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Mechanism-Driven gMG Therapy: FcRn Antagonists and the Rise of Precision Neurology

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Dr. Edmundson:
Welcome to Clinical Countdown on ReachMD. I'm Dr. Edmundson. I'm a neuromuscular specialist practicing at the Swedish Neuroscience Institute in Seattle, Washington.

Dr. Goyal:
And, hello, I'm Dr. Neelam Goyal. I am clinical professor of Neurology and neurological sciences at Stanford and the division of neuromuscular medicine.

Dr. Edmundson:
Today we're diving into some of the biggest challenges in the management of generalized myasthenia gravis or gMG, and we're doing it in signature, countdown style, fast-paced, and focused,

Dr. Goyal:
For decades, our go-to tools have been corticosteroids, broad immunosuppressants and rescue options like IVIG or plasma exchange. They work sure, but at a cost side effects hospitalization, and let's be honest, patient frustration with long-term regimens. And now the landscape is shifting. We have FcRn antagonists and complement inhibitors altering the way we manage MG.

Dr. Edmundson:
That's what today's clinical countdown is all about. In the next 30 minutes, we'll focus on three critical areas. One, recognizing and diagnosing gMG earlier using evidence-based strategies. Two, incorporating targeted therapies like FcRn antagonists into personalized treatment plans. And three, centering care with patient needs, quality of life, and shared decision making. Let's dive right in. Dr. Goyal, what are the most commonly overlooked early symptoms of generalized myasthenia gravis? And why are they so often misattributed? What does that look like in your clinical practice?

Dr. Goyal:
Well, I think, that's a great question. So if we look at all comer myasthenia gravis patients at presentation, about 50% of them will have only ocular symptoms, and that will be droopy eyelids or double vision. Now, there are patients that can present with just bulbar, which could be trouble swallowing, trouble breathing, trouble speaking, and very rarely will patients present with just arm and leg weakness.

And so when we think about MG, it can really come on at any age. We have this bimodal peak where we see patients in their thirties and fifties, but it can come on in the pediatric population and it can also come on in the elderly. And so if we think about symptoms of droopy eyelids or double visions, we can imagine that in the old elderly population, this could be misattributed to many other ocular symptoms.

Also, other things like trouble swallowing, trouble speaking, and the elderly population can also be misattributed to things like stroke and could prompt the physician to be looking in different areas. The other typical feature of myasthenia gravis is fatigue. And typically we think about this as fatigable weakness, but of course, the symptom itself of fatigue can be very non-specific, and that can also be difficult. So when I think about my clinical practice, because both you, and I are neuromuscular medicine specialists, we often see patients where there's already a concern for myasthenia gravis. However, I do see that patients can take many months before they get to us, and the concern for myasthenia is present.

Dr. Edmundson:
Absolutely. I agree with all of that. Particularly that, in our clinical practice, myasthenia is often already on our radar. And one of the biggest challenges in diagnosis outside of sort of a sub-specialized setting is just knowing of myasthenia gravis. There are also times where, we'll see sort of watchful waiting even in the setting of textbook signs where someone is coming in with fatigable ptosis, and then not necessarily getting those definitive diagnostic tests early on, either because it wasn't thought of or maybe it was thought of but, the testing is delayed because it's either complex or not always easy to do in the case of some of the electrodiagnostic testing.

Dr. Goyal:
Yeah, absolutely. And I think I am glad to say that we're seeing less of that. And I think once there is a patient where they have the textbook signs, because especially for our generalized MG patient, the vast majority, about 90% will have antibody testing. They are getting antibodies done and they're getting to the diagnosis. But definitely the patients with ocular restricted MG, which only has antibodies positive in about 50% of the patients or are seronegative patients, I can definitely see that there are delays because electrodiagnostic testing, especially single fiber EMG is not available in the community practice. Also, there can be long delays for the patient to even get to a community neurologist, and then of course, even more delays when they get for them to get to a subspecialist, including us.

