Hello, my name is Vera Brill. I'm from the University of Toronto, the University Health Network. And this is a CME that is going to review the highlights, the research highlights, on myasthenia gravis, that were presented at the American Academy of Neurology meeting in 2023 this year. So my disclosures are shown on this next slide for your information.

What is myasthenia gravis? We might look at this quickly. It's one of a group of rare autoimmune diseases. The classical feature, or trademark, is fluctuating and intense weakness in specific muscles groups, such as the bulbar muscles, the limbs, and the ocular muscles. This disorder is often due to the presence of specific antibodies against acetylcholine receptors, these are AChR-Ab+ patients, and the most common initial presentation of myasthenia gravis is weakness of the ocular muscles. So far, we actually have four drugs approved by the FDA. We have eculizumab, efgartigimod, ravulizumab, and very recently, rozanolixizumab went from in development to approved by the FDA. And in development still is zilucoplan.

So the American Academy of Neurology meeting was held in Boston from April 22nd to 27th of this year, and there was a virtual part as well as in-person section of the meeting. And the abstracts that we will refer to have been published in the Journal of Neurology. We'll discuss the treatments approved, starting with efgartigimod. That is a neonatal Fc receptor inhibitor, or antagonist, and it is approved for the treatment of AChR-Ab+ generalized myasthenia gravis, so those who have the acetylcholine receptor antibodies. And the approval was based on the ADAPT study. This was a 26-week randomized placebo-controlled phase three trial evaluating efgartigimod in patients with generalized myasthenia gravis, contrasted with those treated with placebo.

And then, at the end of the ADAPT study that led to the approval of this drug for myasthenia gravis, 90% of the patients entered the ADAPT+ extension study. And the aim of the extension study was to evaluate the long-term safety and efficacy of efgartigimod. And you can see the antibody status was positive in 111 patients in the ADAPT+. The ADAPT study allowed enrollment of a subsection of patients who did not have the acetylcholine receptor antibody, and so were AChR-Ab-, and there were 34 of those who went into ADAPT+.

The most common adverse events that were noticed were headache in about a quarter, mostly mild to moderate, and concomitant COVID-19 infection, nasopharyngitis, diarrhea, and upper urinary tract infections. These side effects did not increase in frequency with repeated cycles, and across the patients, they looked at data from those who had been at least one year in open label therapy, the median number of cycles each year was five, because this is an on-demand treatment, meaning that you're treated with an IV infusion, and then you're retreated depending on when the effect wears off and you get worse again. The treatment cycle is an infusion once a week for four weeks.

The primary endpoint was the change in activities of daily living, MD-ADLs, from baseline, to the end of the first cycle, in AChR-Ab+ patients, and it was minus five. Patients had up to 14 further cycles. A more objective measure, the quantitative myasthenia gravis score, also changed, and also was measured at the end of cycle one in AChR-Ab+ positive patients, as minus 4.7. And patients had up to seven cycles depending on worsening of this. The change, reduction, in receptor totally was about 60%, and in AChR-Ab antibodies was 56%. So these results suggest that long-term efgartigimod treatment is well tolerated, and results in consistent and repeatable reductions in IgG antibody levels, and improves clinical outcomes in patients with generalized myasthenia gravis. So this just helps shore up the results of the 26-week double-blind placebo controlled study.

Then there was a cut done, looking at patients who'd had disease for less than three years, compared to those who had disease for more than six years, to see whether efgartigimod had effect in those with

longer duration disease. And you could see that the numbers tend to drop when you cut it like this, but the percentage of responders was 79% about in ADLs in the less than three years, compared to 24% on placebo. And the responders in those longer than six years with disease was 57% with efgartigimod, compared to 22% with placebo. And the percentage achieving minimal symptom expression was very similar in both those groups. So really, when you look at this, you can see that a greater percentage of those with disease last less than three years responded, but you still had a good response rate in patients with disease longer than six years. And the minimal symptom expression, that is an ADL of zero or one, achieved was similar in both groups.

Then there was a presentation of two cases of pembrolizumab-induced MG treated with efgartigimod. These are checkpoint inhibitors used in cancer patients. The first was a 68-year-old female with metastatic gall bladder cancer, who had the ocular and limb weakness starting one month after she got the drug. She has antibodies, acetylcholine and striated muscle antibodies, but no thymoma. The ptosis got a little better on prednisone. Some of the bulbar weakness and gait instability improved when she was put on prednisone, 60 milligrams a day. As it was tapered, her symptoms recurred at 30 milligrams a day, and she was given efgartigimod, and after the second infusion of a four-week cycle, she improved. She had to have a second cycle of efgartigimod because she still had persistent symptoms, but then her symptoms resolved mostly, although she was still on slowly tapering prednisone dose. And checkpoint inhibitor MG does not respond well to treatment, so this is very promising that she started to respond.

