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DRUG EVALUATION

Zilucoplan: An Investigational Complement C5 Inhibitor for the Treatment of Acetylcholine Receptor Autoantibody–Positive Generalized Myasthenia Gravis

James F. Howard Jr.[a], John Vissing[b], Nils E. Gilhus[c], M. Isabel Leite[d], Kimiaki Utsugisawa[e], Petra W. Duda[f], Ramin Farzaneh-Far[f], Hiroyuki Murai[g] and Heinz Wiendl[h]

[a]Department of Neurology, University of North Carolina School of Medicine, Chapel Hill, NC, USA; [b]Department of Clinical Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [c]Department of Clinical Medicine, University of Bergen and Haukeland University Hospital, Bergen, Norway; [d]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK; [e]Department of Neurology, Hanamaki General Hospital, Hanamaki, Iwate, Japan; [f]UCB Pharma, Cambridge, MA, USA; [g]Department of Neurology, International University of Health and Welfare, Narita, Chiba, Japan; [h]Department of Neurology, Institute of Translational Neurology, University of Münster, Münster, Germany

ABSTRACT

Introduction: Generalized myasthenia gravis (gMG) is an autoimmune disorder in which pathogenic autoantibodies damage the neuromuscular junction, causing disabling or life-threatening muscle weakness. Most treatments nonspecifically inhibit aspects of the immune system, do not directly address the causal mechanisms of tissue damage, and often have side-effect profiles that negatively impact patients. Understanding of the central pathogenic role of the complement cascade in gMG is advancing, and a new complement-targeting treatment is under investigation.

Areas covered: We provide an overview of gMG etiology, the complement cascade, current treatments, and the investigational gMG therapy zilucoplan. Zilucoplan is a small, subcutaneously administered, macrocyclic peptide that inhibits cleavage of complement component C5 and the subsequent formation of the membrane attack complex.

Expert opinion: In a randomized, double-blind, placebo-controlled, phase 2 clinical trial, zilucoplan demonstrated clinically meaningful complement inhibition in patients with acetylcholine receptor-positive gMG. Zilucoplan, a first-of-its-kind cyclic peptide targeting C5, appears to be a therapeutic option for the treatment of gMG based on available pharmacokinetic/pharmacodynamic data and phase 1 and 2 efficacy, safety, and tolerability data with limited long-term follow-up. Zilucoplan use earlier in the treatment paradigm would be suitable in this population should phase 3 efficacy and safety data be equally favorable.

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Autoimmune diseases; complement activation; complement C5; corticosteroids; generalized myasthenia gravis; membrane attack complex; neuromuscular junction

1. Introduction

1.1. Generalized Myasthenia Gravis

Myasthenia gravis (MG) is an autoimmune disease characterized by chronic generalized or localized muscle weakness that is worsened by exercise or repetitive muscle use [1]. The prevalence of MG varies globally from an estimated 15 to 179 - per million people [2]. Ocular weakness (eg, ptosis and diplopia) is the first presenting symptom in up to 86% of cases, and 80% of these patients will progress to generalized MG (gMG) [3,4]. Although the disease course varies, most patients with gMG reach maximum disease severity within 1 to 2 years of symptom onset with no further progression thereafter [3,5].

The symptoms of gMG impair daily functioning and the work, leisure, and social activities of most patients, leading to reduced income, emotional burden, frequent use of healthcare resources, and a decreased quality of life (QoL) [6–11]. Prolonged muscle weakness can potentially increase the risk of obesity, osteoporosis, and respiratory infections [12]. At some point in the evolution of their disease, approximately 20% of patients experience respiratory muscle weakness that progresses to a life-threatening state known as myasthenic crisis [5,6,13]. In addition to gMG disease burdens, patients must frequently navigate comorbidities such as thymic malignancies and related conditions; other autoimmune diseases such as thyroid disease, pernicious anemia, systemic lupus erythematosus, rheumatoid arthritis, neuromyelitis optica spectrum disorder, and inflammatory myopathies; and toxicities associated with long-term use of corticosteroids and immunosuppressants [14–19].

Normal neuromuscular transmission is mediated by the binding of presynaptic acetylcholine to acetylcholine receptors (AChRs) in the postsynaptic membrane of the neuromuscular junction (NMJ). In MG, this transmission is impaired by autoantibodies that bind to AChRs or to functionally related molecules [1]. Anti-AChR antibodies are present in 80% to 88% of patients with MG, and contribute to early-onset (i.e., prior to 50 years of age), late-onset (i.e., ≥50 years), thymoma-associated, and ocular MG disease

CONTACT James F. Howard Jr. howardj@neurology.unc.edu Howard Department of Neurology, UNC School of Medicine, CB#7025 2200 Physician Office Bldg, Chapel Hill, NC .27599-7025, USA

[#]Dr Farzaneh-Far is a former employee of and current consultant for UCB Pharma, Cambridge, MA, USA

subtypes [5,20,21]. A smaller proportion of patients (<10%) harbor autoantibodies against muscle-specific kinase (MuSK) or lipoprotein-related protein 4 or are seronegative for all three autoantibodies [22–25]. The differences in MG antibody subtype have a major impact on treatment decisions [12]. This article focuses primarily on patients with anti-AChR antibody-positive (AChR$^+$) gMG.

A key mechanism of signal impairment in gMG involves the anti-AChR antibody-mediated activation of the complement cascade, which has been shown to induce architectural changes to the postsynaptic membrane [5,26,27]. Detailed evidence for the role of complement in MG in humans and animal models has been recently reviewed [28,29]. Other anti-AChR antibody-mediated mechanisms of signal impairment include functional AChR blockade and the process of receptor cross-linking, internalization, and degradation (i.e., antigenic modulation) [5,30,31].