Dr. Edmundson:
Thank you, Dr. Goyal. That brings up an interesting point, which is that in many cases, particularly in patients who are generalized and those who have antibodies, the diagnosis is oftentimes more prompt, than in cases where someone is seronegative or has an atypical presentation or those patients with pure ocular symptoms. In your clinical experience, what does the delay in treatment mean in terms of, access to care and long-term outcome in those patients who have a bit of a delay in diagnosis?

Dr. Goyal:
Yeah, I think that's a very important question. So I think there's a few different things. One is if you delay diagnosis, then you're delaying treatment. And we think of myasthenia gravis as a reversible disease, but there's definitely certain areas like the ocular muscles, neck muscles, if patients develop neck drop, that if you don't treat them early, then they can actually become very resistant to treatment. So we want the early diagnosis, we want the early treatment so we can prevent some of this irreversible weakness that can develop. Also, there is data that suggests that early aggressive therapy can lead to better outcomes. So definitely early recognition matters and, and we do have these tools to diagnose patients faster. But now the question is once we have a diagnosis, how do we get the treatment right? And this is where FcRn antagonists are really changing the game, especially for our patients that have very active disease early on, our patients that have poor tolerance to steroids. So let's starts with the basics. Why does the FcRn pathway matter in gMG?

Dr. Edmundson:
Yeah, so the FcRn pathway is essentially an antibody recycling system. FcRn receptors bind to IgG antibodies that have been endocytosed into endothelial cells and other cells. IgG antibodies that are bound to FcRn receptors are protected from degradation and then released back into circulation IgG antibodies that are not bound to FcRn receptors when their endocytosed get broken down in lysosomes. So the FcRn system is really important for binding, protecting, perpetuating IgG, autoantibody IgG antibodies, giving them a longer half-life. This can include pathogenic autoantibodies such as acetylcholine receptor antibodies and MuSK antibodies.

Dr Goyal:
So Kristen, what is the role of the neonatal FC receptor in gMG pathophysiology and how do FcRn antagonists work?

Dr. Edmundson:
The reason that FcRn system is a good target for therapy is that when FcRn receptors are blocked, this increases the amount of IgG antibody that is unbound resulting in more degradation of IgG.

So you have a, rapid reduction in circulating IgG with FcRn blockade. The clinical effect is that pathogenic autoantibodies are also degraded, they're not perpetuated. And that, results in less sort of autoimmune attack at the neuromuscular junction, which is the thing actually driving myasthenia gravis clinically, we think that these work by allowing for improved neuromuscular transmission and symptom relief. Now, there are several FcRn antagonists that are available clinically, currently, efgartigimod, rosanolixizumab and nipocalimab are the three that are available. All of these have slightly different mechanisms of action. but in general, nipocalimab and rosanolixizumab are antibodies themselves. They're antibodies that are designed to bind and block FcRn receptors. In contrast, efgartigimod is an engineered Fc fragment of an IgG antibody, not an entire antibody, but just the Fc fragment that's designed to bind with high affinity two Fc receptors. So they all work in a fairly similar way, which is binding to and competitively blocking those FcRn receptors, leaving more unbound IgG, more IgG degradation, more degradation of autoantibodies and less pathologic autoantibodies circulating.

Dr. Goyal:
Well, thank you, Dr. Edmundson, that was an excellent summary of FcRn blockade and, and how it works in myasthenia. How do FcRn and antagonists compare with traditional approaches like corticosteroids, cholinesterase inhibitors, IVIG or plasma exchange?

Dr. Edmundson:
Great. So there are a variety of ways that the FcRn antagonists differ from many of these therapies. So contrasting FcRn antagonists with, cholinesterase inhibitors, cholinesterase inhibitors like Mestinon or pyridostigmine are great in terms of helping manage symptoms, but they actually don't reduce the underlying burden of autoantibody. contrasting FcRn antagonists with, traditional immune suppressants, mycophenolate and azathioprine can play an important role in myasthenia gravis management, but they take a long time to have clinical effect.

