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Marinos Dalakas
Thomas Jefferson University

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Progress in the therapy of myasthenia gravis: getting closer to effective targeted immunotherapies

Marinos C. Dalakas\textsuperscript{a,b}

\textbf{Purpose of review}

To provide an update on immunomodulating and immunosuppressive therapies in myasthenia gravis and highlight newly approved, or pending approval, therapies with new biologics.

\textbf{Recent findings}

Preoperative IVIg is not needed to prevent myasthenic crisis in stable myasthenia gravis patients scheduled for surgery under general anesthesia, based on controlled data. Rituximab, if initiated early in new-onset myasthenia gravis, can lead to faster and more sustained remission even without immunotherapies in 35\% of patients at 2 years. Biomarkers determining the timing for follow-up infusions in Rituximab-responding AChR-positive patients are discussed. Most patients with MuSK-positive myasthenia gravis treated with Rituximab have sustained long-term remission with persistent reduction of IgG4 anti-MuSK antibodies. Eculizumab in the extension REGAIN study showed sustained long-term pharmacological remissions and reduced exacerbations. Three new biologic agents showed promising results in phase-II controlled myasthenia gravis trials: Zilucoplan, a subcutaneous macrocyclic peptide inhibiting complement C5; Efgartigimod, an IgG1-derived Fc fragment binding to neonatal FcRn receptor; and Rozanolixizumab, a high-affinity anti-FcRn monoclonal antibody. Finally, the safety of ongoing myasthenia gravis immunotherapies during COVID19 pandemic is discussed.

\textbf{Summary}

New biologics against B cells, complement and FcRn receptor, are bringing us closer to successful targeted immunotherapies in the chronic management of myasthenia gravis promising an exciting future for antibody-mediated neurological diseases.

\textbf{Keywords}

B cells, complement, myasthenia gravis immunotherapy, neonatal Fc receptor

\textbf{INTRODUCTION}

Myasthenia gravis remains the prototypic antibody-mediated autoimmune disease with a gratifying response to various nonspecific immunotherapies if properly applied. At least 75\% of the patients can be successfully managed with a combination of corticosteroids and a maintenance immunosuppressant, whereas treatment with IVIg or plasmapheresis are effective for severe cases or acute worsenings [1,2–4]. For the chronic management of myasthenia gravis, however, there are challenges. At least 15\% of patients can be refractory or incompletely responding to available therapies whereas in several others, long-term steroids and immunosuppressants are not well tolerated, especially with comorbidities, necessitating the need for better therapies. New biologics are now evolving into powerful tools changing the algorithm or the timing of the various therapeutic regimens promising clinical remission with minimal long-term side effects.

The review provides an update on the current therapies in the chronic management of generalized myasthenia gravis highlighting the promising results of emerging targeted immunotherapies, approved or waiting approval after successful phase II and III clinical trials.
KEY POINTS

- Eculizumab offers an effective, well tolerated and sustained remission in chronic management of myasthenia gravis.
- Ravulizumab (ALXN1210) seems a very promising second generation eculizumab with long-lasting effect.
- Zilucoplan is the first subcutaneous anticomplement agent effective in myasthenia gravis.
- Efgartigimod and Rozanolizumab are the first effective agents against FcR whereas Nipocalimab is in the offing.
- Myasthenia gravis and the various immunotherapies do not make the patients more susceptible to infections during COVID-19 pandemic.

