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

Treatment Advances in Generalized Myasthenia Gravis: *A Pathophysiology-Driven Framework Leveraging FcRn Therapeutics*

Chapter 1

Dr. Bril:
This is CME on ReachMD, and I'm Dr. Vera Bril. Here with me today is Dr. Neelam Goyal.

Dr. Goyal, let's dive right in with a discussion of the neonatal Fc receptor, or FcRn. Could you please describe its mechanism of action for our audience?

Dr. Goyal:
Yes, absolutely. Happy to do so, and I'm happy to be part of this podcast today.

So FcRn stands for neonatal fragment crystallizable receptor, and it's an MHC class I-like molecule. The reason why it has the word neonatal in it was because it was first discovered in the 1980s on epithelial cells of neonatal rats, where it was found to mediate transfer of IgG from mothers' milk to neonates. However, since then, it has been found to be widely distributed in various mammalian organs and known to play an important role in IgG homeostasis. It's important to know that it also has a separate receptor for albumin, which we'll discuss later when we talk about FcRn antagonists and toxicity.

So going back to the basic, this receptor helps to recycle IgG molecules. So if we imagine an IgG molecule, the Fc region of that molecule has a few residues that attach to the FcRn receptor. And these residues are pH dependent, so when we have low pH, they bind tightly, and when that pH increases, then that connection is less strong. So let's imagine in the blood we have IgG molecules floating in the blood. So the IgG molecules are taken into the endothelial cells and endosomes. And these endosomes have the FcRn receptor, and the IgG bind to that receptor. And because the IgG are bound to the receptor, they evade lysosomal-mediated degradation and are sent back into the blood. And so this is why the half-life of IgG is about 21 days, whereas the half-life of IgA and IgM is much shorter, to about 5 to 6 days.

So what happens when you have these antagonists? Then your endogenous IgG, those floating around in the blood, those that are the good ones and the bad ones that we see in antibody-mediated disease, those molecules, when they're taken into this acidic endosome, won't be binding to the receptor because we have an antagonist there. And so then more of these IgG molecules will go into the lysosome and then will be degraded. So effectively, FcRn helps to recycle IgG. It helps to increase the half-life of IgG. And if you block the FcRn, then you decrease the levels of IgG in your body, including those that are pathologic.

So what is happening right now in development? And I know, Dr. Bril, you're going to go into this in much more detail, but currently we have 2 FcRn antagonists that are approved for myasthenia gravis. And one of them, efgartigimod, is an Fc fragment. And then the next one, rozanolixizumab, is a full IgG4 molecule. We also have 2 more in development, nipocalimab as well as batoclimab. And those are full IgG molecules, IgG4 and IgG1.

So now we have an animation sequence to really help you visualize the normal role of the FcRn and how FcRn antagonists interact with the FcRn to impact IgG recirculation. I'll pause here for animation.

[Animation plays.]

We hope this animation sequence has clarified the critical role of the FcRn in both normal IgG recirculation, as well as how FcRn antagonists can decrease the overall levels of pathogenic IgG, such as those observed in myasthenia gravis.

So now, Dr. Bril, let's look at the data. What does our audience need to know about key data coming out of clinical trials and even real-world data related to the use of FcRn antagonists in the management of myasthenia gravis?

Dr. Bril:
Thank you, Dr. Goyal. So this is a very exciting time for people treating myasthenia gravis patients, because we have this entire new therapeutic molecule, FcRn inhibitors, and there are several of them in development or approved, and they also show similar results. So efgartigimod was the first and rozanolixizumab the second. Nipocalimab is before the FDA for a priority review. We've had efgartigimod since December 2023 and rozanolixizumab since June 2023, and they are approved for generalized myasthenia gravis with acetylcholine receptor antibodies, with respect to efgartigimod, and rozanolixizumab for acetylcholine receptor and MuSK-positive antibodies.

Before getting to phase 3 trials, all of these compounds underwent phase 1 studies in healthy volunteers, where pharmacokinetics were done and safety was evaluated. Phase 2 trials were then done with different doses and endpoints to help direct the phase 3 trial development. And all have had positive phase 3 studies. Batoclimab had a positive phase 3 study in China, but there's an ongoing worldwide phase 3 study, and so that has not yet finished development.

