FcRn and Myasthenia Gravis

Dr. Richard Nowak:

I will be talking today about FcRn and myasthenia gravis. My name is Dr. Richard Nowak, associate professor of neurology at the Yale School of Medicine. These are my relevant disclosures.

Our learning objectives today will be to describe the role of FcRn in myasthenia gravis, describe the efficacy of treatment options for MG that target FcRn. Compare the safety of the treatment options for myasthenia gravis that target FcRn. Let's just start at the very beginning. What is myasthenia gravis? Specifically, what is autoimmune myasthenia gravis? This is a rare condition that is characterized by fluctuating muscle weakness, specifically weakness that involves the ocular muscles, bulbar muscles, and limb muscles. Many individuals are characterized by having acetylcholine receptor autoantibodies that target their neuromuscular junction. In fact, many patients present as their initial symptoms having ocular symptoms. Things like diplopia or orthosis. In fact, up to 90% of individuals, their initial symptom does involve an ocular finding or symptom.

Treatment is very highly individualized and often includes medications that are off-label. Things like azathioprine or mycophenolate are not uncommon. Non-steroidal immunosuppressive therapies that have been used for myasthenia gravis in the past and also currently. However, there are five drugs that are FDA approved, eculizumab, efgartigimod, ravulizumab, rozanolixizumab and zilucoplan.

Symptoms and diagnosis. As I noted on the prior slide, the condition is characterized by having fluctuating symptoms fluctuating weakness on exam. It's not unusual for patients to report things like difficulty with chewing, specifically fatigue in chewing, difficulty with swallowing. Symptoms such as choking with certain consistency of food. Shortness of breath, and more proximal than distal muscle weakness. In fact, the characteristic is really proximal weakness that's fatigable. As we consider the diagnosis and the approach to making a diagnosis for our patients with myasthenia gravis, certainly the physical examination and their clinical presentation is very important.

We think about this as an autoimmune condition, it's very typical for us to move forward with serologic evaluation as well as electrodiagnostic studies. In fact, 70 to 80% of individuals do have autoantibodies directed against the acetylcholine receptor, and that is something that helps us and sometimes definitively establishes a diagnosis. However, we also have electrodiagnostic studies such as the repetitive nerve stimulation test, which is approximately 60 to up to 70% sensitive at picking up an abnormality in those that have this condition. We have also the single-fiber EMG that can be used in select patients where their diagnostics have been unrevealing, so they don't have the presence of autoantibodies or the repetitive nerve stimulation testing is normal. Single-fiber EMG can be 95+% sensitive, but it is less specific for a neuromuscular junction disorder such as myasthenia gravis. The interpretation of that test is something that needs to be considered in the context of the clinical presentation for a patient and their presence or absence of autoantibodies, for instance.

I also wanted to note that a smaller group of autoimmune myasthenia gravis patients have other antibodies besides the AChR autoantibodies. MuSK antibodies can be seen in somewhere between five to maybe up to 10% of individuals with generalized myasthenia gravis. Lrp4 antibodies can also be present in some of our autoimmune EMG patients, but the presence of that antibody is observed in maybe somewhere between two and 4% of all patients with myasthenia gravis. Again, the most common autoantibody here is the acetylcholine receptor binding autoantibodies. Looking at myasthenia gravis in general and focusing on, well, what is really the burden of disease? The way I think about myasthenia gravis is that it has a range of severities from mild to severe, and then we have those that have moderate disease. This is a study that was done by Cutter et al. that looked at a sample of registry

patients and who self-reported disease burden based on the MG-ADL scale and also the MG-QoL scale. The MG-ADL is a patient-reported clinical outcome measure that ranges from zero to 24 at max. The higher score represents a greater disease burden.

The mean MG-ADL score in this registry population was 6.2. And 6.2 represents moderate or greater disease burden based on patient self-reported clinical outcome measures. It's important to note that our patients do deal with a great disease burden if you take a registry sample. Similarly, the MG-QoL is a patient-reported quality of life outcome measure. It specifically addresses symptoms that affect our MG patients. Again, this ranges from zero to 60, and if you look at the self-reported scores here most patients in fact do have moderate or greater disease severity based on these scales. Again, the focus of this slide is to really communicate with the community that there are a number of patients that have continued ongoing active disease that is potentially not adequately managed at this time. Looking more so at the general pathophysiology. I noted before that this is an autoimmune condition. It's a T-cell dependent B-cell mediated autoimmune disorder via IgG autoantibodies. This slide represents where the acetylcholine receptor autoantibodies target the postsynaptic neuromuscular junction. There's three main ways that this disease can actually affect the neuromuscular junction.