IMMUNOTHERAPIES AS RELATED TO CLINICAL SUBTYPES AND CIRCULATING ANTIBODIES

The main myasthenia gravis subtypes requiring systemic immunotherapies with steroids, steroid-sparing immunosuppressants, IV Ig or plasmapheresis are patients with early-onset generalized myasthenia gravis (EOMG), when the disease starts before the age of 50 years and peaks in the 40s, and late-onset generalized myasthenia gravis (LOMG) starting in the 60s and peaking in the 70s [1**,2–6]. These patients invariably present with weakness in the extraocular, facial, and bulbar muscles with diplopia, dysphagia and dysphonia, fatigable weakness in neck and proximal limb muscles, and in severe cases, involvement of the respiratory muscles. The main differences in therapeutic decisions relate to: consideration for thymectomy only in EOMG, except for thymomas that require excision in all MG subtypes; selecting a well tolerated immunosuppressant for women with EOMG planning pregnancy; consideration of comorbidities in LOMG that influence the choice of medications and treatment duration; and type of autoantibodies. Patients with anti-AChR antibodies, detected in 85% of the patients with the aforementioned phenotypes, respond to the same therapies; this also applies to 6 to 8% of seronegative myasthenia gravis patients who probably have low-affinity or low-titre anti-AChR antibodies. In contrast, patients with antibodies to Muscle-Specific-Kinase (MuSK), behave therapeutically differently. Anti-MuSK antibodies are of the IgG4 subclass and do not fix complement, not responding to anticomplement therapeutics as discussed below. Further, their thymus lacks histological alterations, not requiring thymectomy, and do not respond to antianticholinesterases.

STARTING AND MAINTAINING IMMUNOTHERAPY: WHAT IS NEW

MG is a chronic disease requiring prolonged use of corticosteroids and immunosuppressants or immunomodulators. A step-by-step therapy remains as follows:

**Anticholinesterases**

Pyridostigmine, 60 mg four times daily, remains the earliest therapeutic step offering mild symptomatic but transient help in AChR-antibody-positive myasthenia gravis.

**Corticosteroids**

It is the first-line drug starting with an escalation dose of 20 mg daily increasing it – as needed – even...
Once stability is established, usually after 6 weeks, slow tapering to every-other day begins, aiming to reach the lowest possible dose that controls the disease with minimal side-effects. Immunosuppressants (Azathioprine, Mycophenolate Mofetil, Cyclosporine, Tacrolimus)

These drugs are used to facilitate reduction of prednisone and maintain long-term stability, even though their efficacy remains variable, inconclusive, and not confirmed in large controlled studies. As there are no evidence-based comparative studies, the choice of selecting an immunosuppressant still varies among practitioners, with most preferable being mycophenolate 2000 mg daily (going up 3000, if needed) or Azathioprine (150 mg daily) [1**,2–4]. A number of recent studies have shown that discontinuation or marked reduction of mycophenolate increases the risk of myasthenia gravis exacerbation after 3 months supporting the view of efficacy and the need for long-term administration [7–10]. At least 30% of patients undergoing mycophenolate taper relapsed when the mean dose was reduced to 888 mg/day or was tapered quickly (8.4 vs. 62.4 months in nonrelapsed) [7–10]. After several years of disease stability; however, mycophenolate can be tapered provided the dose reduction is
slow, not more than 500 mg/day every 12 months [10]. My preference is even slower, tapering it by 250 mg yearly. Cyclosporine, up to 150 mg twice daily, and Tacrolimus 0.1 mg/kg are two other options in refractory myasthenia gravis based on large and mostly uncontrolled series [11]. The efficacy of Tacrolimus has now been strengthened with a new controlled study [12] with evidence that it can be successfully lowered, after long-term stability, from 3 mg/day to almost 1 mg/day without exacerbations [13].

**Intravenous immunoglobulin and plasmapheresis: new data**

For urgent relief in patients with severe disease and significant worsening including crises, plasmapheresis (every other day, six times) or intravenous immunoglobulin (IVIg) 2 g/kg, remain the best options [14]. Plasmapheresis may be more preferable in a crisis acting faster but the choice between the two is overall determined by practical issues such as availability, age, comorbidities, venous access or specialized hospital settings.

The effectiveness of IVIg in acute exacerbations in myasthenia gravis patients requiring hospitalization was again confirmed in a prospective uncontrolled phase-III study [15*]. A new prospective, randomized, double-blind study in 47 stable myasthenia gravis patients, 25 randomized to IVIg and 22 to placebo, assessed whether IVIg can prevent myasthenia gravis crisis in stable patients scheduled for surgery. The study showed that preoperative administration of IVIg is not needed in well-controlled patients scheduled for surgery under general anesthesia to prevent myasthenic crisis [16**]. The study is useful considering the frequent requests we receive from surgeons or anesthesiologists whenever general surgery is planned even on clinically stable myasthenia gravis patients.