In contrast, FcRn antagonists often work much more rapidly clinically. the studies show that some patients may respond within a week or two of starting therapies. Now not all patients may respond that quickly, but certainly that this, class of drugs, FcRn antagonists, works more quickly than our traditional oral immune suppressants. Contrasting FcRn antagonists with corticosteroids, corticosteroids are very broadly immune suppressive and carry a lot of other side effects in terms of, metabolism, diabetes risk, weight gain, bone thinning, changes in skin. There are side effects with FcRn antagonists, but they tend to be less broadly immune suppressive and, don't have necessarily the same spectrum of side effects that we see with corticosteroids.

FcRn antagonists contrasted with plasma exchange is interesting. Plasma exchange is the mechanical removal of antibodies, including autoantibodies. Now, plasma exchange does probably do some things that are different than FcRn antagonists that removes other inflammatory proteins as well. But the FcRn antagonists, are less invasive than plasma exchange. Plasma exchange requires, either port placement or having a large catheter placed and then requires a lot of time at, a center where plasmapheresis can actually be performed or requires patients to travel to these specialized centers. Contrasting FcRn antagonists with IVIG, we don't entirely understand the mechanism of action of IVIG.

And there may be several ways in which it works, though. One of these is likely that IVIG competitively binds to FcRn receptors, with our own endogenous antibodies. So IVIG's mechanism of action may include the FcRn system. And really the difference there comes down to modes of administration. There are FcRn antagonists that are now available, not just iv, but also subcutaneous and some can be self-administered. And also the duration of treatment IVIG infusions typically take several hours. and in contrast, FcRn antagonist administration is usually somewhere between a few minutes to up to an hour depending on the agent. I will say that, for many of these classes of drugs, their role in myasthenia treatment is not necessarily, replacement. So we wouldn't necessarily replace all use of corticosteroids or all use of oral steroids SPAR agents with FcRn antagonists. for instance, in a patient who's presenting early on, I may want them to have sort of a rapid clinical effect, and that may be a scenario in which I use an FcRn antagonist, but I might simultaneously start them on a traditional oral immune suppressant with the idea that over time that oral agent may have more clinical effect enabling me to take the patient off of something that is more infusion or injection based. So these really are sort of another tool, in our arsenal to treat patients with myasthenia gravis.

Dr. Goyal:
Yeah, thank you for that summary and, and I completely agree, with some of the differences that you highlighted, both in terms of their impact upstream versus downstream, and how really we can use these FcRn antagonists as complementary to some of the medications that we already have. So, Dr. Edmundson, when you think about initiating an FcRn on a patient who is this patient sitting in front of you, what are the characteristics of the patient or the clinical story that makes you reach for an FcRn antagonist?

Dr. Edmundson:
Think that's a great question. so some of it comes down to disease severity, disease subtype, the sort of needs of each individual patient, and unfortunately, insurance coverage does end up playing a role from time to time. Patients who have anti acetylcholine receptor antibody positive gMG or anti-US antibody positive gMG, the FcRn antagonists are actually labeled for these with sort of variable labeling by antibody, depending on the specific agent. there may be some data that patients with zero negative, myasthenia may also respond to FcRn antagonists, but we don't necessarily have a label indication at this point in time from the FDA. in general the patients who I'm gonna consider for an FcRn antagonist are folks who are, presenting with significant symptoms either early on in their disease or in spite of treatment with other agents.

So if someone is coming in and is newly diagnosed, if their disease is severe, and I feel that it needs to be controlled more rapidly than I might expect to see with some of our traditional immunosuppressants, that's a scenario in which I may consider and discuss FcRn antagonists with a patient. Similarly, if someone is coming in having already been treated with several agents and I'm not having an adequate response to those agents, that's another instance in which I might reach for, this class of drugs. Overall, really important to engage with patients sort of, based on their individual case, their individual needs and their individual preferences.