The second case was a 78-year-old female with metastatic urothelial carcinoma. She presented with bulbar leg weakness and myalgia, she had ocular and bulbar weakness after two doses. Her antibodies were negative. IVIg didn't really help her. She got respiratory failure after the second dose of pembrolizumab. She was given prednisone, up to 80 milligrams a day, and plasmapheresis. She improved so they could extubate her, but then she aspirated and had to be reintubated. She was given rituximab and more PLEX was started. She got thrombocytopenia and a GI bleed, PLEX was stopped after three cycles, and efgartigimod was started two days after the last PLEX, and she improved on this therapy. But then, she passed away unfortunately with urosepsis two days after the second dose. So there was a promising start to a response to efgartigimod in a very sick patient who then passed. But efgartigimod may be an option for checkpoint inhibitor-induced myasthenia gravis.

Eculizumab, we know this is a monoclonal antibody, a complement inhibitor, it targets complement protein C5. It is approved for patients with AChR-Ab+ generalized myasthenia gravis. It was tested in patients with refractory MG to begin with. Open label extension was done. And an interesting observation in the open label therapy is that some patients were able to discontinue concomitant therapies. So if you look at the patients who were starting on eculizumab, 94 of them, you can see how many concomitant therapies they were on. One third were not on any, but everybody else was on one, two, or three. And the concomitant treatments are shown there.

And after eculizumab treatment, it was found that a lot didn't change, but doses were reduced in a third, increased in a small number. And then, those 22% could stop azathioprine, and the percentages who could stop the other drugs are shown in the table at the right side. So about one quarter of patients with generalized myasthenia gravis, treated with eculizumab, were able to discontinue one or more concomitant therapies. And that's very exciting for patients, because they were doing well, and could come off some of their other drugs. And the hope with these newer therapies is that they will allow withdrawals of other therapies.

Ravulizumab is also a complement inhibitor, but it lasts longer, so can be given intravenously every eight weeks, instead of more frequently, like eculizumab. It is approved for patients with generalized myasthenia with AChR-Ab positivity. And the CHAMPION myasthenia gravis study results are shown here. It was a 26-week phase three randomized double-blind placebo controlled trial, demonstrating the

efficacy and safety of ravulizumab in patients with AChR-Ab+ generalized MG. Patients who completed the randomized study could then go into an open label extension, although they were kept blinded, as to their original treatment arm.

The aim of this study was to determine whether ravulizumab treatment lets patients with AChR-Ab+ positive generalized MG get to a post intervention status of improved, with or without getting to minimal manifestation status. So if you treat a patient and then they're improved, that would be a positive outcome here. Minimal manifestation status of ADLs of zero or one was not a requirement. So if you look at ravulizumab, you can see that the one quarter improved with MMS, minimal manifestations, and another 20% or so without, compared to the results in placebo. Interesting. Without minimal manifestations, 22% of placebo got better.

Those who continued ravulizumab at week 60, you can see how many improved and got to MMS, and those who didn't. And these are placebo who went into open label, and the numbers resemble those who continued ravulizumab. So during the double-blind study, it was apparent that ravulizumab-treated patients are more likely than those receiving placebo to get to a post intervention status of improved, with or without minimal manifestations. And the proportion of patients getting to PIS with continued treatment increases in the open label extension, suggesting that longer term treatment is needed for some patients.

And then, the timing of the first response to ravulizumab, how quickly do you respond in this study, and the first response was achieved by about half the patients after one infusion, and then, by week 12, by two thirds. A few patients do respond quite a bit later, so several months are necessary. The same is true with eculizumab. Most of the patients respond early, but there are some late responders. But this shows a very rapid response in the patients.

And then, another interesting question is, does it matter if you had IVIg use before or not in your response to ravulizumab? And this poster shows it does not. It was rescued during the double-blind study, but patients, quite a few of them, were on IVIg before they came into the study, and being pretreated or treated previously with IVIg did not influence response to ravulizumab in ADLs and QMGS score, as shown by this table.

The next drug that has been approved by the FDA recently for generalized myasthenia gravis is Rozanolixizumab. And this approval was based on a phase three study, which was a three arm study of rozanolixizumab seven milligrams per kilo, 10 milligrams per kilo, or placebo, given subcutaneously, once a week for six weeks. This is humanized IgG4 monoclonal antibody, also inhibits Fc receptors, and reduces immunoglobulins and the acetylcholine receptor. Interestingly, in this study, they also allowed recruitment of those who did not have antibodies to acetylcholine receptors. And rozanolixizumab showed greater reductions in the ADL score than placebo in a broad range of patients, the top line results are shown at the top. And then, you see those who had one prior therapy, two prior therapies, a lower baseline severity on QMGS, a higher baseline severity, lower disease duration, higher disease duration, so it was effective across all these subcategories. And also, you see then the adverse events at about 82% compared to 67% in placebo. So this was an effective treatment.