IVIg is extensively used as maintenance therapy or as steroid-sparing agent, even though the scientific merit (considering the short-lasting benefit), cost, and long-term efficacy have not been established. A retrospective analysis failed to show long-term remission with IVIg [17,18]. The need to establish efficacy in the chronic management of myasthenia gravis led to two controlled trials that have been completed (ClinicalTrials.gov NCT 02473952, 02473965), but not yet published. The same applies to subcutaneous Immunoglobulin (SCIg). A prospective, open-label, phase III trial in patients with mild-to-moderate exacerbation (transition from MGFA class I to II/III or class II to III), showed that SCIg (2 g/kg), over 4 weeks, is well tolerated and effective in reducing myasthenia gravis disability measures [19,20]. SCIg ensures more consistent serum IgG levels with reduced wearing-off effect at the end of each treatment cycle, and although it might be suitable for certain patients with poor venous access or underlying risk factors, a comparative study is needed to determine if it is as good or more preferable to IVIg in maintaining remission.

**Progress in target-specific biologic therapies**

A number of biologics directed against key immune molecules approved for various autoimmune diseases (1), can also target the same molecules within the myasthenia gravis immune network. The most successful results today have been with agents directed against: B-cells and autoantibodies (1); complement (2+); and the neonatal FcRn Receptors (3+) (Fig. 1), supporting the pathogenic role of autoantibodies in MG pathogenesis.

**Agents against B cells**

B-cells are involved not only in complement activation and antibody production but also in antigen presentation and cytokine release including IL-1, IL-6, and IL-10 [21]. Accordingly, targeting B cells in myasthenia gravis may restore immune balance [1**2–4].

**Rituximab**

This is the main anti-B-cell agent on the market, approved for some systemic autoimmune diseases, that has been extensively tried in myasthenia gravis. Rituximab is a chimeric monoclonal antibody against CD20, a 297 AA membrane-associated phosphoprotein present on all B cells, except stem cells, pro-B cells, and plasma cells [1*,2,21], that depletes only circulating B cells but not B cells in the bone marrow and lymph nodes [1*,21,22].

On the basis of many uncontrolled studies, Rituximab, 375 mg/m² once a week for 4 weeks, or 2 g (divided in two, 1 g each, biweekly infusions), has been effective in 50–70% of myasthenia gravis patients [22–28]. In a 10-year outcome, the data seem remarkable regarding safety, sustained clinical improvement, tapering of other immunotherapies, in-hospital cost, and impact on childbearing potential [26]. The success is impressive in MuSK-MG [26–28]: in a multicenter, blinded, prospective review, 58% (14/24) rituximab-receiving patients reached the primary outcome compared with 16% (5/31) of controls ($P = 0.002$), after a median follow-up of 3.5 years; further, 29% of rituximab-treated patients required a mean-prednisone dose of 4.5 mg/day, compared with 13 mg/day required by 74% of controls ($P = 0.001$ and $P = 0.005$) [28].

In a phase II, placebo-controlled trial; however, where 52 AChR-MG patients received two cycles of
rituximab separated by 6 months, the primary outcome based on the proportion of patients achieving greater than 75% reduction in the mean daily prednisone dose after 48 weeks, was not met [29]. This study was underpowered while the selected outcome had low probability of showing effectiveness. A new retrospective study with prospectively collected data from 72 patients compared the effect or rituximab in 24 patients treated early, within 12 months of disease onset, to 48 patients treated at a later time when their disease was therapy refractory. The study conclusively showed that the median time to remission was shorter for new-onset vs. refractory disease after rituximab treatment compared with conventional immunosuppressive therapies; further, the first 24 months a larger proportion of patients had had fewer relapses with minimal or no need for additional immunotherapies. These results are compelling pointing out that rituximab performs even better in new-onset generalized myasthenia gravis being safer than conventional immunosuppressants.