1.2. The Terminal Complement Cascade

Complement-mediated destruction of the NMJ, initiated by the presence of pathogenic autoantibodies, is a major cause of MG pathology [26,28,32,33]. The complement cascade is a critical part of the immune system that is initiated by any one of three separate pathways (alternative, classical, and lectin; Figure 1A). All three pathways first converge at complement component 3 (C3), with a second convergence point at C5. C5 is cleaved to produce C5a and C5b, with subsequent recruitment of C6, C7, C8, and C9 to yield the pore-like terminal complement complex C5b-9, also known as the membrane attack complex (MAC) [32,34]. Accumulation of the MAC on the postsynaptic plasma membrane of the NMJ mediates tissue damage and destruction of the delicate cytoarchitecture and electrochemical integrity of the postsynaptic membrane (Figure 1B) [27,32]. The complement cascade is implicated as a key mediator of cell and tissue damage in numerous other inflammatory and autoimmune disorders including immune-mediated necrotizing myopathies [35], paroxysmal nocturnal hemoglobinuria [36], neuromyelitis optica [37], and atypical hemolytic uremic syndrome [38]. It has been hypothesized that complement and inflammation also play a role in amyotrophic lateral sclerosis [39].

2. Overview of the Market

2.1. Treatment options

Symptomatic treatment with acetylcholinesterase inhibitors is recommended as a first-line treatment for MG. Pyridostigmine is the most widely used drug in this class. Some patients with mild disease experience adequate symptom control with this class of drugs alone, requiring no further treatment [1]. However, in patients with moderate or severe MG, the efficacy of these agents is usually limited and/or temporary, requiring concomitant use of immunotherapeutic interventions. Side effects of acetylcholinesterase inhibitors include nausea, diarrhea, abdominal pain, urinary urgency, increased salivation, sweating, and/or increased weakness [1,17,40,41].

Many patients with anti-AChR$^+$ MG present with thymus pathology [5]. International consensus guidance recommends thymectomy in patients with thymoma and in patients ≤60 years of age with anti-AChR$^+$ antibodies irrespective of thymus pathology [5,42,43]. While differences in regional treatment approaches exist, thymectomy may also be considered in select patients with ocular symptoms only and, in rare cases, in seronegative patients who do not respond to initial treatment [5,17,43].

Oral prednisone, prednisolone, or other glucocorticoids are commonly used immunotherapeutic options after first-line therapy and may also be used as alternatives or additions to symptomatic and other immunosuppressive treatments initiated as first-line therapy [5,17,43]. The benefits of corticosteroid agents for patients with MG are well established; however, long-term use often leads to side effects such as weight gain, osteoporosis, hypertension, diabetes, acne, and mood disorders [17,44]. Nonsteroidal immunosuppressive drugs, such as purine inhibitors (e.g., azathioprine and mycophenolate mofetil) and the cyclophilins (e.g., cyclosporine and tacrolimus), provide clinical benefit without corticosteroid-related adverse effects [17]. However, these treatments can cause nausea, hepatic enzyme increases, diarrhea, hypertension, leukopenia, and an increased risk of severe infections or malignancy, especially with long-term use, as is typical in patients with MG [17]. Potential teratogenic side effects of some immunosuppressive treatments limit their use in women who are or could become pregnant [12,45,46].

The anti-CD20 monoclonal antibody rituximab has emerged as a gMG therapy [46]. Although the randomized, placebo-controlled BeatMG trial showed no clear benefit of rituximab in patients with AChR$^+$ gMG who were receiving steroid treatment [47], other studies suggest potential clinical benefit in patients with anti-MuSK$^+$ MG who had not responded to standard therapy, as well as in patients with new-onset, non-MuSK$^+$ gMG [48–51]; however, more studies are needed to better understand the value of this treatment option.

The promise of gMG treatment strategies targeting inhibition of the complement cascade was affirmed when eculizumab, an intravenous monoclonal antibody that inhibits C5, demonstrated efficacy in patients with non-thymomatous gMG for whom prior therapy had failed, leading to its approval for use in the United States (anti-AChR$^+$ gMG), European Union (anti-AChR$^+$ refractory gMG), and Japan (anti-AChR$^+$ gMG with symptoms poorly controlled by high-dose intravenous immunoglobulin or plasma exchange) in 2017 [52–56]. The eculizumab label contains a warning against life-threatening and fatal meningococcal infection, thus requiring vaccination prior to use [53,57]. Eculizumab is generally reserved for patients whose disease is treatment-resistant, is ineffective for patients harboring rare C5 mutations in the eculizumab-binding site, and incurs a high financial cost [53,56–58].

Intravenous immunoglobulin (IVIg) and plasma exchange (PLEX) are used in patients with treatment-resistant disease or as a rescue treatment for myasthenic crisis [43,59]. Their utility can be attributed to effects that include complement system modulation and neutralization or removal of antibodies and cytokines [5]. Both IVIg and PLEX are generally considered short-term interventions because of contraindications, treatment risks, lack of long-term efficacy data, and burdensome administration [43,59].