All of the studies, all of the phase 3 trials, which is where I'm going to focus my attention, are very similar in that they include patients with generalized myasthenia gravis and they include similar endpoints, such as the MG-Activities of Daily Living and the Quantitative Myasthenia Gravis score. The regulatory authorities and specifically the FDA has approved drugs based on changes in ADL, and that is why the ADL is followed in patients with generalized myasthenia gravis.

There are slightly different inclusion criteria, but not strikingly different. The ADL score at baseline for efgartigimod had to be 5 or greater, with at least half the points coming from non-ocular items. In efgartigimod, patients were randomized to IV efgartigimod or IV placebo given every week for 4 weeks and then followed by an observation period where patients had to worsen before they were re-treated. And in this study, ADL responders were 67.7% compared to 29.7% for placebo. And in the QMG, which was a secondary, 63.1% responded to drug compared to 14.1% to placebo. And as the degree of improvement increased, the placebo response fell off.

Then rozanolixizumab had a study where patients were randomized to 1 of 2 doses of rozanolixizumab or placebo. This drug was given subcutaneously. And again, patients here had to be antibody positive, either acetylcholine or MuSK, the ADL score had to be 3 or more points, but 3 points at least had to be non-ocular, and the QMG score had to be at least 11.

And in this study, patients showed decline in ADL, meaning an improvement in the score in both drug groups compared to placebo. The improvement started within the first 2 weeks of therapy, actually within the first week in many patients, but increased over the next several weeks, up until about week 4, and these were weekly subQ injections for 6 weeks followed by an observation period. And the decline with efgartigimod was also that rapid.

What was interesting with rozanolixizumab was that the MuSK-positive patients showed a dramatic improvement in both drug groups and a worsening in placebo, and that led the FDA to approve rozanolixizumab for both acetylcholine receptor- and MuSK-positive disease. Similarly, if the degree of improvement increased, then the placebo response rate dropped off.

Nipocalimab is an IV drug and was studied in a phase 3 study of nipocalimab with a loading dose and then IV treatment every 2 weeks or placebo. And again, the change from baseline in the ADL score started within the first week and continued through up until the end of the study at weeks 22 to 24 with a separation from placebo. In this study, seronegative patients did not respond, and the QMG also responded, significantly dropping very early, within the first 2 weeks.

So the trial data has shown us repeatedly that the ADLs improve; the Quantitative Myasthenia Gravis scores improve. They all do so within the first 1 to 2 weeks of therapy, and the effect is maintained after recurring cycles of treatment. The cycles have been, to a large part, on-demand treatment so that after treatment, as the patients are observed and they get worse, they're re-treated. And basically, the patients have shown repetitive responses to the FcRn inhibitor without a decline or a habituation in response. So this is all very exciting.

In Chapter 2, we'll address navigating antibody status in myasthenia gravis and how the potential benefits of FcRn antagonists may help in selecting a therapeutic agent for our patients. Stay tuned!

Chapter 2

Dr. Goyal:
Welcome back. In the previous chapter, we covered the mechanisms and clinical implications of FcRn inhibitors in gMG. Now in Chapter 2, we're looking at antibody status and therapy selection.

Dr. Bril, please take us through approaches to assessing aspects of patient presentation, some of the clinical tests used, as well as identifying a patient's autoantibody status when you suspect a myasthenia gravis diagnosis.

Dr. Bril:
Thank you, Dr. Goyal. So let's talk about our patient presentation. As you know, most patients present with ocular symptoms such as double vision or ptosis. They may also have bulbar muscle involvement such as difficulties with speaking, swallowing, or chewing. They also will have some axial weakness, proximal limb muscle weakness. Depending on the state of respiratory involvement, they may have difficulty breathing and shortness of breath and fatigue, which is a very common complaint. All of these muscle groups, if they're involved, get weaker with persistent efforts and repetitive efforts, which is one of the ways to suspect a diagnosis of myasthenia gravis, meaning that they have fatigable weakness. It is unusual to present with limb weakness without ocular involvement, but sometimes people will present more with bulbar involvement. But all presentations are possible.