And then, if we look at change from baseline in ADL scores, the green line, and then the mean 43-day change here in QMGS, the red line is QMGS. So we can see that with cycles they maintain their improvement. A cycle is six weeks of therapy, and then there was a rest period of up to eight weeks, and then they could have another cycle if they developed worsening symptoms. So rozanolixizumab efficacy was maintained up to six week treatment cycles, across multiple specific outcomes, with an acceptable safety profile. Again, headaches and infections that were readily controlled, mainly with over-the-counter medications for the headaches. Nobody had to withdraw from this study because of any of the adverse events that were studied. Interesting, rozanolixizumab also showed efficacy in muscle specific

kinase, or MuSK-positive, myasthenia gravis patients, and the approval from the FDA is for acetylcholine receptor positive and MuSK-positive patients. And this is the first Fc receptor inhibitor approved for both those categories.

Zilucoplan is another complement inhibitor that inhibits C5, and complement inhibitors reduce formation of the membrane attack complex resulting from the complement cascade, and therefore reduces destruction of the postsynaptic membrane. And this was to look at the benefits of zilucoplan in different subpopulations within the study, those who had less severe disease, an ADL less than nine, an ADL greater than 10, baseline QMG less than 17, greater or equal to 18, and then duration of disease less than five years or more than five years. And we can see separation of the placebo group from the zilucoplan group with this daily subcutaneous therapy that showed benefit, regardless of disease severity or duration.

What other research can we talk about? Well, an interesting presentation looked at the incidence and prevalence of myasthenia gravis in the United States using a claims-based analysis. Interestingly, the numbers are higher than the historical information that we had, and this is important because, as we're developing new treatments, we should be able to identify and know how many of our people are affected by this disease. And you can see here the prevalence rate that goes up quite a bit with age, and the incidence, number of new cases per 100,000 per year. So these are rather high numbers and higher than they were overall, so that's an important bit of information.

And then, what about autoantibody profiles in seronegative myasthenia gravis? Seronegative myasthenia gravis are those patients who don't have the acetylcholine receptor antibodies and don't have MuSK antibodies by regular testing. And what this study shows is that if you use cell-based assays for acetylcholine receptor antibodies or MuSK positive antibodies, you identify more patients as having antibodies. These patients have antibodies that have weaker affinity, but it is important to identify them because it is most likely that if you wish to get reimbursement for the novel therapies, you're going to have to show the presence of antibodies. So at least 10% of myasthenia gravis patients, 10% to 15%, don't have detectable antibodies. But then, you can detect antibodies in a certain number of these doing cell-based assays. So you have to know what your lab does and where to send it in order to get proper testing.

What about pregnancy in myasthenia gravis patients? This study aimed to look at the status of having antibodies on pregnancy and neonatal outcomes. Interestingly, patients who were antibody-negative had a higher risk of ICU admission, had a higher risk of intubation, had a higher risk of C-section, had a higher risk of neonatal myasthenia gravis, which is explained by the transfer of antibodies that cross the placental membrane, so something was being transferred in these mothers. And unplanned pregnancy in three quarters. So this is really the first report of the association between a negative serological status and a poor pregnancy outcome, and really is important for future preconception counseling and pregnancy monitoring. A very startling result.

And then, there is an international electronic database that has been launched for myasthenia gravis. This is an observational database that's international for MG patients. This was based on the MS registry, which was very good. And there are estimated to be more than 80,000 myasthenia gravis patients. And so, in collaboration with MSBase Foundation, this has been developed, and it will use existing IT infrastructure, data security, privacy compliance, governance structures, of that registry. And this launched, the MGBase launched, in December, 2021. So there will be a lot of information coming out of this.

So what have we learned about myasthenia gravis from the AAN this year? First, long-term treatment with the Fc receptor, efgartigimod, is well tolerated, and with this agent, earlier treatment leads to a better response. About one quarter of the patients with generalized MG, treated with long-term

eculizumab, could discontinue one or more of their concomitant medications, lessening the therapeutic burden on patients. Ravulizumab-treated patients are more likely than those on placebo to have an improved status, with or without minimal manifestations. The first response to ravulizumab was achieved after a single infusion in about half the patients, and then in two thirds of the patients by week 12. Interestingly, previous IVIg treatment did not influence the response to ravulizumab. Rozanolixizumab treatment showed greater reductions in ADL scores and placebo in a broad range of patients with generalized MG, with less and more severe disease and with different durations, and efficacy was maintained over six cycles, each of six weeks, over six cycles of treatment.

Daily zilucoplan showed consistent improvements in MG specific efficacy outcomes, regardless of disease severity or duration. The incidence and prevalence of MG in the US are higher than prior estimates have shown, and this diagnosis needs to be kept in mind. There's a clinical need to implement clustered acetylcholine receptor cell-based assay testing when evaluating seronegative MG patients. An MGBase and international electronic database for MG was launched in December, 2021, so we can get a better understanding of the current status of MG today. Thank you.