PERSPECTIVES ON SELECTED MYASTHENIA GRAVIS POSTERS AND ABSTRACTS FROM AMERICAN ASSOCIATION OF NEUROMUSCULAR AND ELECTRODIAGNOSTIC MEDICINE (AANEM)

Editor's Note: This is a transcript of an online course released in November 2024.
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Introduction

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Myasthenia gravis is an autoimmune disease that causes dysfunction at the neuromuscular junction. The fluctuating muscle weakness associated with this disease greatly impacts patients' activities of daily living. Historically, acetylcholinesterase inhibitors have been used as initial treatment to counter the pathophysiologic changes associated with myasthenia gravis. While available in different formulations, the use of acetylcholinesterase inhibitors is constrained by its limited efficacy as demonstrated by validated outcome measures. In addition, frequent patient administration is required, which may impact treatment adherence.

General immunosuppression, including corticosteroids, tacrolimus, cyclosporine, mycophenolate, azathioprine, among others, are almost always used if symptoms persist on acetylcholinesterase inhibitor therapy. These general immunosuppressants do not address the underlying disease mechanism and are associated with a variety of adverse events and potential for secondary infections. Consequently, the risk vs benefit must be carefully considered when using these agents.

In cases of severe exacerbation or crisis, intravenous immunoglobulin (IVIg) and/or plasma exchange can be used for acute symptom control. Oftentimes, patients require inpatient hospitalization for administration of divided doses, such as in the case of IVIg, or multiple sessions, such as in the case of plasma exchange. While efficacious in most patients, maximal response may not occur until days or weeks after completion of therapy.

The limitations of available therapies with respect to safety, efficacy, and frequency of administration add to the burden of disease experienced by patients with myasthenia gravis and indicate a need for improved therapies. Among more than 300 studies presented at the 2024 American Association of Neuromuscular & Electrodiagnostic Medicine Annual Meeting in Savannah, Georgia, 4 studies related to treatment options intended to address the disease burden experienced by patients with myasthenia gravis are discussed in this CE activity.

Cyclic and Every-Other-Week Dosing of Intravenous Efgartigimod for Generalized Myasthenia Gravis: Part A of ADAPT NXT

Study results presented by Dr. Ali Habib and colleagues at the 2024 American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) Annual Meeting

Analysis by Nicholas Silvestri, MD: In summary, similar clinically meaningful improvements were observed in MG Activities of Daily Living or MG-ADL score at week 21 in patients with generalized myasthenia gravis receiving either fixed cyclic dosing or Q2W dosing of efgartigimod. Minimal symptom expression was achieved in nearly half of participants in each efgartigimod treatment group. This is an important study because similar improvements in quality of life were observed with 2 differing efgartigimod regimens in patients with generalized myasthenia gravis, and this study provides patients and clinicians with increased flexibility in additional dosing approaches.

Let me discuss the methods of this trial. This was a phase 3b study investigating the efficacy, safety and tolerability of efgartigimod administered either every other week or in fixed cycle dosing regimens in patients with generalized myasthenia gravis. The fixed cycle arm received 4 once-weekly efgartigimod infusions with 4 weeks between cycles. Efgartigimod was dosed at 10 mg/kg for a 21-week period and the primary endpoint evaluated the change in Myasthenia Gravis Activities of Daily Living (MG-ADL) score from baseline to week 21.

The key findings were that a total of 69 patients were treated; fixed cyclic dosing in 17 patients and every-other-week dosing or Q2W in 52 patients. Least squares mean of the change from baseline in MG-ADL to week 21 was -5.1 in the fixed cyclic arm and -4.6 in the Q2W arm. The changes were similar in both treatment groups throughout the study period duration. The clinically meaningful improvements in mean standard error of the MG-ADL total scores were observed as early as week 1 and maintained over time in both treatment arms. Minimal symptom expression, which is defined as an MG-ADL score of 0 or 1, was achieved in 47.1% of patients in fixed cyclic regimen and 44.2% of patients in the Q2W arm. Treatment was well tolerated; COVID-19, upper respiratory tract infection and headache were the most common treatment-emergent adverse events.

Here are my thoughts and analysis of this study. I think this is a very important study because it further adds to the evidence that doses of efgartigimod can be given flexibly, based on patient response to treatment. In fact, in the clinical world, there are patients that might benefit from every-other-week dosing due to slight return of symptoms towards the end of an off period of a cycle and the "4 on, 4 off" method. My hope is that this evidence will allow for more flexible dosing to be approved by payors as the optimal dosing of efgartigimod in general remains an unanswered question and is likely different from patient to patient.