We have number one, blocking antibodies that prevent the acetylcholine from actually getting to the acetylcholine receptor and hence causing muscle weakness. We have modulating antibodies that increase the internalization of the acetylcholine receptors, and so less receptors the less likely the neurotransmitter is able to engage with a postsynaptic junction and cause muscle contraction, hence resulting in muscle weakness. Then we have binding autoantibodies that can also activate complement, a very critical component of the immunopathophysiology here where there's binding of the complement, and then there is actually the formation of what's termed membrane attack complex that essentially pokes holes and destroys the surface of the motor end plate, again causing a reduction in the available receptors, again translating into muscle weakness. MuSK antibodies are IgG4, and they are not known to have any role in the complement system. They're more so akin to blocking antibodies. LRP4, the characterization of those is not clearly understood at this point in time. That's something that is an area of active research.

Switching gears a little bit in terms of FcRn and MG. This is an important slide to understand, well, what is it that we're doing? What is it that we're potentially targeting by the FcRn and understanding the IgGs? I noted this a little bit earlier that MuSK autoantibodies are IgG4. Whereas AChR autoantibodies, it's important to note that these are IgG1 and IgG3 subtype. But taking a step back, looking at the endogenous IgG binding to FcRn and reducing IgG from entering lysosomes, the way that the FcRn works is that it protects IgGs in that they bind to that particular receptor and they essentially get spit back out without being degraded. It increases the ability or allows for the IgGs to be recycled over time. This, as we talk about the targeting strategies for FcRn, what is it that they're doing? But if we were able to block the FcRn, what we would then do is reduce the recycling of endogenous IgG or specifically autoantibodies like the acetylcholine receptor antibodies, which are IgG. We essentially reduce the levels of not only IgG in total, but also pathogenic autoantibodies by targeting the FcRn receptor.

This is another way to look at this, but the end is the same. I think the concept here is to really understand that by targeting or antagonizing the FcRn, we're reducing the recycling, and hence that translates into lowering IgG and hence lowering pathogenic autoantibodies. Looking at the history of treatment, so these are reports that are summarized here, looking at the overall mortality of myasthenia gravis over the last century, essentially. Mortality was as high as 90% as reported around 1920. Mortality has declined over time as critical care has improved and just in general medical care has improved. The biggest, I think, step in terms of reducing mortality at least as I see it occurred somewhere between the mid-1960s into the 1970s. Why is that timeframe important? That is around the time where myasthenia gravis was recognized or characterized as being an autoimmune condition.

Prior to that time, it was not clear why myasthenia gravis... What the underlying driver to myasthenia gravis was. Prior to that time, treatments such as neostigmine or pyridostigmine were offered, but it was not clear that targeting the immune system would have any benefit.

Really getting into the 1970s immunosuppressive therapies started to be initiated. Things like corticosteroids and then later things like cyclosporine and cyclophosphamide, azathioprine. Then fast forwarding to present time over the last five to eight or so years, we have targeted treatment strategies that have emerged. The first targeted treatment strategy was eculizumab, which targeted C5 complements. Here we have the most recently FDA approved treatments. The way that I see these as falling into two main buckets, we have the neonatal FC receptor antagonist, and then we have the complement inhibitors. Under the FcRn antagonists, we have efgartigimod, which is intravenous. We have efgartigimod, which is the hyaluronidase, which is the subcutaneous formulation. Then we have rozanolixizumab. These are all FDA approved FcRn antagonists at this time. Then looking at the other bucket, the C5 complement inhibitors, we have eculizumab and ravulizumab, which are both intravenously administered medications. Then we have zilucoplan, which is the most recently C5 complement inhibitor therapy that we have approved. I'll get into the details of each of these and some of the nuances in the upcoming slides.

Looking at the treatments in late stage development, we have a number of FcRn antagonists, nipocalimab and batoclimab specifically. These have recently completed Phase III registrational clinical trials, so more information to come likely in the coming next several months with these. Then we have what we have labeled here under, "Other." These are... The first one is a C5 complement inhibitor, but the others are targeting different aspects of the immune system. What is myasthenia gravis? It's important to note that this is a T-cell dependent B-cell mediated via IgG autoimmune conditions. For instance, we have medications that target B cells inebilizumab, for instance, is an anti-CD19 B-cell depleting strategy. That Phase III clinical trial has recently been completed. We have medications that target, for instance, interleukins, satralizumab specifically in that Phase III trial was recently reported. Again, the treatment landscape and late stage development medications, it's important to follow the literature. But I think that as the years go on we'll have most certainly additional targeted treatment strategies, so an ever-evolving therapeutic landscape for autoimmune myasthenia gravis, clearly.