The need for follow-up infusions in responders remains empirical as AChR-antibody measurements and CD20+ B cells are unhelpful [22]. Some prefer a repeated infusion when clinical relapse occurs; others, use 2 g every 6 months or 1 g every 3 months to ensure stability [21]. The most promising marker, identified in other rituximab-responsive patients with autoimmune diseases, is the reemergence of CD27+ memory B cells [31,32]. In one uncontrolled study, no myasthenia gravis relapses occurred when the CD27+ memory B cells were below the therapeutic target, whereas their resurgence was associated with clinical relapses [33]. In contrast to AChR-positive myasthenia gravis however, where rituximab has insignificant effect on AChR-antibody titers [30**,31–33], in Musk-MG there is marked reduction of IgG4-Musk antibodies after 2–7 months [34*], coinciding with clinical remission based on retrospective long-term (1.5–13 years) data in nine Rituximab-treated patients [34*]. Most patients had sustained improvement for several years with IgG4-musk antibodies being even undetectable within 2 years [34*]. In one patient, who did not respond, MuSK-IgG4 antibodies remained unchanged. The data support the view that short-lived antibody-secreting cells are the main producers of Musk antibodies.

Other anti-B-cell agents and third-generation anti-CD20/CD19

Belimumab, against soluble BAFF, and Atacicept against Blys, are effective in lupus erythematosus [35]. As BAFF plays a role in myasthenia gravis (1), a trial with Belimumab was completed in 39 AChR and MuSK-positive patients; the drug was, however, ineffective [36]. The newer agents include: Occreluzumab, a humanized monoclonal antibody against CD20, approved for MS [37] but not yet tried in MG; Ofatumumab that targets not only the large loop of CD20 but also small epitopes closer to B-cell membrane causing more effective B-cell lysis [37]. A patient with refractory myasthenia gravis unresponsive to IVIG, mycophenolate and rituximab normalized after two ofatumumab infusions with sustained depletion of circulating B lymphocytes [38]; Obinutuzumab, a third-generation anti-CD20, approved for chronic lymphocytic leukemia, causes profound peripheral B-cell lysis, including lymphoid B cells [1**,35,37]. Obinutuzumab almost cured a myasthenia gravis patient with CLL [39]; and Ublituximab, another glycoengineered anti-CD20, currently in phase-II MS trials, and Inebilizumab, an anti-CD19 monoclonal that additionally targets pro-B cells, plasmablasts, and some plasma cells, now approved for NMOSD [37], may be future considerations in refractory myasthenia gravis.

Anticomplement biologics

Eculizumab (Soliris)

This is a monoclonal antibody against complement C5 that intercepts the formation of MAC fixed by the AChR-antibodies at the end-plate (Fig. 1). Eculizumab is the first drug approved for refractory myasthenia gravis, that constitutes 10–15% of myasthenia gravis patients, based on encouraging results in a phase-2 study [40] that led to phase-III randomized, 26-week trial (REGAIN). Statistically significant improvements in MG-Activities of Daily Living (MG-ADL) and Quantitative-MG (QMG) scores from baseline to week 26 were noted in 62 eculizumab-randomized patients compared with 63 placebo-randomized ones [41]. Myasthenia gravis exacerbations occurred in 10% of the eculizumab group, compared with 24% in the placebo, whereas 10% of eculizumab-receiving patients required rescue therapy compared with 19% in the placebo. Eculizumab is very expensive, but as its benefit is noticeable within the first 4–8 weeks, unnecessary costly administrations could be avoided early after treatment initiation.

Patients completing REGAIN entered the open-label extension (OLE) study in which 117 refractory myasthenia gravis patients were treated with 1200 mg eculizumab every 2 weeks for a mean period of 22.7 months [42*]. The study showed reduced exacerbation rate by 75%, maintenance of improved functional abilities throughout a 3-year period, and achievement of minimal manifestation or pharmacological remission in 56% of patients.
demonstrating long-term safety and sustained efficacy [42]. Another subgroup analysis from REGAIN and OLE evaluating the response to eculizumab over an 18-month period in patients receiving chronic IVIg before participating in REGAIN, showed also sustained eculizumab efficacy [43]. The placebo-receiving patients in REGAIN experienced rapid improvements in assessment scores when treated with eculizumab in the OLE with lower exacerbation rate compared with placebo.