Dr. Goyal:
Yeah, I think I would agree, I think the unique thing about FcRn is they can definitely have a role early in the treatment course of patients, especially in patients where there are comorbidities where we would consider steroids to have greater side effects. So, Dr. Edmundson, how do FcRn and antagonists fit into personalized treatment plans, monotherapy versus combination therapy?

Dr. Edmundson:
That's a great question, and again, it really varies by patient. One thing that I'll often consider, particularly when I'm looking at monotherapy versus combination therapy, is thinking about how do these drugs work? So, as I had mentioned, the FcRn antagonists work by reducing circulating IgG autoantibodies, but they don't reduce the actual production of antibodies, right? So, this is a, these are a class of drugs that I might consider combining with traditional steroid steroids or steroid sparing agents, corticosteroids, mycophenolate or azathioprine. We think that they all work in part by sort of reducing cellular immunity and ultimately reducing the amount of antibodies that are being produced. whereas, the FcRn antagonists are actually reducing the antibody levels but not affecting the production of those antibodies. So I might consider some of those other agents to be used in concert with FcRnantagonists.

Things that I wouldn't necessarily combine with FcRn antagonists include IVIG, right? If we're gonna be giving IVIG and an FcRn antagonist simultaneously, essentially that's just gonna accelerate the breakdown of the IVIG itself. now certainly are there instances in which someone on an FcRn antagonist might be having a flare that I might consider using IVIG to treat a flare crisis, perhaps. Although I would say in my clinical practice, if someone is on an FcRn antagonist and worsening, I will oftentimes reach for plex instead of IVIG if possible given that patient's, location and access to a center that that performs plasmapheresis. Additionally, each of these FcRn antagonists, is given a little bit differently, which may impact the way that we use it. Efgartigimod exists in both IV, and subcutaneous forms, including a self-administered subcutaneous, version, and it's given cyclically, so doses of, cycles of four weekly doses followed by a period of time off of drug.

Additionally, rosanolixizumab is, labeled fairly similarly. This is given in a subcutaneous infusion, as cycles of six weekly infusions with a period of time off of drug. In contrast, nipocalimab is only available IV at present, and it's dosed with a single loading dose followed by a once every two week IV infusion. So it's more continuous therapy compared with the efgartigimod and rosanolixizumab, which if used as labeled, are more cyclical therapies. So these factors, methods of administration, and the frequency of dosing would all play a role in which specific agent might be most appropriate for any individual patient, moving forward. Neelam, can you review the differences in efficacy of the pivotal phase 3 FcRn antagonists?

Dr. Goyal:
Yes, absolutely. So we'll start with our first agent, which was efgartigimod. And this was studied in the ADAPT phase 3 study. And this

was an interesting, design. So there were 167 patients that were enrolled and patients that were seronegative or had antibodies to LRP4 or MuSK were also allowed to be enrolled. So patients had four weekly infusions of efgartigimod or placebo, and then they were followed four weeks off. And that eight weeks was considered one cycle. And the primary endpoint was the percentage of patients that were MG A DL responders and MG A DL responder was you had to be below, you had to decline by two points, and you has to sustain that for four weeks to be an, MG ADL responder. And this primary endpoint was studied only in the AChR antibody positive population.

And so in that first cycle, about 68% of patients that were AChR antibody positive that were on efgartigimod met criteria to be an MG ADL responder versus only 30% in placebo. The medication was very well tolerated. The most common side effects were headache and nasopharyngitis and there were no serious adverse events.

Efgartigimod was also studied in ADA plus, which was the open-label extension. So about 140 patients were treated long-term with up to 17 cycles. In the study, we saw improvements in MG ADL as well as QMG scores as early as one week. And benefits were sustained in multiple cycles. Now, rosanolixizumab was studied in the MYCARIN G here, 196 patients were enrolled. The inclusion criteria was similar to efgartigimod except there were no seronegative patients. So you had to be a either AChR antibody positive or MuSK positive, and you were randomized to placebo, a low dose group, and a high dose group. And the primary endpoint was change in MG ADL after, four weeks after the, six week infusion. And here this was a positive study where there was a statistically significant difference in MG-ADAL improvement for the treatment arm versus the placebo arm. Now, in MYCARIN-G, there were about 11 to 13 patients in the placebo and the low dose and high dose and all patients in the placebo group, the average was actually worsening of MG ADL, where we saw improvement in the treatment arm. And that allowed for an indication for MuSK positive MG patients as well, or rosanolixizumab regarding safety the medication was well tolerated. There were similar side effects as we saw with efgartigimod with, low grade, infection, headache, diarrhea, and pyrexia.