For clinical testing, we do electrodiagnostic tests, and these include repetitive nerve stimulation studies, which are widely available – not very sensitive but widely available – so that with repetitive nerve stimulation, the amplitude of the compound muscle action potential declines by 10% or more. We do imaging. We do imaging of the chest to look at the anterior mediastinum to exclude the presence of a thymoma, which can be present in 15% of patients or different percentages depending on the series.

But at this point, it is also very important for us to do serologic testing for the acetylcholine receptor antibody and the MuSK antibody and LRP4. We like to use a lab that will test in sequence for each of these antibodies. 85% of the population will have anti-acetylcholine receptor antibodies, and 7% to 9% may have MuSK antibodies, and less than 1% will have LRP4.

There still remains a segment of patients who have fatigable muscle weakness, abnormal single-fiber electromyography, or repetitive nerve stimulation studies who will not have any antibodies but still will have myasthenia gravis. It is important to retest patients. Sometimes your lab sensitivity is not where it should be, or sometimes there's seroconversion. There may be other antibodies in these seronegative patients that we're not aware of at this time. So of course, we can't test them.

So the antibody profile is very important for our patients. Now, these antibodies are IgG antibodies, and therefore, Fc receptor inhibitors are effective against these antibodies. However, some other novel agents, such as complement inhibitors, are not effective against Ig4 disease, and that would be MuSK disease. So it's important to know the antibody status for when we are selecting therapies. In addition, for seronegative patients, because the studies did not show benefit in these patients or have not yet been done, it is difficult to get payers to allow patients who are seronegative to receive these novel therapies, so it's extremely important to test for the antibody profile.

Dr. Goyal, could you briefly describe the risk-benefit profiles of the traditional treatments used for myasthenia gravis? Also, how do our traditional approaches to myasthenia gravis compare with what we know so far about the safety and efficacy of FcRn antagonists?

Dr. Goyal:
Yeah. Thank you, Dr. Bril, for reviewing the presentation and diagnosis of myasthenia.

I think before we get into traditional therapies, it's worthwhile to quickly review the physiology and the pathophysiology that we see in myasthenia gravis. So in normal physiology, the action potential goes down the nerve and then, at the nerve terminal, acetylcholine is released, which then goes across the synapse and attaches to acetylcholine receptors on the muscle, which then leads to depolarization and muscle contraction. So that's what happens when you are trying to move your muscles.

So what happens in myasthenia gravis is that we believe this is a T cell-dependent but B cell-mediated disease. So it starts with some abnormality and thymus-mediated autoreactivity that then leads to the B cells making pathogenic antibodies. And then these antibodies go on, through various mechanisms, to activate complement, at the acetylcholine receptor, which then leads to reduced transmission and muscle weakness.

And so when we think about traditional therapies, we can start by grouping them into symptomatic and then immunosuppressants or immunomodulators. So the first medication that we use for our patients after diagnosis is acetylcholinesterase inhibitors. And the specific one that we use is pyridostigmine. So if you think back into the pathophysiology or physiology, when the nerve releases these acetylcholine molecules, because we don't want repetitive activation of the receptor, there is an enzyme called acetylcholinesterase. And so these medications block this enzyme, effectively leading to increased amount of acetylcholine in the synaptic cleft. So you haven't really treated the underlying disease, which is development of these pathogenic antibodies or their attack against the

acetylcholine receptor. You are increasing the number of acetylcholine so that those receptors that are still healthy can be activated. And so that's why this is called symptomatic therapy.

The benefits are that it's oral, it can be prescribed very quickly, and it does help some of our patients. However, the downside is that it doesn't have high levels of efficacy in some of our patients. And the main side effect profiles are due to cholinergic symptoms such as increased salivation, lacrimation. There can be abdominal cramps as well as muscle fasciculations and muscle cramps.

Then we move on to immunosuppression, or immunomodulatory therapy. The first one that I'll discuss is steroids. So steroids are widely used in myasthenia gravis. They work to suppress the immune system. The benefits are that they have low cost, they're easy to prescribe, and they work relatively quickly, within weeks. However, the downside are their many, many short- and long-term toxicity. And so really, we use steroids because they work quickly; however, as soon as they are starting to work, we are working very hard to get our patients off of this medication.

