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Advancing Treat-to-Target Care in Generalized Myasthenia Gravis: Earlier Diagnosis, Standardized Assessment, and Precision Use of FcRn-Directed Therapy

Dr. Muppidi:

Hello, this is Dr. Srikanth Muppidi, Clinical Professor in Adult Neurology at Stanford University School of Medicine. This is CE on GLC. Today, I'll be highlighting the key messages presented at Impact Live Series by GLC. We'll be talking about myasthenia gravis.

Myasthenia gravis is probably the most well understood autoantibody-mediated disease. There are a number of different types of antibodies, including AChR, MuSK, LRP4, and some patients have seronegative myasthenia gravis, which means that we currently don't know the type of antibody they have. AChR antibody causes damage to the postsynaptic membrane in different ways, including complement deposition, binding, blocking, and internalization of the AChR receptors, reducing the transmission of flow at the neuromuscular junction, whereas MuSK antibody binds to MuSK receptor, which in turn prevents clustering of the AChR receptors and then reduces safety factor and causes weakness. LRP4 is a little less understood. There have been number of therapies that have been developed over years, but a small proportion of patients still tend to have refractory disease beyond 2 years, in spite of some of the therapies that have been approved more recently. Some of this retrospective data comes from therapies that were prior to the recent therapies, but nevertheless, even now we still see patients who are quite refractory to currently available therapies and requiring escalation therapies.

Over the years, we are using different types of outcome measures in MG to capture patient symptom burden. You can think of MG outcome measures are based on who is reporting them. For example, there are clinician-reported outcome measures that capture the disease burden as a physician examining the patient. There are patient-reported outcome measures which basically capture symptom, function, and daily impact and disability as they are experienced by the patient. There are measures which are mixed that are performance-based. They have some aspects from the physician, some aspects from the patient.

When you think of any outcome measures, we have many different features that will help you understand if an outcome measure is valid, reliable, what is considered a meaningful change that actually translates to improvement in patient correlation of the outcome measure with other measures, as well as Rasch analysis. Some of these psychometric analysis is beyond the time required for this discussion, but it's important as you are using outcome measures for myasthenia or any other disease to understand a little bit more in detail how the measure was built and what it's supposed to capture.

When patients think of myasthenia gravis, they think of many, many different symptoms. If you were to ask patients, they think that myasthenia gravis can affect different aspects beyond what sometimes physicians appreciate. There are obviously ocular or speech symptoms, but many patients feel they have pain in their muscles, they have profound degree of fatigue, and other musculoskeletal symptoms.

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Beyond the symptoms that they experience in this study, there are about 16 symptoms per patient, it clearly impacts their emotional well-being, physical impact, social impact, and all of these are experienced by patients as one single thing and not separate things. When physicians look at outcome measures, they are looking at specific outcome measures that sometimes don't capture every one of them.

There are many number of outcome measures that are currently available for myasthenia. The most commonly used one is MG-ADL, which is the primary outcome measure. It is patient reported, might require some guidance the first time the patient is doing it. All of the symptoms are as reflected based on the myasthenic symptom nature. It can be easily adopted in clinical practice. Less commonly used outcome measure is QMG, predominantly used in clinical trials, requires some equipment and time. MG Composite might be a good outcome measure if you want to incorporate some physician examination. It's a composite measure and it has both features from MG-ADL and physical examination. The final goal of therapy tends to be MSE, which is defined as MG-ADL of 0 or 1. There are other classifications that sometimes are required, such as MGFA classification, for example. And some insurances require when you want to use novel therapies, they would like an MGFA classification. They would like an MG-ADL of the patient.

Over the years, as we had newer therapies that have been developed in myasthenia, how we think about myasthenia, how we think about the goalposts of myasthenia have changed, and I think we're able to raise the bar. Many years ago, we used to only use QMG as an outcome measure in clinical trials, which was completely physician reported and examined. And since then we are using MG-ADL. Now we are looking at post-intervention status, or how does the patient look after a particular intervention? Have they improved, and how much they have improved? Again, physician reported, but I personally like MSE—Minimum Symptom Expression and MG-ADL of 0 or 1, again gives it back to the patient and gives them an opportunity to decide if their symptoms are well controlled or not. And I really like the fact that the bar has been raised and hopefully continues to be raised as newer therapies become available.

This is reflected by a recent comprehensive care goals in myasthenia gravis, which looked at what should be the goal of taking care of patients with myasthenia gravis.

One of the ways to think about it is that we want patients to have sustained minimal symptoms, but at the same time not have too many treatment-related adverse events. So you want to marry both of them: good symptom control, not significant adverse events.

And also this particular comprehensive care goal manuscript by experts internationally also suggested perhaps we should be thinking about using targeted and novel therapies or aggressive therapies at the beginning to rapidly control the symptom burden, especially if they are not controlled with conventional therapies within 1 year of symptom onset.

One of the newer therapies that has been approved are called FcRn inhibitors. We have known FcRn as a mechanism for IgG recycling for a long period of time. FcRn binds to IgG and then helps with recycling. Some of you might be thinking, why is it called neonatal? It was called neonatal because originally this was thought to be the mechanism where IgG is transferred from mother to the fetus, it was discovered in placenta. But the name has stuck, even though the FcRn mechanism is seen in many other tissues and important for IgG recycling, and not only just for transfer of maternal immunoglobulins to the fetal immunoglobulin.