Dr. Edmundson:
The VIVACITY MG3 study assessed nipocalimab in patients with generalized myasthenia gravis. The VIVACITY MG3 study included a broad antibody positive population, including patients with anti acetylcholine receptor antibodies, anti-MuSK antibodies, and anti LRP4 antibodies. Patients who were in this study achieved up to a 75% reduction in autoantibody levels and sustained MG ADL over 24 weeks. There were indirect treatment comparisons that showed greater and more sustained MGADL improvement versus other FcRn blockers at several time points up to 24 weeks. This study showed a comparable rapid onset at week one and sustained efficacy through 24 weeks with statistical superiority at select time points. Adverse events and discontinuation rates were similar to placebo 5.1 versus 7.1 respectively. The VIVACITY MG study, was a study of 68 patients who were randomized either to nipocalimab 54 patients or to placebo, which included 14 patients.

In this study, 94% of patients were acetylcholine receptor antibody positive and 6% were MuSK antibody positive. A total of 57 of the 68 patients, or 83.8% completed treatment through day 57. The efficacy for this study showed a statistically significant dose response in MG ADL improvement at day 57, with 42.9 to 64.3%, response in nipocalimab groups compared with 14.3% in the placebo group. There were significant differences for a 60 milligram per kilogram single dose, as well as 60 milligram per kilogram given every two weeks. Additionally, both the QMG and the MG QLLR, which are different, disease severity measures than the MG ADL, changes in these measures trended positively, but were not statistically significant, which was likely impacted by COVID-19 related disruptions to this study.

In terms of safety for this study, there were treatment emergent adverse events and 83.3% of patients treated with nipocalimab versus 78.6% of patients treated with placebo, with the most common treatment emergent adverse events including diarrhea, headache, and nasopharyngitis. Overall rates of infection were 33.3% in, nipocalimab treated patients compared with 21.4% of placebo treated patients. Importantly, there were no deaths and no discontinuations related to treatment emergent adverse events. In terms of clinical relevance, other FCN antagonists have a cyclical dosing compared with nipocalimab, which is a fixed dosing. Now, there are pros and cons to each of these. an agent with a cyclical dosing, strategy can gradually be spread out. It's perhaps a bit more adaptable, where, in the instance of efgartigimod, if patients, have more severe disease, we might treat them with four week cycles followed by four weeks off drug, followed by four week cycles. If someone seems to respond to that and may not need quite as frequent treatment, that can be spread out to four weeks on, six weeks off, or four weeks on, eight weeks off. In contrast with nipocalimab, the fixed dosing of an IV infusion every two weeks gives less flexibility, but also we may see less wearing off because patients are getting, are getting more consistent, more regular dosing, of this agent.

Dr. Goyal:

Thank you for that great summary. I think I will just add that, nipocalimab is now approved for pediatric population 12 plus, and this is the first FcRn that's available for our pediatric population, which is great to have that additional option for our, pediatric patients with myasthenia. So moving on, Dr. Edmundson, how do you bring the patient voice into treatment planning? what tools or strategies help integrate preferences into shared decision making?