The next group of medications are called nonsteroidal immunosuppressants, or steroid-sparing agents. And just like their title, they're really used to suppress the immune system in the long haul. So the downside of these medications is they can take 3 to 6 months, 6 to 12 months, even greater than 12 months to work. However, they help us to reduce the dependence on steroids. So the commonly used medications in this class include mycophenolate mofetil, azathioprine, tacrolimus, methotrexate, and internationally, cyclosporine as well. And so, again, these medications are oral, easy to prescribe, relatively low cost, but they take many, many months to work. These medications are also nonspecific. They are stopping any fast-dividing cell, which is our immune cell. So they work to suppress the immune system, but in a non-targeted way.

The next class of medications you can consider as medications that we typically use for crisis, and that's intravenous immunoglobulin and plasma exchange. The benefit of these medications is that they work very quickly, within days; however, in an outpatient setting, they are hard to prescribe, in that you have to get insurance authorization, and they require IV access or access for apheresis.

The last 2 therapies that I'll describe are rituximab, which is a CD20 agent. So this medication is going to reduce the B cells. This medication has high efficacy in MuSK antibody-positive disease, and we believe that in some patients, we can really use this as first-line therapy. However, its role in AChR antibody-positive disease is mixed. This was studied in 2 trials, BeatMG and more recently, RINOMAX, and showed variable efficacy. Perhaps if used early in AChR antibody-positive disease, we will see greater benefit. The downside of rituximab, because it is a direct target of B cells, is increased risk of infections, especially viruses. Patients do need to have their hepatitis serology checked, and they may need antivirals during therapy.

And the last treatment I'll discuss is thymectomy. So thymectomy is indicated for AChR-positive generalized MG, even in patients that don't have thymic hyperplasia or any evidence of thymus on their CT of the chest. And this was studied in the MGTX trial, and we saw benefit with thymectomy, really at the 2- to 3-year mark, with better outcomes and lower dependence on steroids and immunosuppressive agents such as azathioprine.

Like was mentioned earlier, we do have other agents, such as complement inhibitors that we don't consider traditional therapy, but more novel therapeutics. However, due to the goals of this podcast, we won't be discussing the complement inhibitors today.

So, Dr. Bril, your question about how do traditional therapies compare to FcRn antagonists, I think the most important thing is that our traditional therapies work well, but there's a few things that are left on the table. One is that we still have about 10% to 15% of patients that are refractory. Second, we still have a lot of patients that are doing well but still have a high burden of disease with MG-ADL above 5. And third, because a lot of our medications are nonspecific, there's multiple off-target toxicity that it's really worthwhile to focus on and reduce.

So I think the benefits of the FcRn antagonists is we're really talking about very targeted therapy, and also they work very quickly. So if you have a new-onset MG that has moderate disease, that has bulbar symptoms, you could really use these agents to avoid the use of medications like steroids early in the course.

So that is the end of Chapter 2. So in Chapter 2, we discussed the presentation and the role of antibody status when thinking about treatments in myasthenia gravis, and we also discussed the traditional therapies and how they compare to FcRn antagonism.

So stay tuned for Chapter 3, where we'll be discussing the adverse event profiles of FcRn antagonists and provide strategies for managing them and monitoring patients treated with FrRn antagonists. Stay tuned.

Chapter 3

Dr. Bril:

Welcome back. In Chapter 2, we looked at antibody status and therapy selection in generalized myasthenia gravis. Now in Chapter 3, we're moving on to adverse events.

Dr. Goyal, let's continue with our focus on patients being treated with an FcRn antagonist. What type of adverse events might we expect to emerge?

Dr. Goyal:
So let's talk in generalities, and then we'll talk about the specifics of the 3 agents where we have the best data.