Concomitant Corticosteroid Use With Ravulizumab in Adults With Anti-Acetylcholine Receptor Antibody-Positive Generalized Myasthenia Gravis: Phase 3 CHAMPION-MG Open-Label Extension Final Results

Study results presented by Dr. Michael Nicolle and colleagues at the 2024 AANEM Annual Meeting

Analysis by Nicholas Silvestri, MD: This study demonstrated decreased corticosteroid use over 4 years in patients with generalized myasthenia gravis who were acetylcholine receptor antibody-positive and treated with ravulizumab. And this is an important study because while corticosteroid therapy may be used for additional symptom control in patients with generalized myasthenia gravis who are acetylcholine receptor antibody-positive, prolonged therapy is associated with undesirable side effects. This study demonstrates a potential for corticosteroid dose-sparing treatment approach with the use of ravulizumab.

Let me discuss the methods of this study. The CHAMPION-MG trial was a 26-week, double-blind, randomized, placebo-controlled trial of ravulizumab. Patients were treated concomitantly with corticosteroids but could not have their dose of corticosteroids adjusted during the 26-week period. This study reports the results of the open-label extension, which started at week 26. At week 26, patients could receive ravulizumab with permitted corticosteroid adjustments at the physician's discretion and corticosteroid use was assessed at each study visit.

If ravulizumab was initiated at week 26, dosing was either by blind induction or bridging, followed by a dose of either 3,000 or 3,600 mg according to body weight at week 28 and every 8 weeks thereafter. The study duration was 4 years in length.

The key findings of this study and the data that were available for 161 patients enrolled in the open-label extension and received ravulizumab for up to 164 weeks. A total of 113 patients were receiving corticosteroids during the open-label extension period. At the start of the open-label extension, 58% of patients were treated with more than 10 mg/ day of corticosteroids. At the last reported dose, 37% of patients were treated with more than 10 mg/day of corticosteroids.

Over the course of the open-label extension, the percent of patients who received corticosteroids at less than or equal to 10 mg/day rose from 42% to 63%. Fourteen or 12% of patients discontinued corticosteroids by the last visit. The mean corticosteroid dosage per patient decreased from 17.5 mg/day at the first open-label extension dose to 11.7 mg/day at the last assessment.

And here are my thoughts and the analysis of this study. I think this is an incredibly important study as it demonstrates the steroid-sparing effect of ravulizumab in patients with myasthenia gravis. We are all well aware of the myriad side effects of steroids, and it's imperative that we aim to get our patients off of these medications as quickly as possible by using other agents. It's very encouraging that ravulizumab has a relatively fast onset of action, which should allow us to be able to taper steroids quickly after initiating treatment with this medication. The main unanswered question that remains is when steroid tapering can begin and how fast it can be done, although this likely varies from patient to patient.

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Efficacy and Safety of Nipocalimab in Patients With Generalized Myasthenia Gravis: Topline Results From the Double-Blind, Placebo-Controlled, Randomized Phase 3 VIVACITY-MG3 Study

Study results presented by Dr. Tuan Vu and colleagues at the 2024 AANEM Annual Meeting

Analysis by Nicholas Silvestri, MD: In summary, a clinically and statistically significant improvement was observed in the Myasthenia Gravis Activities of Daily Living score at week 24 in patients with generalized myasthenia gravis treated with nipocalimab compared to placebo. Nipocalimab was well tolerated and comparable, in adverse events, to placebo. This is an important study because nipocalimab was well tolerated and demonstrated significant improvements in the quality of life of patients with generalized myasthenia gravis inadequately controlled on standard-of-care therapy. This study provides patients and clinicians seeking additional symptom control with an additional treatment approach.

Let me describe the study. In terms of methods, this was a phase 3 study investigating the efficacy and safety of nipocalimab over 24 weeks. It included patients who were seropositive, and those were either anti-acetylcholine receptor antibody, muscle-specific tyrosine kinase (MuSK) antibody, lipoprotein-related protein 4 (LRP4) antibody-positive, as well as seronegative patients, all of whom were Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV and inadequately controlled on standard-of-care therapy. Patients were then randomized to 1:1 to nipocalimab plus standard-of-care vs placebo and standard-of-care, very similar to other trials that have recently been performed. The primary endpoint evaluated the mean change in MG-ADL score from baseline over weeks 22, 23 and 24 in seropositive patients. And secondary endpoints included the change in the quantitative myasthenia gravis score or the QMG.