Dr. Edmundson:
Yeah, that's such an important question. it's really important to align, the therapy that we're using with patient priorities, and that can mean talking to them about what their life looks like. Are they working, do they have children? How flexible is their schedule? Do they wanna be traveling? So we are really understanding what their goals are for the way that their living, their life as we choose which agents to use. Since some agents may align better with the patient's priorities than others. One thing that I find really important is using patient reported outcome measures. And what this looks like in my clinical practice is really doing an MG ADL score with every patient to every visit. It's a great tool because it can also be used in between visits for patients to not only tell us about their symptoms, but sort of quantify the severity of their disease at any given time, even if they're not physically in the office. It can be helpful to use open-ended questioning, sort of asking them about what matters and asking them how they feel about a specific proposed TRA plan of therapy, to really offer opportunities for discussion. What do you find to be the most common psychosocial and quality of life challenges with patients with gMG and how do they affect those patients' clinical outcomes?

Dr. Goyal:
Great. Yeah, I think that's a great, question. And I think something that we are becoming more and more aware of, recently. So we think of myasthenia gravis as a pure motor disease, but really when we talk to patients, we can see that there are multiple other symptoms or challenges that they're facing that might be both part of the disease and also a burden of treatment. So with the disease, we previously talked about fatigue, and so fatigue can be a large component that can have a big impact on their quality of life. We know patients with myasthenia gravis can also have multiple mood disorders, so it can affect their sleep, they can have depression anxiety. With myasthenia gravis, not only are there fluctuations with periods of flares and remissions, but because this is a disorder of neuromuscular junction transmission, we know that symptoms are worse later in the disease. So there's this unpredictability of symptoms that can have a big impact. Also, we know that about a third of patients require caregiver support, which can impact both the dynamics within the home and also their caregivers' ability to work. And really all of this can lead to social isolation and really how our patients are interacting with the rest of society.

Dr. Edmundson:
Yeah. in your practice, what are some practical ways that you can make, quality of life sort of a core clinical outcome in caring for your patients with generalized myasthenia?

Dr. Goyal:
Yeah, I think, it's a big challenge because we really have these short, 30 to 40 minutes where we're really trying to take a lot in. But I think as you mentioned earlier, we can use, outcome tools like the QOL15r and really I think it's about talking to the patient and really understanding what else beyond the motor symptoms and the typical side effects of medications are impacting their quality of life. So really, doing a screening for mental health, considering referral for counseling or even things like physical therapy or occupational therapy. We know that a lot of our patients can have secondary deconditioning because they have a fear of exercise. And so that's something that's important to address as well. Really, at the end of the day, gMG isn't just about antibody levels, it's about helping patients live the life they want. That means earlier diagnosis, smarter use of therapies like FcRn antagonists and always keeping quality of life at the center.

Before we wrap up, let's do a quick lightning round where Dr. Edmundson and I will ask each other questions and we'll ask for a one line quick 30 second answer.

So, what's the most overlooked early sign of gMG?

Dr. Edmundson:
I would say in general, it's actually not just one single sign, but the fluctuation in symptoms because oftentimes patients will experience a symptom, and whether that's ptosis or diplopia or arm weakness or choking when they show up in the doctor's office, that isn't there. So recognizing that fluctuation, that variability in myasthenia.

What is one red flag that should push you to order antibody testing right away?

Dr. Goyal:
Because at presentation, 50% of patients will have only ocular symptoms and 85% of patients will have ocular present symptoms at presentation. I would say you see droopy eyelids, double vision think MG.

Next question. What's the biggest mistake to avoid when starting treatment?

Dr. Edmundson:
I would say undertreatment is actually the biggest thing to avoid. We'll sometimes see patients who have pretty significant myasthenia symptoms, including generalized symptoms who are just put on mestinon and then stay on that until they end up seeing a, a subspecialist. One last question. What is a practical way to bring the patient voice into clinical care for myasthenia?

Dr. Goyal:
So I would say, let's see, practical way is take a good social history, understand what does the house situation look like? Are they married, are there children taking care of them? What does that look like? And then I would say the second thing is when you get to the next steps of here are treatment options and counseling. I'll often give a few options and then pause there and ask the patient what really is important to them and what, what is the value system that we should be prioritizing when we're thinking about what's the next medication to start or to peel back.

Dr. Edmundson:
Well, this certainly has been a fascinating and educational conversation.

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