So the most common side effects that we're seeing with FcRn inhibitors is a slight tick up in infection. And these are typically mild like nasopharyngitis and UTIs, and then the other one is headache. So with efgartigimod specifically, the main things that we're seeing are these headaches, URIs, and UTIs. Efgartigimod is available in an IV formulation, which is weight based, and a subcutaneous formulation, which is a standard dosing. The subcutaneous formulation is associated with injection site reactions. When I've used this medication, this injection site reaction can actually be quite bothersome to the patient, but what's important to know is that over time, the body does get used to it, and the injection site reaction does reduce. So it is worthwhile to let the patient know that that might be expected.

For rozanolixizumab, again, similar side effects with headache, but we're also seeing diarrhea and pyrexia. Rozanolixizumab is also a subcutaneous injection given in cycles, and there, we're also seeing injection site reactions. However, these tend to be milder. I've had less complaints from patients and generally tolerable.

With nipocalimab, I don't have real-world experience, but based on the phase 3 data, this toxicity was similar, with infection, headache, as well as muscle spasms and peripheral edema.

One thing that I alluded to earlier is that we have noticed a bit of a signal of cholesterol changes. So the FcRn receptor has a separate domain for albumin. Perhaps for the larger molecules of these antagonists, there could be some interference with albumin levels, so there has been some increase in cholesterol. However, I can say that in my general practice, I'm not routinely checking cholesterol levels to see if there have been any changes, and I haven't noticed anything specific in my patients on these currently approved therapies.

So when thinking about strategies to manage adverse events, I think the most important is counseling. Letting the patients know that they may experience some of these common side effects, such as headache and mild infection, is important. And I think definitely for the subcutaneous formulation, letting them know that a site reaction may be present and will, over time, get better.

So, Dr. Bril, please share your thoughts on establishing a monitoring protocol for both clinical response and adverse events when you start or maintain a patient on an FcRn inhibitor.

Dr. Bril:
Thanks, Dr. Goyal. So it's important with these new therapies to monitor the patient for response because they're expensive, and the payer will want to know that the patients are responding. So you need to use the ADLs as a minimum measure of clinical response, as this was the primary endpoint in all the phase 3 trials.

And it's important to know that cyclical therapy, meaning on-demand therapy, is what a lot of people start off with. So for example, efgartigimod, if you are treating in 4-week cycles, 4 weekly IV infusions then 4 weeks off and then 4 weeks on, 4 weeks off, you have to know if the patients are responding. So usually, when we start the Fc receptor inhibitor, we are going to be seeing the patient at least 3 months, if not earlier. But in the meantime, there's a nursing program with a nurse who is monitoring the patients and their ADL and sending you the information more frequently so that you can check in on patients.

And tracking for the AEs is important. Asking about any upper respiratory tract infection or urinary tract infection, these are the 2 major infections. It's important to know that although these are slightly increased with FcRn inhibitor therapy, that with repeated cycles, the prevalence of these infections does not increase. It's not an increasing curve, but it stays flat – above not having the treatments, but not increasing cumulatively with time.

Laboratory parameters are not really monitored routinely by us in patients who are started on an FcRn inhibitor. If you think you have an immunodeficient patient, then you should measure IgG levels. But this is not really frequent in adults with myasthenia gravis, and we do not routinely measure IgG levels as part of our clinical approach. It may be of interest to measure the levels if you lose response to see if they're still suppressed, but we haven't been doing that routinely at all.

So, Dr. Goyal, how do you approach FcRn inhibitor adverse events in your practice?

Dr. Goyal:

Yeah, I'm glad to hear, Dr. Bril, your approach, because it sounds like mine is very similar. So in terms of efficacy, because the currently approved therapies, efgartigimod and rozanolixizumab, are cyclical, patients can, either when they're due for their next cycle, continue to feel the benefit, so you can increase the duration, or they may have wearing off before they're due for the next cycle, which can be distressing. So I think that monitoring MG-ADL and then continuing communication with the patient is really helpful when they're first starting off, to really think about how you're going to dose each of the cycles.

In terms of toxicity, I agree with you. I'm not routinely checking IgG levels. I'm not checking their AChR antibody titers. It's really monitoring the patient for infection. And I have had some patients that have had increased infection and have chosen to come off the therapy. Even in those patients, I didn't check their IgG levels and really treated them clinically.