In key findings, of the 199 patients enrolled, 153 were positive for acetylcholine receptor, MuSK or LRP4 antibodies. Nipocalimab demonstrated statistically significant improvement in clinical efficacy with a mean change in MG-ADL score from baseline to weeks 22 to 24 of -4.70 compared to -3.25 with placebo and this was statistically significant. In addition, a statistically significant improvement was observed in the mean change in quantitative MG score with a decrease of 4.86 with nipocalimab compared to a decrease of 2.05 with the placebo, again also statistically significant. In general, nipocalimab was well tolerated with adverse effects comparable to placebo.

In terms of my thoughts, this study demonstrates the effectiveness of yet another neonatal Fc receptor (FcRn) antagonist that we can add to our treatment armamentarium for MG. The efficacy and safety of this medication are similar to those on the market, although the dosing is a bit different. This is an important study because, if approved, it provides us with another option to offer our patients who may choose one FcRn antagonist over the other for various reasons, including perceived convenience, route of administration and frequency of dosing. The remaining, and provocative, unanswered question is, which FcRn antagonist is truly superior in treatment of MG or if it varies from patient to patient for as yet unclear reasons?

Long-Term Safety and Efficacy of Zilucoplan in Generalized Myasthenia Gravis: 120-Week Interim Analysis of RAISE-XT

Study results presented by Dr. James Howard, Jr. and colleagues at the 2024 AANEM Annual Meeting

Analysis by Nicholas Silvestri, MD: In summary, this ongoing, phase 3, open-label extension study demonstrated a 97% incidence of treatment-emergent adverse events in patients receiving daily subcutaneous injections of zilucoplan. By week 120, patients receiving zilucoplan observed a mean reduction in the MG-ADL score of 7.14. And this is important because this study demonstrates the long-term safety and efficacy of zilucoplan, the first once-daily subcutaneous regimen. These results expanded upon the available treatment options with favorable self-administration profile.

Let me describe the methods here. This was an ongoing open-label extension study of the phase 3 RAISE-XT study to provide further evaluation of the long-term safety and efficacy of zilucoplan in patients with acetylcholine receptor antibody-positive generalized myasthenia gravis. Patients self-administered subcutaneous zilucoplan at a dose of 0.3

mg/kg per day. The primary outcome was the incidence of treatment-emergent adverse events. The change in MG-ADL score from baseline to week 20 was also analyzed for patients receiving zilucoplan 0.3 mg/kg or placebo in qualifying studies.

In terms of key findings, a total of 200 patients enrolled in RAISE-XT with a median exposure to zilucoplan of 2.2 years, with a range of 0.1 to 5.6 years. At the start of the open-label extension, 93 subjects continued zilucoplan and 90 switched from placebo to zilucoplan. A treatment-emergent adverse event was observed in 97% of patients and a serious treatment-emergent adverse event occurred in 40.5% of patients. And the common treatment-emergent adverse events included COVID-19 infection in 35.5% of patients and worsening of myasthenia gravis in 29.5% of patients. At week 120, the mean reduction from baseline in MG-ADL score among zilucoplan patients, again, was 7.14.

While we are very fortunate to have a number of new agents available to treat myasthenia gravis, the long-term safety of some of the newer mechanisms of action, including FcRn antagonists and complement inhibitors, remains unknown. This particular study is important because it adds to the growing evidence of the safety of complement inhibitors in the treatment of generalized myasthenia gravis. The remaining unanswered question is to what does safety look like for these agents at the 10-, 15- or 20-year mark or beyond, and really only time will tell.

Wrap Up

Well, I hope you enjoyed the review of these abstracts from the recent AANEM Annual Meeting in Savannah. As you can tell from these posters, as well as many more that were presented, not only this year but in the last several years, it's become quite an exciting time in the treatment of patients with myasthenia gravis. We've had 5 medications approved to treat myasthenia gravis since 2017, those being eculizumab, ravulizumab, efgartigimod, rozanolixizumab, and zilucoplan, and there are many more in the pipeline. So, I think that, as exciting as this year's meeting was, and as exciting as it has been to really use these agents in practice, and see their clinical benefit that they can offer our patients, there's much more to stay tuned for in future meetings. Again, of the many presentations at this meeting, not only those that I presented, there are not only other agents with similar mechanisms of action in development, but completely new agents with different mechanisms of action in the pipeline for our patients with MG. So, there's reason to be hopeful. I think that we'll see a very different treatment paradigm for MG in the next few years going forward and I think this is really great because it's really all for the benefit of our patients. It's improved efficacy, probably improved safety, and probably improved tolerability, compared to conventionally-used agents. And so, the hope that we can realize the dream of being able to treat patients so they have minimal symptoms or preferably no symptoms of MG, but not at the expense of safety is, I think going to be, it's already here, and I think it's just going to expand. So, exciting times, and stay tuned for future presentations.