *Neisseria meningitides* that could not be classified to the known serotypes [54]. Fourteen patients had received at least one vaccination prior to infection. In the REGAIN study, splenectomy was an exclusion criteria.

There are additional downsides to eculizumab treatment. A significant limitation in the use of complement inhibitors for MG is that at present there is no suggestion that the underlying generation of autoantibody is altered by the therapy and, therefore, discontinuation of inhibitor therapy would be expected to lead to rapid return of weakness. The majority of MuSK autoantibodies do not activate the complement pathway and hence complement inhibitors are not expected to be efficacious in MuSK antibody-positive MG, while for double seronegative patients, efficacy is unknown. At approximately 500,000 USD per year, there is significant cost for the healthcare system and limitations on access placed by insurers. The need for frequent dosing has stimulated the development of ravulizumab, which is a modified form of eculizumab with markedly prolonged half-life, allowing dosing every 8 weeks, which is an advantage for patients. A phase III trial for MG is ongoing as of August 2020 (NCT03920293). Another complement inhibitor with a dosing advantage is zilucoplan, a small molecule, which is self-administered daily by subcutaneous injection. It has been found to be safe and effective in a phase II trial [55] and phase III evaluation began in 2019 and is likely to be completed in 2021 (NCT04115293).

8 Neonatal Fc Receptor Inhibition

A rapidly emerging therapy for antibody-mediated disorders is inhibition of the normal antibody recycling system [56, 57]. The neonatal Fc receptor (FcRn) was first characterized for its function in the transfer of IgG in the mother's milk across the baby's gut epithelium into the neonatal bloodstream [58]. FcRn has been found to be expressed in many cell types but most importantly for recycling of IgG in the

vascular endothelium. FcRn transports IgG across the cell surface through binding of the Fc portion of the antibody ultimately trafficking to the lysosome, which has an acidic pH. The low pH supports high affinity binding between the FcRn and the IgG and prevents degradation, ultimately allowing the release of IgG to the extracellular space. This process allows recycling of IgG and is a major determinant of circulating levels of IgG.

Three basic approaches have been taken to inhibit antibody recycling; (i) ABDEGs, (ii) FcRn directed antibodies, and (iii) small molecule inhibitors. ABDEGs are genetically engineered antibodies that competitively inhibit the FcRn. The engineered constructs bind the FcRn on the cell surface and enter cells via receptor-mediated uptake, as does IgG; however, they are inefficiently released back into circulation and therefore undergo lysosomal degradation to a greater extent [59]. These dual properties have advantages in that one can imagine as a therapeutic effect there is the benefit for a rapid termination of affect, which can be modulated based on dosing; of course, this comes at the cost of repeated dosing. The second approach involves FcRn antibodies directed towards the Fc portion of the IgG, which block binding of the FcRn leading to antibody degradation [60]. Small molecules act in a similar fashion and will not be discussed further in this review, and these have not moved to human assessment for MG.

Efgartigimod is the most advanced FcRn inhibitor in clinical development moving towards approval for human use, having completed phase III testing [61]. It possesses an IgG1 Fc fragment that contains a five-residue alteration to increase its binding to FcRn at acidic and physiological pH. Its phase II study, which involved 24 subjects with generalized MG with AChR antibodies, suggested no significant safety concerns and improvements in MG-ADL and QMG [62]. Total serum IgG was reduced by close to 40% in the first week of treatment and further reduction to 70% of pretreatment levels over 3 weeks. After the treatment phase, IgG levels remained half of baseline for 3 weeks and 20% of baseline at 8 weeks. Similar reductions were observed for AChR antibodies. Improvement in QMG and MG-ADL compared with placebo was found and maintained during the observation period. Antibodies against efgartigimod were identified but no clear effect on pharmacological properties of the drug was identified.

Argenx released results in May 2020 for the phase III study involving 167 AChR antibody-positive generalized MG patients (NCT03770403) [63]. The randomized placebo-controlled trial identified clinically meaningful improvement in MG-ADL in 44 of 65 drug-treated patients compared with 19 of 64 in the placebo arm treated over 4 weeks with the MG-ADL as primary endpoint at 8 weeks. Slightly more than half of efgartigimod-treated patients were significantly improved 2 weeks after starting treatment. Adverse effects in the phase II and III studies were no different between placebo- and drug-treated patients.

Rozanolixizumab is a human anti-FcRn IgG4 monoclonal antibody [64] and has completed a phase II study in MuSK and AChR antibody-positive patients. The study design was more complex than the typical phase II investigations in MG. Patients received rozanolixizumab or placebo weekly for three doses of 7 mg/kg and then monitored for 4 weeks then randomized again to receive three weekly doses of 4 or 7 mg/kg of study drug. The MG-ADL assessment between the groups demonstrated statistical superiority for the treatment group while the number of subjects with a reduction of ≥ 3 points of MG-ADL was close to 50% percent in the rozanolixizumab group compared with slightly over 10% in the placebo group. Each dosing group was superior to placebo. Despite the improvement in MG-ADL, QMG was no different among groups. Total and AChR antibodies were reduced by nearly 70% at the end of the study. Headache was a common adverse effect leading to withdrawal of three patients from the study. Results of the phase II study have only been reported in abstract form [56]. A phase III study has been initiated (NCT03971422).

Two other FcRn-directed antibodies have completed phase II testing for MG without published results but appear to be moving to phase III investigation. Nipocalimab is a human monoclonal antibody high-affinity binding to the FcRn in the picomolar range [65]. A phase II study in MG has been completed with positive results reported by the company (NCT03772587) [66]. Batoclimab is a human monoclonal antibody that binds the FcRn, inhibiting recycling, and has completed a phase II study of generalized MG AChR antibody-positive patients (NCT03863080), but no results have been published or posted; however, press releases indicate a phase III trial is to be organized. As reported in abstract form, the phase I investigation demonstrated safety and lowering of IgG levels similar to the other FcRn inhibitors [56].

9 Concluding Comments

We are living in a time that is transforming the therapeutic options for MG patients and, in contrast to many standard therapies, these are being evaluated with randomized trials in the context of a greater understanding of basic pathophysiology [67]. The challenge lies in integrating these therapies with established treatments. Inexpensive prednisone remains the most consistently effective drug for MG and targets elimination of lymphocytes that drive the pathology, but also has numerous, often intolerable, adverse effects and its cost does not consider the expense of its complications. The complement and FcRn inhibitors

appear unlikely to influence autoantibody generation and are not uniformly effective. The COVID-19 pandemic has compromised clinical trial performance and has added a layer of complexity for agents that are designed to drastically reduce antibody-producing cells, which are key to viral immune attack, but may also limit the excessive inflammatory response observed in some SARS-CoV-2 infected patients [68]. Patients with MG and investigators in the field are cursed and blessed to live in interesting times.

Declarations

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Conflicts of interest/Competing interests HK has served as an advisor to Alnylam Pharmaceuticals, Cabelleta Bio, Takeda Pharmaceuticals, Ra Pharmaceuticals, and UCB Pharmaceuticals; and is CEO and CMO of ARC Biotechnology, LLC, based on US Patent 8,961,98. He is principle investigator of MGNet (U54 NS115054), which is funded through collaboration between NCATS and NINDS. The remaining authors have no conflicts.

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Authors' contributions HJK was invited to provide the review. SA, MA, and HJK performed literature review and wrote initial drafts of the manuscript. PS reviewed the manuscript and developed the figure. HJK finalized the submitted manuscript.

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Consent to participate Not applicable.

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