The MG treatment pipeline is robust and includes existing therapeutic targets with improvement on routes of administration [60]. In addition, there are multiple agents in development that target other components of the complement cascade [29,60,61]. Other approaches under investigation seek to reduce

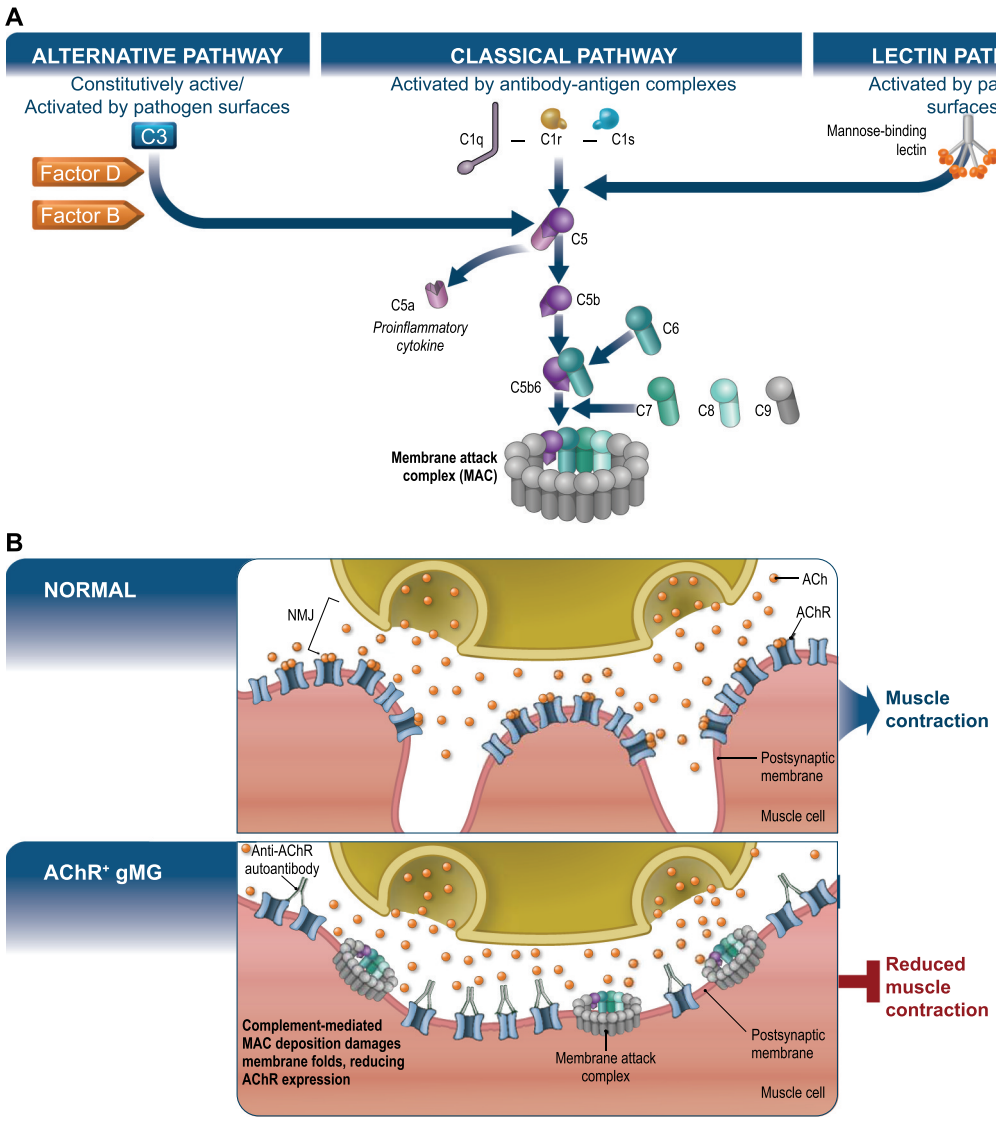


Figure 1. The (A) complement cascade and (B) depiction of the molecular components of a normal vs AChR$^+$ gMG neuromuscular junction and the impact on muscle contraction. Graphics are schematic representations and are not true to scale. In panel A, a truncated version of the full complement cascade is presented with a focus on specific mechanisms relevant to zilucoplan in AChR+ gMG. ACh binds to AChR on normal postsynaptic membrane folds, allowing for normal neuromuscular signaling and muscle contraction. In panel B, autoantibodies against AChR initiate the classical complement cascade, resulting in the deposition of MAC on the postsynaptic membrane, damage to the membrane fold structure, and reduction of AChR expression, resulting in attenuated neuromuscular signaling and muscle contraction. ACh, acetylcholine; AChR, acetylcholine receptor; AChR$^+$, acetylcholine receptor positive; C[*x*], complement component [*x*]; gMG, generalized myasthenia gravis; MAC, membrane attack complex; NMJ, neuromuscular junction.

autoantibody production via the fragment crystallizable neonatal receptor (FcRn), proteasomes, or proinflammatory cytokines and chemokines, or depletion of B and plasma cells via targeting of other cluster of differentiation antigens (e.g., anti-CD19) [62].

2.2. Unmet Treatment Needs

Despite current standard-of-care treatment, data from the MG Patient Registry, the largest patient-reported database of patients with MG, reflect a high degree of disease burden for many patients, suggesting a continued need for additional treatment options [6]. Suboptimal response to initial therapy or intolerable side effects seem to be associated with younger age and female sex [63]. These factors may contribute to the higher disease burden experienced by these two populations and may be reflective of clinician reluctance to prescribe more aggressive treatment because of associated side effects and long-term risks that may disproportionately impact these patients [6]. In a cross-sectional study of neurological centers in Japan, patients with MG reported decreases in employment or income due to their disease, as well as reduced social positivity and activity [7]. In a cross-sectional study of Norwegian and Dutch patients with MG, current treatment with non-steroidal immunosuppressive therapies negatively impacted health-related QoL [64]. Taken together, these data suggest there is room for improvement in patients' disease-related QoL that may be enhanced with novel treatment options.

3. Introduction to Zilucoplan

3.1. Primary Characteristics

Zilucoplan is an investigational, small (3.5 kDa), 15-amino acid macrocyclic peptide designed to inhibit terminal complement

activation, a consequence of anti-AChR-mediated initiation of the complement cascade (Figure 2A; Box 1). Zilucoplan binds C5 with high affinity and specificity to prevent downstream assembly of the MAC by a dual mechanism: 1) inhibiting the cleavage of C5 by C5 convertase into C5a and C5b (Figure 2B) and 2) binding to preformed C5b to sterically block interaction with C6. Targeting C5 preserves proximal cascade effects including C3b-mediated opsonization, C3a inflammatory response, and immune complex clearance. Zilucoplan is self-administered once daily as a subcutaneous (SC) injection of approximately 5 seconds [65].