Well, our CME today is focused on FcRn. In the role of FcRn antagonists and myasthenia gravis, I wanted to at least highlight some of the key complement inhibitors that are available to us. First, we have eculizumab that was approved in 2017 by the FDA with a treatment indication being patients with acetylcholine receptor positive generalized myasthenia gravis. Again, this is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity. It's a medication that again is administered intravenously weekly for four weeks, and then a maintenance dose is given every two weeks thereafter. All patients need to be immunized against meningitis, and it does have a box warning against meningococcal infections. Ravulizumab again was approved back in 2022 where the treatment of acetylcholine receptor [inaudible 00:15:48] positive generalized myasthenia gravis is very similar to eculizumab in terms of its mechanism of action, but its administration maintenance is every eight weeks.

Again, meningococcal immunizations are required and it has a box warning for meningococcal infections. Zilucoplan is a C5 complement inhibitor. It's a peptide as compared to the monoclonals that I presented in the prior two slides. It was approved in 2023, again, for patients with acetylcholine receptor positive generalized myasthenia gravis. It's administered daily subcutaneously by patients, so it's a self administered. It doesn't currently have a box warning. However, as a C5 complement inhibitor, patients do need to be vaccinated against meningitis. Switching back to FcRn inhibitors/antagonists, efgartigimod was approved in 2021 for the treatment of patients with acetylcholine receptor positive generalized myasthenia gravis. As noted earlier, this is an FcRn blocker or antagonist. It's given on a

cycle basis. What does that mean? Each cycle is given weekly, times four weeks. Then the cycles then can be administered based on how the patient is doing clinically.

Some patients have a four to five or six week break between cycles. Some patients can go for an extended period without requiring additional efgartigimod treatment. This medication does not require any vaccinations and does not have a boxed warning. I wanted to touch on efgartigimod ADAPT and the ADAPT+ study. ADAPT was a placebo controlled randomized three clinical trial that compared efgartigimod versus placebo. Again, these were weekly infusions, and then the separation from one cycle to the next cycle was five or more weeks depending on how a patient did clinically. I'll point out that the eligibility for this clinical trial was those with generalized myasthenia gravis based on the MGFA class between two and four, acetylcholine receptor autoantibody positive or seronegative patients required an MG-ADL of five or higher and needed to be on one or more stable generalized myasthenia gravis treatments and had to have an IgG level of six or higher grams per liter.

This study schematic also details, which I think is also important to understand the open-label extension or ADAPT+ where we have patients on more long-term treatments for up to three years. I'd like to share this data for you based on how patients did on long-term FcRn antagonists, specifically with efgartigimod. Again, this is looking at efficacy based on the MG-ADL score and the QMG score for patients with generalized myasthenia gravis. Again, demonstrating that those that received efgartigimod did better in terms of having a greater improvement in their MG-ADL score. If you just simply compare, for instance, two or higher, over 80 or near 90% of patients achieve that bar as compared to about 45% of the placebo arm. As you make the cut a little bit more strict, for instance, looking at a three or higher improvement in score, it's still 80 but then the placebo is closer to about 30%. Looking at the physician-reported clinical outcome measures, specifically the QMG, looking at a three or greater score improvement in total score, we have 64% as compared to about 27 or so percent in the placebo arm.

Again, demonstrating efficacy in the ADAPT+ or in the open-label extension study here. Then looking at safety in terms of treatment, emergent adverse events. Again, there is no specific safety signal identified that was of concern. I will point out that the most common treatment emergent AE was headache at 24%. There were patients that had COVID-19. Again, some of the study was done during that time at around 15%. The nasopharyngitis was reported at about 13% or so. Again, no significant safety signals identified, but it's important to know as you use potentially efgartigimod in clinical practice that up to about 24% of individuals might report a headache with treatment. Not super uncommon from that perspective. Getting into some of the details with efgartigimod hyaluronidase, this was approved in 2023. Really the only difference here is that this is subcutaneously administered as the main difference, but a clinical trial nonetheless was completed. Here this slide is a schematic for the ADAPT SC study.