Ravulizumab (Ultomiris)
Ravulizumab (ALXN1210), is a humanized monoclonal antibody functionally similar to eculizumab, that binds with high affinity to C5 preventing the generation of complement activation products C5a and C5b-9 [44**]. Ravulizumab provides a sustained complement inhibition and has an increased half-life relative to eculizumab requiring less frequent dosing (once every 8 weeks, compared with once every 2 weeks for eculizumab). Ravulizumab has gained Food and Drug Administration (FDA) approval for PNH. A phase III FDA-approved study is currently ongoing in myasthenia gravis patients.

Zilucoplan
Zilucoplan is a synthetic, macrocyclic peptide that binds C5 with sub-nanomolar affinity inhibiting its cleavage into C5a and C5b-9. Zilucoplan is administered subcutaneously. In a phase 2 trial, 44 patients with generalized myasthenia gravis received daily subcutaneous injection of either 0.3 mg/kg zilucoplan, 0.1 mg/kg zilucoplan or placebo over 12 weeks [45**]. Patients on the higher dose achieved a mean reduction (from baseline) of 6 points in the QMG score, compared with 3.2 reduction in the placebo group, and 3.4 points reduction in the MG-ADL score compared with 1.1 point on placebo (scores>6 suggest that ADL are moderately/severely impacted by the disease). No serious adverse effects were observed. The rapid, meaningful, and sustained improvements over 12 weeks implied that maximal complement inhibition is necessary for pronounced disease suppression, leading to an ongoing Phase III trial.

Modulation of Fc and neonatal Fc receptors
The neonatal Fc receptor (FcRn) is involved in IgG transport and homeostasis and relates to IgG catabolism; antagonizing FcRn, results in rapid and sustained reduction of IgG autoantibodies [1**,46]. On this basis, the following three drugs are now tested in phase-III MG trials:

Efgartigimod (ARGX-113), an IgG1-derived Fc fragment binding to FcRn was tested in a phase-II randomized, double-blind, placebo-controlled, trial in 24 myasthenia gravis patients on their standard-of-care therapy [47**]. Twelve patients received four doses over a 3-week period of 10 mg/kg intravenous efgartigimod and 12 placebo. Although the primary endpoints were safety and tolerability, all patients receiving efgartigimod showed a rapid, within 2 weeks after the last dose, decrease in the total IgG and anti-AChR autoantibody levels; 75% of patients showed a rapid and long-lasting improvement in four efficacy scales coinciding with the maximal IgG-lowering and reduction of AChR-antibody levels. The AChR-antibody levels returned to normal within 8 weeks. The study concluded that Efgartigimod was not only safe and well tolerated but also effective leading to a phase III trial. This is an exciting and novel therapeutic approach as it does not cause widespread immunosuppression but a seemingly safe and meaningful reduction of IgG and AChR-antibody levels.

Rozanolixizumab, a high-affinity human anti-FcRn IgG4 monoclonal antibody that results in marked decreases in IgG concentrations (75–90% from baseline). A phase II study was conducted in 43 AChR-positive and Musk antibody-positive generalized myasthenia gravis patients, randomized to three, once weekly, subcutaneous infusions of placebo or 7 mg/kg rozanolixizumab on days 1, 8, and 15 [48]. After 4 weeks, patients were re-randomized to three doses of either 4 or 7 mg/kg rozanolixizumab. Although, like efgartigimod, the primary outcome was safety, a statistically significant improvement in the MG-ADL score was noted in the rozanolixizumab group, especially with the high doses, without any difference in the rate of infections between all groups [49]. A 68% decrease in IgG and AChR autoantibodies were noted leading to a phase III study.

Nipocalimab, a monoclonal antibody that binds with picomolar affinity to FcRn. The drug allows occupancy of FcRn throughout the recycling pathway promising higher efficacy. A phase II study is underway in myasthenia gravis with similar endpoints as Efgartigimod and Rozanolixizumab.

