

# Efgartigimod

## A novel antibody depletion therapy in myasthenia gravis

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Autoimmune myasthenia gravis (MG) is a prototypical, antibody-mediated disorder involving fluctuating ocular and generalized skeletal muscle weakness. In over 90% of patients with generalized MG, serum antibodies develop against one of 3 endplate proteins (acetylcholine receptor [AChR], muscle-specific tyrosine kinase [MuSK], and lipoprotein receptor-related 4). Antibodies are pathogenic in their disruption of normal neuromuscular transmission and their presence is usually diagnostic.<sup>1</sup> However, while antibody levels are a biomarker in MuSK MG,<sup>2,3</sup> they do not correlate well with disease severity or treatment response in AChR antibody-positive MG; AChR antibody titers generally fall with immunosuppressive therapy whether or not the patient improves clinically.<sup>4</sup>

This confirms that MG pathophysiology is more complex than a mere reflection of the auto-antibody titer. However, therapeutic plasma exchange (TPE) lowers both immunoglobulin G (IgG) and AChR antibody levels, and is predictably effective in most patients with MG.<sup>1</sup> A course of 5–6 TPE sessions during exacerbation rapidly lowers all IgG subtypes, including AChR antibodies, by approximately 60%–70%. Total serum IgG levels and AChR antibodies remain below baseline for 6 weeks.<sup>5</sup> Limitations of TPE include lack of widespread availability, transient benefit, and need for central venous access in some patients, which is associated with more complications.<sup>6</sup> An agent with similar effect as TPE to rapidly deplete IgG and fewer limitations would have substantial therapeutic potential.<sup>5</sup>

Antagonists to the neonatal Fc receptor (FcRn) promise to fill this role in MG and other antibody-mediated disorders. In early life, FcRn mediates transfer of humoral immunity from mother to fetus. In adults, interaction between FcRn and IgG allows for IgG recycling and protects IgG from degradation. Conversely, inhibition of FcRn accelerates removal of IgG and promotes clearance of endogenous pathogenic antibodies.<sup>7</sup>

In this issue of *Neurology*®, Howard et al.<sup>8</sup> present the first phase 2 randomized, controlled trial of a FcRn receptor antagonist in MG. The study included 24 adults with AChR-positive generalized MG. For inclusion, myasthenic weakness was severe enough to impair activities of daily living, but not so severe to necessitate enteral feeding tubes or respiratory support for myasthenic crisis. Mean disease duration was 10.8 ± 10.3 years. Patients were maintained on stable, standard of care therapies and randomized to receive 4 weekly efgartigimod infusions over 3 weeks or placebo. Follow-up assessments continued for 8 weeks after the last infusion.

The primary outcome was safety. Side effects in this small trial included headache, myalgia, and asymptomatic reduction of total serum lymphocyte and monocyte counts. One patient in the efgartigimod group discontinued the study due to lack of efficacy. Overall, efgartigimod was well-tolerated and no serious adverse events occurred. The safety profile in MG mirrored that in healthy persons.

Secondary outcomes included 4 validated MG severity scales, including 2 patient-reported measures. Although not powered to demonstrate efficacy, this trial showed early and significant improvement in all severity scales. Seventy-five percent of the efgartigimod-treated patients had

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clinically meaningful and statistically significant,  $\geq 2$ -point improvements in MG activities of daily living scores for a period of at least 6 consecutive weeks, vs 25% of patients on placebo. Although patients were actively treated for 3 weeks, the benefit of therapy generally lasted for several more weeks.

Additional secondary outcomes included biomarkers for efgartigimod mechanism of action in MG. Early and sustained reduction in total IgG levels, IgG subclasses, and AChR antibody titers was observed. This reduction started after the first infusion and reached a maximum at 8 weeks. Total IgG remained reduced by 20% compared to baseline at day 80, the end of the postinfusion observation period. AChR antibody titers reached a maximum reduction of 40%–70% in all but one patient. In contrast to IgG levels, antibody titers had returned to baseline by day 80. Despite this, the clinical benefit was ongoing at the end of the 8 week, postinfusion observation period.

The study had several important limitations, primarily related to being a phase 2 trial. MuSK-positive and seronegative patients were not included. MuSK MG is an IgG4-mediated disease. AChR antibody-positive MG is IgG1 and IgG3 mediated. Patients with double seronegative MG may resemble AChR antibody-positive patients immunologically.<sup>9</sup> As efgartigimod had a similar effect on all IgG subclasses, response differences among these patient groups would not be expected, though this requires further investigation. Second, the study group received a short but intensive treatment course in a period of otherwise stable disease and treatment. This fully reflects neither rescue nor maintenance therapy. Third, patients were receiving stable standard of care treatment. Although therapies were listed, additional detail regarding current and prior treatments would further define this cohort as “refractory” or “nonrefractory.”<sup>10</sup> Finally, FcRn inhibition has the potential to alter serum levels of therapeutic monoclonal antibodies (e.g., eculizumab, rituximab) and understanding the effects of FcRn inhibitors on the pharmacokinetics of these biological agents will be relevant for some patients.

This phase 2 trial of FcRn receptor inhibition in seropositive, generalized MG demonstrates reduction of serum IgG and AChR binding antibodies with parallel improvement in patient-reported and objective MG severity scores. Although

it was a small trial, the findings suggest that FcRn receptor inhibition may represent a viable treatment approach in MG. If the upcoming phase 3 trial demonstrates safety and efficacy in a broader population of patients with MG,<sup>11</sup> several questions will remain regarding the role of efgartigimod in MG treatment. Should its use be confined to refractory MG? Or would it serve as an appropriate initial, bridge, or rescue therapy? Is it too resource-intensive for maintenance therapy? Or would an individualized dosing schedule guided by clinical measures and supplemented by serum IgG levels be employed to guide short-term maintenance therapy in selected patients? Along with TPE, antibody depletion via FcRn inhibition represents a promising emerging therapeutic option for MG.

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## References

1. Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Myasthenia gravis: autoantibody characteristics and their implications for therapy. *Nat Rev Neurol* 2016;12:259–268.
2. Bartoccioni E, Scuderi F, Minicuci GM, Marino M, Ciaraffa F, Evoli A. Anti-MuSK antibodies: correlation with myasthenia gravis severity. *Neurology* 2006;67:505–507.
3. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nat Med* 2001;7:365–368.
4. Sanders DB, Burns TM, Cutter GR, et al. Does change in acetylcholine receptor antibody level correlate with clinical change in myasthenia gravis? *Muscle Nerve* 2014; 49:483–486.
5. Guptill JT, Juel VC, Massey JM, et al. Effect of therapeutic plasma exchange on immunoglobulins in myasthenia gravis. *Autoimmunity* 2016;49:472–479.
6. Guptill JT, Oakley D, Kuchibhatla M, et al. A retrospective study of complications of therapeutic plasma exchange in myasthenia. *Muscle Nerve* 2012;47:170–176.
7. Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol* 2007;7:715–725.
8. Howard JF Jr, Bril V, Burns TM. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. *Neurology* 2019;92:e2661–e2673.
9. Leite MI, Jacob S, Viegas S, et al. IgG1 antibodies to acetylcholine receptors in “seronegative” myasthenia gravis. *Brain* 2008;131:1940–1952.
10. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology* 2016;87:419–425.
11. An Efficacy and Safety Study of ARGX-113 in Patients With Myasthenia Gravis Who Have Generalized Muscle Weakness (ADAPT). Available at: [clinicaltrials.gov/ct2/show/NCT03669588](http://clinicaltrials.gov/ct2/show/NCT03669588). Accessed April 17, 2019.

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