Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting: https://reachmd.com/programs/cme/implementing-the-latest-diagnostic-and-treatment-approaches-for-generalized-myasthenia-gravis/32961/

Released: 12/15/2025
Valid until: 12/15/2026
Time needed to complete: 30 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Implementing the Latest Diagnostic and Treatment Approaches for Generalized Myasthenia Gravis

Announcer:
Welcome to CE on ReachMD. This activity, titled “Implementing the Latest Diagnostic and Treatment Approaches for Generalized Myasthenia Gravis” is provided by Prova Education.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Narayanaswami:
Hello. This is CE on ReachMD. I am Pushpa Narayanaswami, Professor of Clinical Neurology at the Harvard Medical School and Vice Chair of Clinical Operations at the Department of Neurology, Beth Israel Deaconess Medical Center in Boston, Massachusetts.

Today, I will be highlighting the key messages presented at a satellite symposium by Prova Education at the AANEM meeting in San Francisco, California. Thank you for joining me.

We're talking here quickly about the autoimmune pathology in acetylcholine receptor antibody-positive myasthenia gravis. As you all know, myasthenia gravis is a T-cell-dependent, B-cell-mediated disorder where the peripheral naïve repertoire of B cells that live in the bone marrow or the periphery receive antigenic stimulation and T-cell help in the thymus. They differentiate into a memory B-cell pool, which then differentiates into short-lived plasmablasts.

And these long-lived plasma cells are the ones that produce the antibodies to the acetylcholine receptor that then can modulate, block, or bind the acetylcholine receptor. And these binding antibodies activate complement that then destroys the postsynaptic muscle membrane.

Here, you see multiple aspects of treatment and the places that they can act on, and we'll talk a little bit more about that.

Autoantibodies in myasthenia gravis are directed mostly to the acetylcholine receptor, and these are the IgG1 and IgG3 subclasses. They are also directed in a smaller proportion of patients, to the muscle-specific kinase receptor, and these antibodies are of the IgG4 subclass. And they can also be directed toward other neuromuscular junction proteins, such as the low-density lipoprotein receptor-related protein 4 that actually helps to activate MuSK. Most of these antibodies are of IgG class, but not all of them.

What are some of the unmet treatment needs in myasthenia gravis? We do have a proportion of patients that do not respond to multiple standard therapies, and we've referred to them in the past as refractory, and said maybe 10% of patients are refractory. I think the term refractory is evolving, and it may be difficult to use it at this time, but we do know that not all patients respond to all therapies. And those are the patients who need other therapies, and we have to do treatment after treatment to find something that works—and sometimes

we don't.

And a fair proportion of patients do have problems with adverse events of medications. The adverse effects may be mild and short-lived, or they may cause permanent, long-lived side effects—chronic side effects—such as in the case of glucocorticoids.

Patients with MuSK myasthenia gravis can be a challenge to treat. They often don't do well with pyridostigmine or symptomatic therapy. They may not be effective, or they may get worse, and they may not do well with traditional therapies. They do sometimes respond to corticosteroids and some of the usual nonsteroidal immunosuppressant agents, but oftentimes they need something like rituximab.

Myasthenia gravis during pregnancy and breastfeeding—or the choice of treatments in a woman of childbearing age—is always an issue. Some of them, like mycophenolate, are teratogenic, etc.

And then a crisis in myasthenia gravis—the emergency of myasthenia gravis with respiratory involvement—when either IVIg or plasma exchange are ineffective. Not a lot of patients are in this category, but there are some.

And in addition, access to plasma exchange is not universally available, and we may want also something that is—that has more persistence. So we do treat the crisis, but obviously we want to avoid crisis in the future and to up the ante with the treatment of the underlying disorder.

So, in order to treat patients—especially as we have evolving treatments—we have to have in mind: Where do we want to get to with these patients? Where do we want to get to when they come to the office and they tell us these symptoms? How do we want to deal with that? What do we want to get them to?

So the first definition was something that we developed in the Myasthenia Gravis International Consensus, published in 2016. And we said we want to look at both the effectiveness of the treatment—where we get them—and also look at side effects.

So, in terms of effectiveness, how do we operationalize it? We say, well, these are patients who we want to get to the MGFA—Myasthenia Gravis Foundation of America—post-intervention status: minimal manifestation or better, which is basically they don't have any symptoms or disability from the disease. But when we examine them, we may see a few signs, such as mild eye closure weakness, etc., and that is not doing anything to them or—or disabling them.

And then we do have to also characterize the side effects. And how are we going to do that? We used the CTCAE, which is the Common Terminology Criteria for Adverse Events used in oncology. And we said we will accept side effects that—where patients are asymptomatic, or they're minimally symptomatic, and we only need to do observation.