3.2. Pharmacokinetics and Pharmacodynamics

In a phase 1 multiple-dose study, in which healthy volunteers received single doses (0.5 to 4 mg/kg) or multiple, once-daily SC administrations of zilucoplan 0.2 mg/kg, plasma concentrations were consistent with the *in silico* pharmacokinetic models and between the single- and multiple-dose parts of the human study. Exposures were consistent and showed low variability across all participants, with maximum plasma concentration observed 3 hours postdose [66]. The approximate half-life was 7 days across all dose levels [67]. Steady-state plasma levels were predicted to be achieved at day 11 at a 0.2-mg/kg dose level [66].

The pharmacodynamic profile of zilucoplan was explored in the phase 1 single- and multiple-dose groups of healthy volunteers using an *ex vivo* antibody-sensitized sheep red blood cell (sRBC) lysis assay [68] to assess the classical pathway of complement activation. Inhibition in the hemolysis assay (i.e., suppression of complement activity) was rapid and dose-dependent, with near-complete inhibition observed approximately 3 hours postdose [66,67].

These pharmacodynamic results were confirmed in a 12-week phase 2 study of patients with gMG, in which a zilucoplan 0.3-mg/kg dose resulted in 97% inhibition in the sRBC lysis assay (Figure 3). The zilucoplan 0.1-mg/kg dose resulted in rapid and consistent, yet submaximal, inhibition of sRBC hemolysis at approximately 88% [65]. Furthermore, zilucoplan exhibited equipotent binding and inhibition of hemolysis induced by C5 variants, including the mutation associated with poor response to eculizumab [65,69,70].

3.3. Clinical Efficacy

The efficacy of zilucoplan for the treatment of anti-AChR$^+$ gMG was assessed in a 12-week, randomized, double-blind, placebo-controlled phase 2 trial (ClinicalTrials.gov identifier: NCT03315130) in patients aged 18 to 85 years with a clinically confirmed diagnosis of Myasthenia Gravis Foundation of America (MGFA) Class II–IVa gMG [70,71], presence of AChR autoantibodies, and Quantitative MG (QMG) score [72] of ≥12 points, with a score of ≥2 on at least four items [65]. Patients were stratified based on the screening QMG score (≤17 vs ≥18 points) and randomized to receive once-daily SC zilucoplan 0.3 mg/kg (n = 15), zilucoplan 0.1 mg/kg (n = 15; however, only 14 received at least 1 dose of study drug), or placebo (n = 15) [65]. Patients maintained stable doses of standard-of-care treatments, including pyridostigmine, corticosteroids, and immunosuppressive drugs, throughout the study. The primary and key secondary end points were least square means change from baseline to week 12 in QMG score and MG-Activities of Daily Living (MG-ADL) score [73], respectively. Reductions of at least 3 points on the QMG and 2 points on the MG-ADL were considered clinically meaningful [74,75]. Additional end points included change from baseline to week 12 in the 15-item MG Quality of Life–Revised (MG-QoL15r) [76] and MG Composite (MGC) [77] scores and the proportion of patients who required rescue therapy with PLEX or IVIg. Statistical analyses of the end points used zilucoplan 0.3 mg/kg versus placebo as the primary comparison, and all efficacy evaluations were based on a one-sided 0.10 significance level [65].

At baseline, patients (N = 44) were considered moderately to severely affected by gMG, with a mean (SD) QMG score of 18.8 (4.3), and approximately 60% were classified with MGFA Class III or IV gMG. Treatment with zilucoplan 0.3 mg/kg resulted in rapid, clinically meaningful, and statistically significant improvements compared with placebo in QMG score at 12 weeks (least squares mean [SEM] difference, −2.8 [1.7]; P = 0.05) and MG-ADL score (−2.3 [1.3]; P = 0.04; Figure 4A and 4B; Table 1). Ten of 14 patients (71%) in the zilucoplan 0.3-mg/kg group achieved a clinically meaningful improvement in QMG score (≥3-point decrease). A rapid onset of action was demonstrated with separation between treatment groups as early as 1 week after treatment. Similar trends were observed for the MG-QoL15r and MGC scales (Figure 4C and 4D; Table 1) [65]. No statistical interaction of the treatment effect of zilucoplan 0.3 mg/kg with immunosuppressive therapy, IVIg, or PLEX was found for any of the four efficacy scales. The zilucoplan 0.1-mg/kg group showed a delayed and less-pronounced response than the 0.3-mg/kg group, with statistically significant differences versus placebo observed for the QMG, MG-ADL, and MG-QoL15r end points (Table 1). Use of rescue therapy with PLEX or IVIg, administered at the investigator's discretion, was reduced with zilucoplan treatment versus placebo (Table 1) [65].

At the end of 12 weeks, participants from the phase 2 trial were eligible to enter an open-label extension period in which zilucoplan-treated patients continued at the same dosage and placebo recipients were randomized 1:1 to receive once-daily zilucoplan 0.3 mg/kg or zilucoplan 0.1 mg/kg [65,78]. Patients who received zilucoplan 0.3 mg/kg from the start of the double-blind treatment period through week 24 (n = 13) experienced sustained reductions from baseline in QMG score (mean [SEM] difference, −7.8 [1.3]; Figure 4A) as well as in MG-ADL, MG-QoL15r, and MGC scores (Figure 4B–D). Further, placebo recipients who crossed over to zilucoplan 0.3 mg/kg after 12 weeks (n = 7) experienced rapid improvements on all four scales that were sustained at week 24 (Figure 4). The results of this study supported the 0.3-mg/kg dose that is currently under investigation in a pivotal phase 3 study of zilucoplan for the treatment of gMG (RAISE; NCT04115293).