Other target-specific, biologic therapies in myasthenia gravis trials
Other biologics, approved for various autoimmune diseases, target the same key molecules within the myasthenia gravis immune network (1) (Fig. 1). Among them, the most relevant to myasthenia gravis are the Janus Kinase (JAK) inhibitors (Tofacitinib, Ruxolitinib, and Baricitinib directed against T-cell signaling factors associated with antigen presentation that suppress T and B cells while maintaining
Treg-cell function. Ruxolitinib has been effective in MuSK-positive myasthenia gravis [49]. Agents against cytokines and cytokine receptors targeting IL-6 and IL-17 are relevant to pathogenesis of myasthenia gravis by affecting the induction of Tregs and antibody production [50]. Of interest, Tocilizumab, an IL-6 receptor antagonist approved for rheumatoid arthritis, was effective in two refractory-myasthenia gravis patients resistant to rituximab and IVlg [51].

**Coronavirus disease-2019 and myasthenia gravis immunotherapies**

Although coronavirus disease-19 (COVID-19) infection, like most other viruses, can potentially worsen patients with preexisting autoimmunity like myasthenia gravis, there is no evidence that myasthenia gravis patients stable on common immunotherapies are more susceptible to COVID-19. If clinically stable and not lymphopenic, there is no compelling or data-driven reasons to change any of the immunosuppressive therapies they are receiving and disturb clinical stability [52*]. For patients on monthly IVlg, there may be even a theoretical advantage that IVlg offers additional protection because of natural autoantibodies; if IVlg is not infused as home infusion, switching to self-administered subcutaneous IgG might be an option to diminish exposure [52*]. For patients on rituximab, the infusion intervals can be prolonged to more than 6 months, because both, B-cell reduction and clinical benefit, can persist longer [21,35]. Just published data suggest possible beneficial effect of anticomplement therapies [52*,53]. Complement is an integral component of the innate immune response to viruses with evidence that C3 activation exacerbates SARS-CoV-associated ARDs; further, lung biopsies from COVID-19 patients show abundant complement deposits [53]. It was proposed that complement inhibition may alleviate the inflammatory complications of COVID-19 and on this basis, eculizumab is undergoing a trial for ARD [52*,53]. Theoretically, therefore, eculizumab may even have added protection in myasthenia gravis. General suggestions were also offered by the International MG/COVID-19 Working Group enhancing the view to continue current treatments, including participation in the ongoing FcRn trials, but follow standard precautions [54].

**CONCLUSION**

Recent trials with rituximab and biologics targeting complement and FcRn receptors are major steps towards targeted immunotherapy in the chronic management of myasthenia gravis. The results are particularly important not only for myasthenia gravis but also for other antibody-mediated neurological diseases as they demonstrate that suppressing pathogenic autoantibodies can lead to sustained remission. The effect of rituximab opens the way for trials with other more effective third-generation anti-B-cell agents currently on the market. The exciting results from five clinical trials with new biologic agents, three against complement and two against FcRn receptor, are setting up the stage for new agents now in the offing within this family of drugs, promising even safer and more sustained benefits confirming the prediction that ‘the future of MG immunotherapies is not what used to be’ [55].

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:  
* of special interest  
** of outstanding interest

1. Dalakas MC. Immunotherapy in myasthenia gravis in the era of biologics.  
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29. Brauner S, Eriksson-Dufva A, Albert Hietala M, et al. Comparison between rituximab treatment for new-onset generalized myasthenia gravis and refractory generalized myasthenia gravis. JAMA Neurol 2020; 77:582–592. This phase II trial in 44 generalized MG patients showed that daily subcutaneous injection of zilucoplan, achieves rapid, meaningful, and sustained improvements over 12 weeks in the OMGG score and MG-ADL, compared with placebo without serious adverse effects, leading to a phase III trial.


32. The review summarizes and defends the view that myasthenia gravis patients, stable on common immunotherapeutics, are not more susceptible to COVID-19 without compelling, data-driven reasons to change any of the immunosuppressive therapies they are receiving. This same applies for IVIG and eculizumab that may even have a theoretical benefit.