I think actually, in the clinical world, a more realistic acceptance of side effect you know, over time, that I've sort of evolved to—a CTCAE 2, where they're mild. We may have to change treatment, but they're still mild and for the most part, tolerable.

So let's talk a little bit about neonatal fragment crystallizable receptor, or the FcRn. And why are we talking about this? Because we're going to talk about some treatments that use this receptor in order to actually cause their effect.

So then FcRn—so the term neonatal implies that they're present or they're important in the neonates. So why are we even talking about them in adult myasthenia gravis, let alone treatment? So if you look here these FcRn receptors were first described in the placenta, and they are also present in the vascular endothelium, in the muscle, etc., of adults.

And if you look here, what is their function in the placenta? They actually are important to transfer maternal IgG. So antibodies that mom has when we immunize mom with immunizations, vaccinations during pregnancies—all of those antibodies that she produces, we like to transfer them, get them to the baby. And the FcRn receptors that are present in the syncytiotrophoblast of the placenta are the ones that actually do this. The IgG antibodies combine to the FcRn receptor on the surface of that syncytiotrophoblast cell. They internalize to form an endosome, and in the acidic pH of the endosome, they bind tightly to the FcRn receptor.

The ones that are not bound to the FcRn receptor can get degraded in lysosomes, but once they bind, they come over to the cell surface on the other side, and they're released from the FcRn receptor into the fetal circulation. And therefore, baby gets the antibodies at a time

when they don't have a mature enough immune system in order to be able to make the antibodies.

So what does that have to do with anything IgG or myasthenia gravis? Well, as you know, IgG has the longest half-life of all immunoglobulins. IgM is a week; this is about 28 days or so. And that is because of this FcRn recycling mechanism.

So here, this sort of blue flag-like structure represents the FcRn so neonatal Fc receptor on the surface of the vascular endothelium. This is the IgG molecule, the Y-shaped molecule, in the circulation. And once it's internalized by pinocytosis into the vascular endothelium, and in that endosome it actually binds to the FcRn receptor. And once bound, it then recycles back to the surface. And that endosome then—the membrane fuses with the cell membrane of the vascular endothelium, and it's released back into the circulation. Any of the IgG that is not bound to the FcRn gets degraded to the lysosomes.

Now, here you see this flag with the little star attached to it, that is an FcRn molecule that is bound to an FcRn antagonist, a group of drugs, we have three of which are approved now. So once the FcRn antagonist binds to the FcRn receptor, native IgG cannot bind to it. So it goes in, it's internalized, it forms in the endosome, it sits in the endosome but it cannot bind to the FcRn receptor because the receptor is already bound by the drug. Therefore, IgG gets degraded to the lysosomes.

What does that mean? It means the antibodies that cause myasthenia gravis get degraded in the lysosome. But this also degrades just routine IgG as well, and therefore causes a fall in IgG levels.

So let's look at the efficacy for the first approved FcRn antagonist, efgartigimod. This is from the ADAPT randomized controlled trial. And the effectiveness or efficacy in this study was judged using the primary outcome of the MG-ADL. And here you see the placebo line and the line here for the efgartigimod group. And this study was over a period of 26 weeks, but this is the first cycle. So they receive injections here, so four injections. And as soon as that injection is over, you start seeing the two curves separating. So four injections a week apart—you see them separating.

There's clearly a drop in the MG-ADL score, much more so in the efgartigimod group compared to the placebo group. So this is for the MG-ADL.

This is for the quantitative myasthenia gravis score, which is a physician-reported outcome measure. And this is the myasthenia gravis composite, which is a composite of a patient-reported outcome and clinician-reported outcome. And this is the MG Quality of Life 15 Revised Questionnaire.

So for all of these outcomes, you see statistically significant, clinically meaningful differences between the two groups. And if you look at responder analysis—a 2-point change in the MG-ADL, which is clinically meaningful—77.8% of patients in the efgartigimod group versus 48% in the placebo group, statistically significant; 74% in the efgartigimod group for the quantitative myasthenia gravis score, or QMG score, versus 26% in the placebo group.

How about rozanolixizumab? Rozanolixizumab is a subcutaneously administered drug. Efgartigimod—the initial trial was IV—now we have subcutaneous versions as well. This is subcutaneously administered; again, cyclically administered, just like efgartigimod—6 injections a week apart. Efgartigimod is 4 a week apart.

And you see similar changes here with the MG-ADL. So this was a 6-week trial—so at day 43, the primary outcome was assessed, and then the observation period carried on for 99 days. And you'll see similar efficacy. Here, you have two drug arms—7 mg/kg and 10 mg/kg—and then you have this placebo in this sort of gray color. Again, you see very similar outcomes.