3.4. Safety and Tolerability

Zilucoplan was well tolerated in the double-blind, phase 2 controlled trial, with no pattern in treatment-emergent adverse

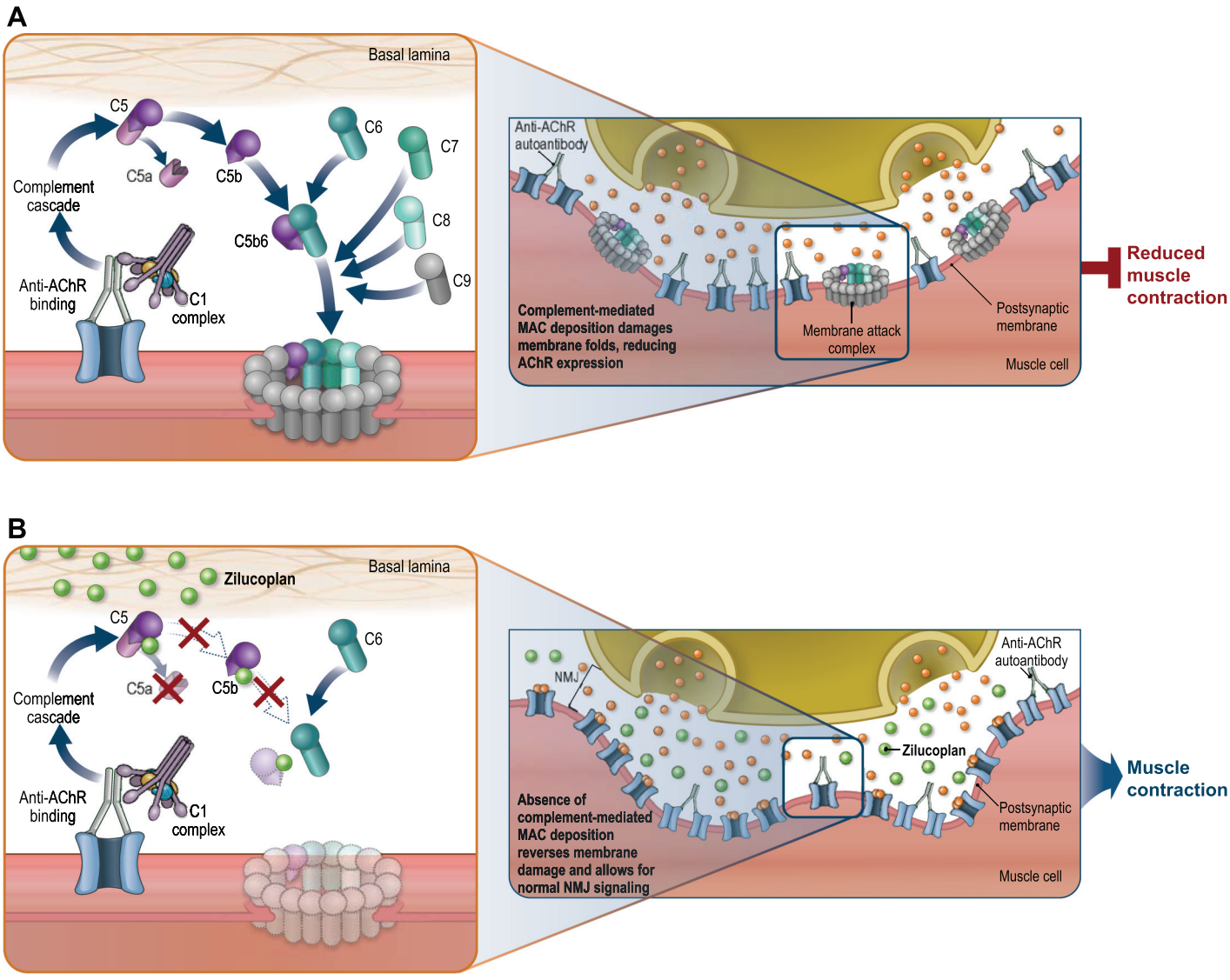


Figure 2. (A) Activation of the terminal complement cascade in gMG and (B) inhibition by zilucoplan. Graphics are schematic representations and are not true to scale. In panel A, cross-linking of AChRs by anti-AChR antibodies initiates the classical complement cascade, leading to cleavage of C5 and assembly of the MAC. In panel B, zilucoplan binds C5 at the location corresponding to C5b, thereby inhibiting both the cleavage of C5 and the binding of C6 to pre-formed C5b, thus preventing assembly of the MAC. ACh, acetylcholine; AChR, acetylcholine receptor; C[*x*], complement component [*x*]; gMG, generalized myasthenia gravis; MAC, membrane attack complex; NMJ, neuromuscular junction.

events (TEAEs) observed across treatment groups: zilucoplan 0.3 mg/kg, 12 (86%) of 14 patients; zilucoplan 0.1 mg/kg, 15 (100%) of 15 patients; and placebo, 12 (80%) of 15 patients. Injection-site reactions occurred in 3 (21%) of 14, 4 (27%) of 15, and 2 (13%) of 15 patients who received zilucoplan 0.3 mg/kg, zilucoplan 0.1 mg/kg, and placebo, respectively. All injection-site reactions in zilucoplan-treated patients were mild. Eight serious TEAEs were reported (zilucoplan 0.3 mg/kg, n = 5/14 [36%]; placebo, n = 3/15 [20%]), but none were considered study drug related. No meningococcal infections, deaths, life-threatening adverse events, or anti-zilucoplan antibodies were reported [65]. These data were consistent with previous experience in other studies [66,67]. No new safety signals were observed during the open-label extension study.