This is a study that compared efgartigimod Sub-Q at a fixed dose to efgartigimod IV, which was a dose based on the patient's weight. The criteria for enrollment were essentially the same as for the original ADAPT, adults with generalized myasthenia gravis, MGFA class two to four, ADL scores of five or higher, and on one or more stable gMG treatments. Here are the efficacy, so you can see the subcutaneous formulation of efgartigimod in green as compared to the intravenous formulation. Again, looking at the MG-ADL score change at the top left corner the patients had drops in their MG-ADL scores. Looking at, for instance, the change from the study baseline of MG-ADL in those with acetylcholine receptor antibody-positive patients, those actually had an improvement in those scores overall. Then the acetylcholine receptor positive population from ADAPT-SC+, which was the open label extension, we're looking at overall population and they have improvement in their MG-ADL scores for the overall population as well as for the population of patients with autoantibody positive disease.

Again, this is looking at the safety profile for ADAPT-SC as well as for the open label extension, which was ADAPT-SC+. No safety signals were identified here. We did note injection site reactions [inaudible

00:23:07] COVID-19 as being some of the more frequent AEs and also some individuals with myasthenia gravis exacerbations. Again, no real difference between the groups identified here. Moving along to the next FcRn antagonist, which was rozanolixizumab approved in 2023. This was approved, again, for generalized myasthenia gravis patients who were either positive for acetylcholine receptor or MuSK autoantibodies. Again, this is a monoclonal antibody that targets FcRn. This is a medication that's given once a week for six weeks, and then subsequent treatment cycles are given based on how an individual patient is doing. Some patients do require additional treatment cycles thereafter. It's given as a subcutaneous infusion using an infusion pump. Again, no boxed warnings were identified or noted here.

This is the MycarinG study in terms of the study schema. This is to enroll a total of 200 patients into three arms. It was a two-to-one design for rozanolixizumab versus placebo. Then the patients were re-randomized in terms of those who had completed or required rescue therapy into receiving different doses of rozanolixizumab. For rozanolixizumab, we have the pivotal study, which was MycarinG. This study enrolled a total of 200 individuals with myasthenia gravis. It's important to note that it also included patients with MuSK autoantibody positive generalized myasthenia gravis, a total of 21 individuals. This was a two-to-one design. There were 67 individuals assigned to placebo, and then 66 and 67 assigned to the two different dosing arms of rozanolixizumab. Looking then at the efficacy for MG-ADL score, we have the overall study population on the far right, looking at the change in MDL score placebo versus the seven mix per kilogram as compared to the 10 mix per kilogram.

Again, demonstrating clinical benefit in that overall population, but we also look at the AChR, which is the middle figure demonstrating a significant change in that study population. Looking at our MuSK patients, again, the numbers here are a lot smaller in that there were a total of 21 individuals randomized in the MuSK cohort, and so some of the confidence intervals are a little bit wider, but we do see most certainly improvement in MG-ADL scores as compared to placebo in both of the dosing arms here. Again, overall demonstrating efficacy in either AChR and MuSK autoantibody positive generalized myasthenia gravis. This is looking at not only the MG-ADL, but we also have the MG composite and the QMG scores. Important to note that we're seeing reductions in both of the additional outcome measures for each of these scores. Safety. Comparing the safety signal. There were no safety issues identified with rozanolixizumab in the overall population or in the MuSK versus AChR subpopulations here.

Then this is our next FcRn antagonist that is currently with the FDA for review. Pivotal trial was recently completed, but just to share with you that this is a monoclonal antibody that targets FcRn. It's administered intravenously and more information to come depending on the decision that's made by the FDA. This is the Phase II clinical trial that demonstrated safety and at least preliminary effectiveness that looked at nipocalimab at a total of four doses as compared to placebo. Here we have the efficacy as determined by change in MG-ADL score at the various different doses. Again, demonstrating that the ADL score does improve with the nipocalimab administration. Again, this was based on the published Phase II clinical trial data and not the Phase III. Here's the relative safety. No safety signals were identified as compared to placebo. On this slide you'll find a summary table that lists the three FDA-approved FcRn antagonists, and the two FcRn antagonists that are in late stage development.