And in terms of numbers too, when you compare these drugs, they're fairly comparable. But here you see reduction in the in the scores for all of these outcome measures. They also looked at physical fatigue, and they separated them into bulbar muscle weakness, muscle weakness, fatigability, and you see similar changes.

Nipocalimab this is the newest kid on the block, approved very recently—is IV, and it's actually given slightly differently, it's not cyclic, it's continuous or fixed therapy. So everybody gets a loading dose of 30 mg/kg IV and then 15 mg/kg every 2 weeks.

And this trial was for 24 weeks. And you see here again the total MG-ADL scores separating between placebo and drug as early as 1

week. And their primary outcome was measured as a composite, or the average, of the MG-ADL between weeks 22 to 24, sort of looking at sustained effect there.

And you'll see that the placebo adjusted here is 1.45; for rozanolixizumab, for both arms it was 2.5–2.6. And here, QMG total score again you see that separation, and you see again a similar nipocalimab versus placebo. When you look at responder analysis or proportion of patients responding, over 60% were in the drug group compared to a little over 40% in the MG-ADL placebo group. And similarly, about a little over 40% for the QMG in the drug group and a little over 20% in the placebo group—all of which was statistically significant.

So this graph actually shows you the reduction of circulating IgG levels with these drugs. So if you look, the reduction starts very quickly. These arrows represent where they got their four doses, and these are the days—it starts very quickly, within a week—and then they get their fourth dose, and then gradually, over the next six weeks or so, you see that the levels of IgG return or increase, but not quite returning to normal. And they got their last injection somewhere here, and then it gradually goes back up, but again, not quite to baseline. And in nipocalimab, however, because they got 2-weekly dosing, it sort of remains down with this continuous dosing pattern.

How about safety of these agents? Well, total adverse events were sort of reasonable between placebo and drug. And mostly these were mild or moderate side effects. And the most common adverse events to the group as a whole were headache, nasopharyngitis, nausea, and diarrhea.

In nipocalimab, we saw a couple of other things. Muscle spasms were seen in a few patients. Peripheral edema was seen in about 11% versus 0 in placebo. There was a mild decrease in albumin, about 7.2%. None of it reached the hypoalbuminemia range, and it still remained within the normal range, but it dropped from baseline.

There was also a signal for increased cholesterol—both HDL, LDL, as well as total cholesterol—levels of the order of about 7 to 8%. It did not cause any vascular side effect, clinical side effect signals in the 24 weeks of the trial.

Infections are always a concern when you reduce the IgG levels. Upper respiratory tract infections and urinary tract infections are something that you'll see often in the trials, and also you may see them in clinical practice. Oral herpes simplex was seen with rozanolixizumab. A rare aseptic meningitis is a side effect.

And headache is not unusual at all with all of these drugs. And oftentimes, even if they're getting it at home, I'll have them take a pill of acetaminophen extra strength 1 gram, before they get their injections or infusions.

So the clinical applications of these FcRn therapies really are quite diverse. There are multiple scenarios you can use them in. You have broad coverage across the acetylcholine receptor antibody–positive and MuSK antibody–positive generalized myasthenia gravis population. You can use them in the setting of failure of conventional therapies, failure of complement therapies. Failure of B-cell depletion, yes, they are an option. But, in either of these scenarios, we have to understand that we are actually addressing the very final aspect, almost final aspect, of the disease pathogenesis. That is, we are removing antibodies after they are formed. And really, patients who respond well with plasma exchange tend to respond really well because of the mechanism of action.

And now we have an option using nipocalimab in the older adolescent to teenage-year population as well, where we may not want to use glucocorticoids.

So let's talk a little bit more about their clinical usage. The indication from the ADAPT for efgartigimod, adult acetylcholine receptor antibody–positive MG. For rozanolixizumab, it's adults with generalized myasthenia gravis, both acetylcholine receptor antibody–positive and MuSK antibody–positive. Nipocalimab—adults and children over the age of 12 years with acetylcholine receptor antibody–positive and MuSK antibody–positive generalized myasthenia gravis.

I talked to you about the dose a little bit. We have, for the efgartigimod, we now have a subcutaneous infusion option. A healthcare professional has to go home and give it to them, or they have to come into the office. But there's also a prefilled syringe, a self-injection, that has now been approved. And so they get 4 injections. So that's over a 3-week period because it's 1 week apart, and the first injection is day 0. And then the typical cycle is 4 weeks after the last dose. That is 7 weeks from the first injection. You repeat it.