3.5. Regulatory Status

In August 2019, the US Food and Drug Administration, which defines rare diseases as those that affect fewer than 200,000 people in the United States, designated zilucoplan as an orphan drug for the treatment of gMG [79]. Zilucoplan is currently in phase 3 development (NCT04115293) and has not been approved for use by any regulatory agency.

4. Conclusion

Anti-AChR$^+$ gMG is a rare, autoantibody-mediated disorder with relevant pathogenic contribution of the complement system that results in chronic fatigable muscle weakness and reduced QoL. The current mainstays of MG treatment include acetylcholinesterase inhibitors (e.g., pyridostigmine), immunotherapy with corticosteroids, nonsteroidal immunosuppressive drugs (e.g., azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus), thymectomy, and IVIg/PLEX (mostly used to treat crisis/exacerbations). Although none of these treatments addresses the cause of MG, immunotherapies can attenuate the underlying immunological

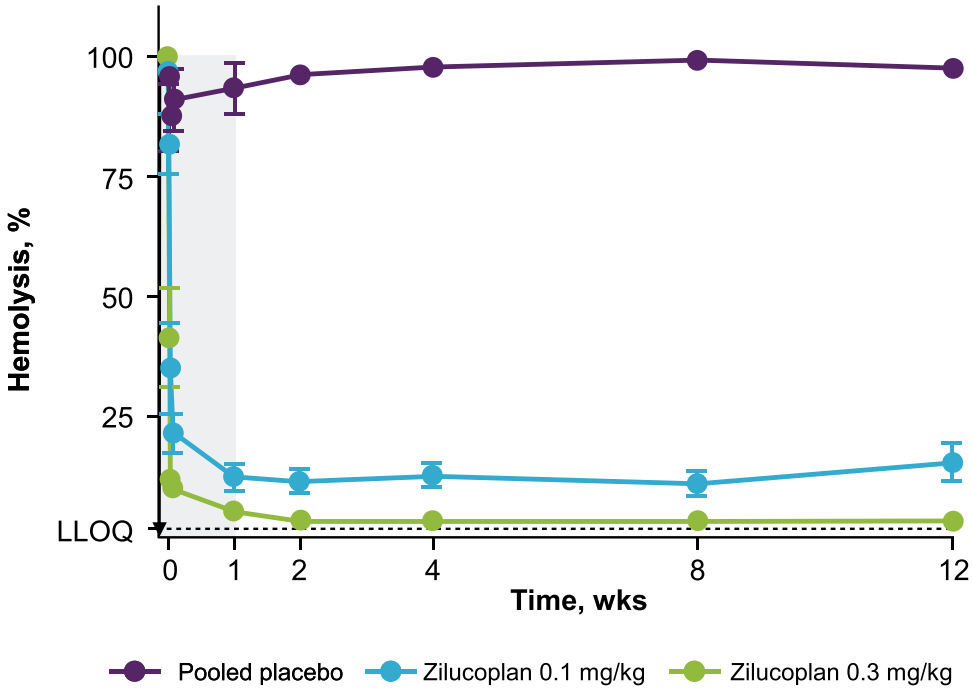


Figure 3. Mean inhibition of complement activity by zilucoplan in a 12-week phase 2 study in patients with generalized myasthenia gravis, as measured by *ex vivo* sheep red blood cell hemolysis assay. Figure reproduced with permission from Howard JF Jr, Nowak RJ, Wolfe GI, et al. *JAMA Neurol*. 2020;77;582–592 [65]. LLOQ, lower limit of quantification.

processes by various mechanisms, leading to a marked improvement in most patients. Nevertheless, some patients continue to experience muscle weakness, with subsequent risk of daily function and QoL impairments, and frequently experience negative treatment side effects. Therapeutic targeting of the complement cascade is a novel strategy that is based on pathological mechanistic rationale, thereby offering the potential for faster and improved disease control with increased tolerability and safety as compared to current conventional therapy. Zilucoplan, an investigational macrocyclic peptide inhibitor of C5 that is self-administered as a once-daily SC injection, produces rapid and robust reductions of complement activity and clinically meaningful improvements in patient- and clinician-reported disease markers, with a favorable safety and tolerability profile based on available phase 1 and 2 study results. Expansion of treatment results will be forthcoming with data from the ongoing phase 3 clinical trial and long-term extensions of the phase 2 and 3 studies.

5. Expert opinion

The available data suggest that zilucoplan may be an important advancement in the treatment of gMG. The rapid effect of zilucoplan – observed with robust, sustained inhibition of complement activity after the first dose and clinical effect after 1 week of once-daily treatment – enhances its potential utility. The favorable safety and tolerability profile of zilucoplan with few TEAEs in the phase 1 and 2 trials supports a potential improvement over current standard-of-care treatments, contingent on favorable safety and tolerability data in phase 3 and long-term extension studies. Zilucoplan may benefit patients (1) whose disease is suboptimally controlled; (2) who are considered to have treatment-resistant disease; and/or (3) who have intolerable side effects from other immunotherapies.

Nearly 29% of the patients treated with zilucoplan 0.3 mg/kg in the phase 2 study did not experience clinically meaningful improvement on the QMG at week 12. It may be that NMJ damage in these patients had progressed such that complement inhibition was unable to affect these structural changes. Another potential reason for this lack of response is that 12 weeks may not have been sufficient for improvement in some of these patients. In the REGAIN double-blind and open-label extension study of eculizumab, the percentage of eculizumab-treated patients achieving an MGFA post-intervention status of minimal manifestations increased from 21% to 46% between weeks 12 and 26 and increased further to 53% at week 104, suggesting that response may develop over time in some patients with MG [80,81]. Lastly, it is possible that a lack of response is related to complement-independent effects of autoantibodies such as steric hindrance of AChR binding or reduced AChR density at the postsynaptic membrane [65].