It's important to understand the similarities as well as some of the distinguishing characteristics of each of these. I'll point out that efgartigimod and efgartigimod SC, these are approved for generalized acetylcholine receptor autoantibody positive patients. The difference between the two is that one is given intravenously versus the efgartigimod Sub-Q, as its name indicates it's given subcutaneously. Then our third, which is rozanolixizumab. This is a subcutaneously administered FcRn antagonist, but approved for adult patients with generalized myasthenia gravis that have either acetylcholine receptor or MuSK autoantibodies. Again, something to keep in mind when considering an FcRn antagonist for patients. Then the two that are in late stage development. Nipocalimab, this is an intravenously

administered medication that appears to be given every two weeks. Again, it's in late stage development and currently with the FDA for review. Again, more to come on this one. Our next FcRn antagonist, which is in late stage development is batoclimab. This is a monoclonal that targets FcRn. This is given subcutaneously.

The Phase II clinical trial, which looked at both safety and preliminary efficacy was a one-to-one-to-one design. This study also included an open-label extension period of the batoclimab, and then a follow-up period that looked at safety and adverse events. Based on the efficacy information here, while this is a study that was underpowered, it demonstrated that patients did have an improvement in their overall MG-ADL score changes, but specifically it was to understand whether or not there was a significant lowering in IgG and pathogenic autoantibodies. Based on preliminary efficacy assessed the study was positive and moved forward to Phase III. But before we get there, I'd like to highlight some of the safety features of batoclimab in the Phase II. Again, looking at the different doses of the batoclimab as compared to placebo, there was no specific safety signal identified or tolerability issues identified in Phase II.

This led then specifically to the Phase III batoclimab study, which is the flux study. This is a study that included an induction regimen as well as a maintenance regimen as well as a long-term extension. The study was designed to understand how much the batoclimab or how much of an FcRn antagonist is really needed to achieve clinical benefit. Again, this is a study that was a one-to-one-to-one design looking at batoclimab at 680 milligrams once weekly versus 340 milligrams once weekly versus placebo. The primary endpoint was the change from baseline to week 12 and the MG-ADL in patients that had autoantibody-positive myasthenia gravis. What's clever about this design and what this design might reveal is understanding thereafter as to how to administer the batoclimab and how often to administer it and what dose is necessary to administer it in the maintenance of our patients with generalized myasthenia gravis.

More information to come as the Phase III registrational trial is completed. I will note though, Phase III clinical trial with the batoclimab was recently completed and published. This was a study that was in China. It was a multi-center randomized study completed between 2021 and 2022. That included individuals with antibody-positive generalized myasthenia gravis, and it was administered weekly at a specific fixed dose of 680 milligrams followed by a four-week observational period. This study did demonstrate a statistically and meaningful difference in the MG-ADL score in terms of improvement. What was reported is that 58% of patients achieved that improvement in the treatment arm as compared to 31%. There were no safety signals identified, and this study was recently published in JAMA Neurology. Again, this is a study that was based in China. What I think is important to underscore is that the Phase III flex trial will offer additional information about both induction and maintenance of use of the batoclimab for individuals with generalized myasthenia gravis. This next slide summarizes the current FcRn antagonists available or currently in late-stage development.

We talked about today, efgartigimod, efgartigimod Sub-Q, and rozanolixizumab. I will point out some distinguishing differences between those three, just to highlight. Efgartigimod is weekly intravenous administration times four weeks as a single cycle that can be repeat administered. Efgartigimod Sub-Q is exactly that. It's a subcutaneously administered weekly treatment. Then the distinction between that and rozanolixizumab is that this is a medication approved for both AChR and MuSK autoantibody-positive patients, again, subcutaneous weekly administration. Both nipocalimab and batoclimab are currently in late-stage development and more information to come in the next several months.

Our clinical pearls are as follows. We have FcRn prevents IgG degradation. Blocking or reducing FcRn activity increases IgG degradation. It's important to understand the role of FcRn, the role of FcRn antagonism and how FcRn antagonists help with lowering IgG and pathogenic autoantibodies. That's

really the key in terms of understanding FcRn, FcRn antagonism, and its role in the treatment of antibody-positive myasthenia gravis.

Numerous therapies are approved and/or in development that target FcRn and reduce IgG and pathologic autoantibodies for myasthenia gravis. There's currently three medications FDA approved that are FcRn antagonists, and there are two that are in late-stage development at this time. FcRn antagonists are blockers, along with medications that interfere with the complement system or complement inhibitors provide clinicians with more options to tailor treatments to care for patients and reduce burden of disease. Thank you again for your attention and participation in today's CME. Hopefully this is of value to your practice. Thank you again.