But as patients do well, if they're doing really well, we try and push it out to 8 weeks, to 9 weeks. Sometimes patients need more frequent dosing. We may have to do it less than the 7-week cycle—so repeat 3 weeks after the last dose, or even more frequently.

Rozanolixizumab is a weight-based dosing, and it is 6 subcutaneous injections, and then repeat 3 weeks after the last dose. So it's a 9-week cycle. For nipocalimab, as I said, it's intravenous. And we talked about the Q2-week cycle. We talked already about the adverse events I think.

And then other precautions. We do need to hold these drugs in the setting of acute infections. If patients call you—counsel them, 'if you have an infection, let me know.' And if they call you with an infection in the middle of their cycle, we've got to stop it.

And the immunization we want to give them all of their age-appropriate vaccinations before we start the treatment. So before the start of a cycle. They don't do anything to the B cell itself, so the patients will be able to put forth the response to the vaccination. But it's possible that the antibodies will get removed or destroyed because of FcRn antagonism. So we start the immunization or give them a flu shot or whatever it is just before the start of a cycle. No live vaccinations during the treatment period because IgG levels may be lower. And caution with live vaccine to a neonate because if mom has been on an FcRn antagonist and the baby is exposed to it, we don't want to give the baby some of the live vaccines when they're born—oral polio vaccine, for instance.

And then in terms of pregnancy, there's really very little human data. For efgartigimod, we have rat and rabbit data that did not show any effect on fertility, embryo-fetal, or pre- or postnatal development. In rozanolixizumab, they did actually primate studies, and they have reported increased embryonic death, reduced body weight, and impaired immune function in the offspring.

Similarly, in nipocalimab.

Drug interactions. So we have to be careful with IVIg, for instance, or with rituximab. Rituximab is a monoclonal antibody, so in the presence of an FcRn antagonist, the rituximab will just be chewed away by the lysosomes. It's not metabolized by the CYP450 system, and there's really no dosing adjustment for renal impairment that is necessary.

How about the pediatric population? Nipocalimab is now approved for generalized myasthenia gravis in children over 12 years. This was based on a 24-week single-arm, phase 2/3 study, tiny study, I think they actually enrolled 8 adolescents, 7 completed a 24-week period, at which the primary outcome was studied. So this is really looking at change from baseline in the IgG. And they had a 72% drop at week 24, and that's on par with efgartigimod or nipocalimab, rozanolixizumab—anywhere from 60 to 75-80%.

Four out of five participants actually achieved minimal symptom expression in the MG-ADL, which means a score of 0 or 1. The maximum score is 24, and so a score of 0 or 1. And the mean change in the MG-ADL at week 24 from baseline was 2.4 points, which is clinically meaningful.

Similarly, the quantitative myasthenia gravis score—this is a physician-reported outcome measure—also changed. That's also a meaningful change of 3.8 points.

No serious adverse events. The profile of adverse events was exactly the same as in adults.

How about pregnancy? We talked about this discovered in the placenta. And so most of this IgG transfer in pregnancy occurs in the third trimester. And so what is the problem here that we worry about? We want to be sure that we maintain adequate IgG antibody levels in response to immunization in the baby and transfer them to the fetus. So mom we have to maintain enough and not have the FcRn chewed away and transfer it adequately to the baby.

So here, in conclusion, the place of these therapies is evolving really rapidly. I use the term bridge therapy now when I start these drugs early on. You noticed when we looked at the efficacy measures in the data there—the graphs—that the effect starts very quickly, 1 week. And I think it's really good to get them started on one of these therapies, get that disease controlled, and at the same time, start another upstream therapy, if you will—something that actually modifies the disease—whether it be corticosteroids or mycophenolate or azathioprine, the 3 most commonly used drugs in North America. And so we refer to that as bridging them across with the other therapies.

Safer adverse event profile than IVIg, especially in older people with comorbidities such as vascular disease, renal disease, where you can't use IVIg. In vascular disease, you sort of run the risk of precipitating a stroke. So that is an advantage, and the approval for adolescents is an advantage.

We talked about the AE profile, and I think despite it being safer, MG is a rare disease. We need a lot of exposures to pick up AEs, so we have to be careful and monitor our patients carefully clinically. There is no data in pregnancy. It's a balance between precipitating myasthenia gravis in the mom in the third trimester versus neonatal infection risk.

And the question remains, I mean, should we measure IgG levels routinely in the newborn if mom has received any of these medications of this class of FcRn antagonist?

And thank you for joining me. It's been a pleasure sharing these insights with you. This is CE on ReachMD.

Announcer:
You have been listening to CE on ReachMD. This activity is provided by Prova Education.

To receive your free CE credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.