From a molecular perspective, zilucoplan may hold some advantages over other gMG treatments. Zilucoplan is approximately 40 times smaller than monoclonal antibodies such as eculizumab, which may enable greater penetration at the NMJ [69]. In addition, unlike therapeutic anti-C5 monoclonal antibodies that rely on the FcRn for their pharmacokinetic stability, the peptide composition of zilucoplan should allow for coadministration with IVIg or novel FcRn inhibitors that are currently in development, without compromising pharmacokinetics.

If phase 2 clinical trial findings can be confirmed in phase 3, complement inhibition may emerge as an essential treatment modality in the neurology toolbox. It will be important to advance understanding and awareness of the role of the complement cascade in MG to supplement symptomatic and global immunosuppressive therapies with disease-modifying treatments. Positive study results for the complement inhibitor eculizumab in the

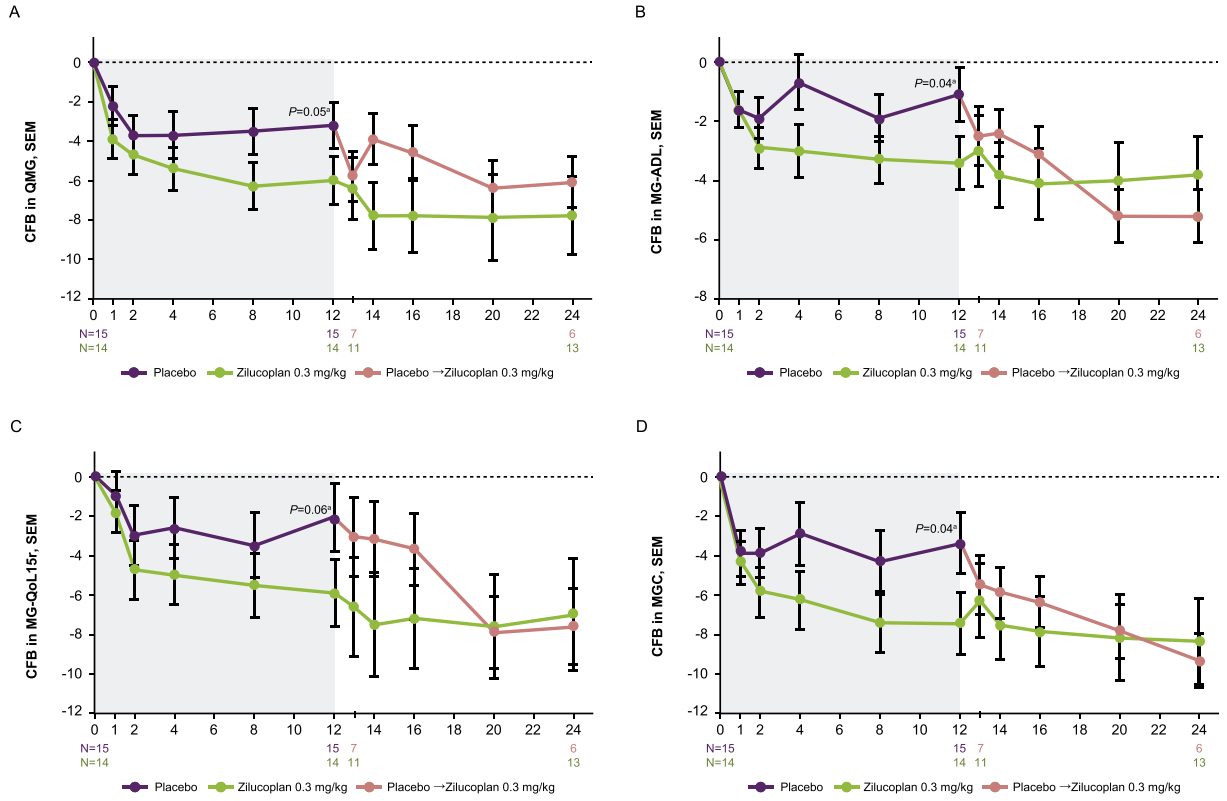


Figure 4. Change from baseline through 12 weeks in the double-blind treatment phase [65] and from weeks 12–24 in the open-label extension treatment phase [78] in the (A) QMG, (B) MG-ADL, (C) MG-QoL15r, and (D) MGC scales. Error bars denote SEMs of least squares mean in all randomized participants who received at least one dose of study drug. Double-blind treatment data were presented in Howard JF Jr, Nowak RJ, Wolfe GI, et al. *JAMA Neurol*. 2020;77;582–592 [65]; open-label treatment data were previously presented at the American Academy of Neurology 2019 Annual Meeting; May 4–10, 2019; Philadelphia, PA [78]. [a]Prespecified significance testing at a one-sided alpha of 0.1 with last-observation-carried-forward analysis of covariance for least squares mean CFB for zilucoplan 0.3 mg/kg vs placebo; placebo recipients were re-baselined to zero upon completion of the 12-week double-blind treatment period. CFB, change from baseline; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MG-QoL15r, 15-item Myasthenia Gravis Quality of Life Revised Scale; QMG, Quantitative Myasthenia Gravis; SEM, standard error of the mean.