Dr. Bril:
Thank you. So, really, what we've learned in this chapter is that it's important to monitor the ADLs in patients starting FcRn antagonist therapy and that monitoring patients for infections is important, but laboratory parameter testing is not done routinely and not necessary.

In Chapter 4, we'll be discussing approaches to integrating FcRn therapy into myasthenia gravis treatment plans. Stay tuned.

Chapter 4

Dr. Goyal:
Welcome back. In Chapter 3, we looked at adverse events associated with FcRn therapy in myasthenia gravis. Now we're going to consider how best to integrate FcRn antagonists into our treatment plans.

Dr. Bril, where are we clinically on identifying the when and the why of incorporating FcRn antagonists into the short- and/or longer-term treatment plans for our patients with myasthenia gravis?

Dr. Bril:
Thank you, Dr. Goyal. So FcRn inhibitor treatment, I think, really replaces immunomodulation therapies such as intravenous immunoglobulin or plasma exchange. FcRn inhibitor therapies work rapidly in the majority of patients, so within 1 to 2 weeks of starting therapy, and produce a significant improvement in overall clinical status. So I tend to use FcRn inhibitors instead of using intravenous immunoglobulin, or IVIG. When would this be? This would be when I'm preparing a patient for surgery and I don't want to use immunosuppressant therapy so that if they need a thymectomy for a thymoma or generalized MG in younger patients, I would use FcRn inhibitors if anticholinesterase therapies were not enough.

Also bridging therapy. So I would start patients on some of the immunosuppressants, the nonsteroidal ones, but they have delayed onset of action. So I would use FcRn inhibitors as a bridging therapy to onset of efficacy of those cheaper oral agents, which are much easier to administer and take regularly.

And finally, I would add FcRn inhibitors to those patients who are not doing well on standard of care therapies or cannot tolerate various therapies so that they may have to come into regular use for a fragment of the patients who do not respond to other therapies, such as refractory patients, or as add-on therapies to standard of care.

Given the fact that payers are really restricting availability to antibody-positive patients, the therapies are useful for acetylcholine receptor, and I expect all of the FcRn inhibitors to work for MuSK-positive patients. There is a study in the MuSK population being done with efgartigimod. Disease severity, as I said, refractory, and those who need an add-on. Previous treatment responses, that is hard to say, because usually they haven't been on another FcRn inhibitor. But we can individualize care for our patients and optimize outcomes with these new therapies.

So those are the 3 preoperative or pre-immunosuppressant: bridging therapy, add-on therapy, and refractory. It remains to be seen whether this would be an option in patients who are in crisis. There are more steps to go through, and so far, there's limited evidence on the efficacy, although I don't see why FcRn inhibitors would not work in that particular situation as well.

Dr. Goyal, please add your thoughts on this topic.

Dr. Goyal:
Yeah, absolutely. So I think you did a great job summarizing and really adding a lot of my thoughts as well. One of my research interests is steroid toxicity – thinking about it, managing it, and mitigating it. And I think these agents really play an important role in that as well. So often, I think about the new-onset MG patients with moderate disease that hasn't responded to an acetylcholinesterase inhibitor; the nonsteroidal is going to take months to work. And typically, 10 years ago, the option would be steroids. IVIG, plasma exchange could be options as well. However, infusion therapy, availability of IVIG can be an issue. So I think this is really where FcRns

can really play a role, where we don't go for the steroid, but we can really go for FcRn inhibitors.

There is data coming out that early, aggressive therapy can perhaps change the course of the disease. As you mentioned, access is definitely an issue. And so we have to practice in our medical environment. But I think that can be an important role as well. And I do appreciate that some patients may require chronic FcRn antagonism therapy. However, because it is being given in cycles, there is an off-ramp. We can use these for short periods, during flares, and then transition them off when that nonsteroidal agent is able to work.

So in summary, we talked about where FcRn antagonism can fit into our current treatment algorithm of myasthenia gravis, which is evolving. We talked about its use early in patients, preoperatively in our refractory patients that haven't been responding to traditional therapies, and as a way to reduce toxicity from our other traditional therapies.

Well, we're glad we had the opportunity to share our perspectives on the current and possible future use of FcRn antagonists in the management of myasthenia gravis. Thanks for listening.