Well, this is one of the main mechanisms. The IgG has a half-life of 22 days compared to other types of Ig products, Ig subtypes like IgA or IgM, which has a half-life of 5 to 7 days. One way to think about it, since the myasthenic antibodies are all IgGs, is there a way we could reduce the IgG level that would reduce the antibody level and then lead to clinical improvement. One of the current ways we do that is by plasma exchange. This excellent study by Dr. Gupta et al showed that patients who have plasma exchange have a clear reduction in their IgG titers, IgG levels, and then also is reflected by changes in their antibody levels.

Of course, plasma exchange is quite intensive, laborious, requires an IV line. What if you could replicate this with FcRn inhibitors and reduce the antibody levels? Would you see the same degree of clinical improvement? Would you see the same degree of AChR antibody reduction?

And this leads to the first drug that has been approved for myasthenia gravis called efgartigimod. As you will be able to see on the left side of the graph here, the blue is efgartigimod, red is placebo. You're able to see there's a dramatic reduction, which is efgartigimod is given weekly, once a week for 4 weeks. You're able to see a dramatic reduction in MG-ADL and other MG-specific outcome measures. On the right side of the figure, you're able to see the Christmas tree plots. The blue is efgartigimod, red is placebo. You're able to see the patients who had efgartigimod, a higher level of improvement in MG-ADL with higher percentage of patients. Compared to placebo,

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the same thing happens with QMG.

The second FcRn therapy that has been approved is called rozanolixizumab. This was studied with two different doses. You're able to again see both different doses compared to placebo have a clear reduction in their MG-ADL and different outcome measures that are used in this clinical trial. And compared to placebo, here the gray bars are placebo and blue and purple are two different doses of drug levels. You'll see there's a higher level of improvement in terms of ADL and QMG and a higher percentage of improvement.

What about the third drug that's been approved? The third drug that's been approved is called nipocalimab, which is given intravenously. This is given every 2 weeks. Patients who had nipocalimab here—blue is nipocalimab, red is placebo—had a higher level of reduction in MG-ADL and QMG, and in the Christmas tree plot again, a higher level of improvement in MG-ADL and QMG compared to placebo. All 3 drugs are currently FDA approved for patients with myasthenia gravis.

What about IgG level reduction? As you're able to see, they're fairly similar across the board for all 3 drugs with efgartigimod, rozanolixizumab in the study were given in a cyclical fashion. Efgartigimod was given once a week for 4 weeks. Rozanolixizumab was given once a week for 6 weeks. So you're able to see after the 4 weeks or after the 6 weeks, there is a return of the IgG level, whereas with the nipocalimab, you're able to see that the reduction in IgG level is persistent.

The 3 drugs have fairly similar efficacy. There are some subtle differences in terms of their frequency of administration, mode of administration. But if you look at the degree of QMG drop, efgartigimod versus placebo, rozanolixizumab versus placebo, or nipocalimab, our MG-ADL drop more than 5 points. MG-ADL more than 3 point drop. Fairly similar extent compared to placebo.

How about safety? All three drugs in the clinical trial are very well tolerated. There were mild issues with well controlled or easy to treat urinary tract infections, but there were no other significant or worrisome safety signals.

One of the challenges that happens is that when you do these trials, we tend to find patients with highly active disease, fairly homogeneous group of patients. It's always interesting to see how this translates to clinical practice.

This is a study from our center where we were able to look at efgartigimod use in clinical practice. Here you're able to see the dark blue bar, which is the ADL score pre efgartigimod and then post cycle 1. You're able to see there's a clear reduction. The light blue bar is post cycle 1. You're able to see compared to the dark blue bar, there's a clear reduction across the board, and some patients achieved an MG-ADL of 0. That's reflected by the star. And so it's kind of reassuring to see that we were able to replicate some of what was seen in clinical trial in our clinical practice.

Not only our center, a different center from UPenn also looked at the trends in MG-ADL, and as you can see, there's a clear reduction in MG-ADL. They also looked at the prednisone dose trend. Again, there was a reduction in prednisone dose trend. About 2/3 of the patients had no side effects reported. Some patients had mild side effects reported, but these were again mild and well tolerated.

How about using these therapies early? Does that make a difference? So there was this one observational study from Germany that looked at using novel therapies, including FcRn and complement therapies as an early add-on therapy versus patients who had these therapies a little bit later in their treatment journey, patients who had these therapies as an early add-on had a greater degree of MG-ADL improvement, greater degree of QMG improvement, greater degree of quality of life improvement, and were less likely to have deterioration compared to those did not get these therapies as an early add-on. And this really emphasizes the fact that we should be able to aim for a higher level of clinical symptom reduction in patients. Using novel therapies would be one of the strategies of achieving that.

Currently, there are 3 FcRn therapies that are approved: efgartigimod, rozanolixizumab, and nipocalimab. The key differences are nipocalimab is given every-2-weeks schedule. Rozanolixizumab is given once a week for 6 weeks, break, and a repeat cycle. Efgartigimod was originally given once a week for 4 weeks, break, and a repeat cycle, although more recent prescriber information allows for a little bit more flexibility. Nipocalimab is intravenous only. Rozanolixizumab is subcutaneous infusion. Efgartigimod is currently available as intravenous subcutaneous injection as well as a prefilled syringe. Adverse events and side effect burden looks fairly similar across the board.

It's always important to think about when you are using these novel therapies regarding immunization, potential pregnancy, any other

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drug interactions. If they are on other monoclonal therapies, if they are on any other monoclonal antibodies, the FcRn therapies will reduce the monoclonal antibody levels of different drugs.

Overall, these therapies are very effective in patients with myasthenia, and they're quite well tolerated. They're safe, and I think these therapies really give us an opportunity to reduce the symptom burden dramatically. I personally am trying to treat my patients aggressively to rapidly reduce their symptom burden, and these therapies really give us an option to achieve that.

Have a wonderful day.

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