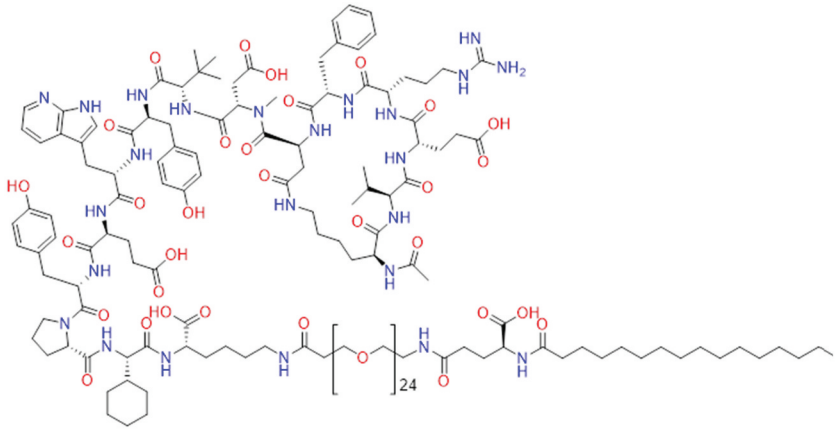
Table 1. Clinical efficacy outcomes at week 12.

			Zilucoplan 0.3 mg/kg vs placebo			Zilucoplan 0.1 mg/kg vs placebo	
Variable	Placebo	Zilucoplan 0.3 mg/kg	Difference	*P* value[a]	Zilucoplan 0.1 mg/kg	Difference	*P* value[a]
N	15	14	NA	NA	15	NA	NA
QMG	−3.2 (1.2)	−6.0 (1.2)	−2.8 (1.7)	0.05	−5.5 (1.2)	−2.3 (1.7)	0.09
MG-ADL	−1.1 (0.9)	−3.4 (0.9)	−2.3 (1.3)	0.04	−3.3 (0.9)	−2.2 (1.3)	0.05
MG-QoL15r	−2.1 (1.7)	−5.9 (1.7)	−3.7 (2.4)	0.06	−7.4 (1.7)	−5.3 (2.4)	0.02
MGC	−3.3 (1.6)	−7.4 (1.6)	−4.1 (2.2)	0.04	−5.3 (1.5)	−2.0 (2.2)	0.19
QMG decrease ≥3, n (%)	8 (53.3)	10 (71.4)	NA	NS	10 (66.7)	NA	NS
Rescue received, n (%)	3 (20.0)	0 (0.0)	NA	NS	1 (6.7)	NA	NS

Notes: Scale scores and differences are reported as least squares mean (SEM). The table includes data previously presented in Howard JF Jr, Nowak RJ, Wolfe GI, et al. *JAMA Neurol*. 2020;77;582–592 [65]. [a]One-sided *P* values based on a pre-specified significance value of 0.10.
MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MG-QoL15r, 15-item Myasthenia Gravis Quality of Life Revised Scale; NA, not applicable; NS, not significant; QMG, Quantitative Myasthenia Gravis.

treatment of gMG have initiated the acceptance of this treatment modality, although these data are in the context of treatment-resistant disease only: pivotal trial inclusion criteria required ≥12 months of inadequate symptom control with ≥2 therapies, and many eculizumab indications are for the treatment of gMG resistant to other treatments, including IVIg and PLEX. Findings from the zilucoplan phase 2 study, in which inadequate response to prior treatment was not required for inclusion and in which there was no statistical interaction of the treatment effect of zilucoplan with prior therapies, suggest that the benefits of complement inhibition need not be reserved for patients with treatment-resistant disease. Future examination of seronegative patients, older patients, patients with severe ocular anti-AChR$^+$ MG, and patients receiving IVIg or FcRn inhibitors may further expand the populations that could benefit from zilucoplan. It stands to reason that introducing complement inhibition earlier in the disease process may help prevent architectural damage of the NMJ; on the contrary, it is unknown whether complement inhibition has the potential to reverse existing architectural damage. The rapid onset of complement inhibition and improvement in symptoms with zilucoplan may suggest potential utility as a rescue treatment for patients with impending myasthenic crisis.

Box 1. Drug summary.

Drug name	Zilucoplan (RA101495)
Phase	Phase 3 ongoing study
Indication	Treatment of acetylcholine receptor antibody–positive generalized myasthenia gravis
Pharmacology description/mechanism of action	15-amino acid macrocyclic peptide/C5 complement inhibitor
Route of administration	
Chemical structure	
Pivotal trial(s)	ClinicalTrials.gov identifier NCT04115293: Safety, Tolerability, and Efficacy of Zilucoplan in Subjects With Generalized Myasthenia Gravis (RAISE)

At-home, once-daily, SC dosing of zilucoplan should make complement inhibition feasible for most patients; however, the value of SC administration may change in the face of novel treatment options with alternate routes of administration.

Cost-effectiveness is an essential variable when addressing gMG management. Studies on the cost-effectiveness of zilucoplan are needed to help physicians, patients, and payer systems better assess the value of the drug and evaluate its place in gMG treatment.

Data gaps remain in our understanding of pathophysiological processes that occur at the NMJ with complement inhibition. It will be important to develop companion biomarkers that help assess the biologic effects of complement inhibition and the individual relevance of the complement system in patients with MG. Until then, given their favorable safety profile and rapid onset of action, an empiric trial of complement inhibitor therapy would be expected to identify most responders within a few weeks of initiation, although late responders have also been recently identified [80, 81]. Furthermore, it is important to better understand whether complement inhibition has effects beyond the attenuation of the damage caused by the terminal complement pathway in MG. Increased risk of serious infection is a potential consequence of complement inhibition, as reflected by prophylaxis recommendations for eculizumab; however, data from patients receiving long-term treatment (≤192 weeks) with eculizumab suggest that risk-mitigation strategies remain effective with continued therapy [53,57,82,83]. Lastly, and as discussed previously, it is unknown whether complement inhibition can reverse complement-mediated NMJ damage once established.

Zilucoplan is a first-of-its-kind, novel cyclic peptide targeting the complement cascade, an essential pathogenic element of gMG. Provided that phase 3 efficacy and safety data are favorable, zilucoplan would be suitable to be used early in the treatment sequence, possibly as first-line treatment.

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Declaration of interest

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