FcRn and Myasthenia Gravis: Treatment Options

Dr. Richard Nowak:

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

Our learning objectives today will be to compare the efficacy and safety of the treatment options for myasthenia gravis that target FcRn.

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. 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.

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.