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Duchenne Muscular Dystrophy: Differentiating Advances in Treatment

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Dr. Hamid:
This is CME on ReachMD and I'm Dr. Omer Abdul Hamid. Today, doctors Nancy Kuntz and Migvis Monduy and I will be focusing on the unmet needs of the current standard of care with prednisone or deflazacort in Duchenne muscular dystrophy, or DMD. Specifically, we will be discussing the emergence of a novel corticosteroid indicated for the treatment of patients with DMD.

Welcome Dr. Kuntz and Dr. Monduy.

Dr. Kuntz:
Wonderful to be here today with you. Hi.

Dr. Monduy:
Thank you for having me.

Dr. Hamid:
Thank you for coming.

Dr. Monduy:
Dr. Hamid, phase 2B data from the Guglieri study demonstrated the efficacy and safety of vamorolone, a novel corticosteroid in the treatment of boys with Duchenne muscular dystrophy. Can you please interpret those data for our learners and tell us why they're important?

Dr. Hamid:
Yes, I'd love to. So, the findings from the phase 2B of Guglieri and his colleagues included its primary, secondary, exploratory, clinical safety, and biomarker endpoints, which we will review. In the study, there were 133 boys with DMD enrolled with a mean age of 5.4 years, and 121 of them were randomly assigned to treatment groups, and 114 completed the total 24-week treatment period. There were several different dosing strategies; a placebo dose, the standard set 0.75 mg/kg per day dose of prednisone, and then two dosing strategies for vamorolone, a 2 mg/kg per day dosing strategy and a 6 mg/kg per day dosing strategy.

The key findings from the trial included that the primary endpoint was met, which was a change from baseline to week 24 time to stand velocity for vamorolone at the 6 mg/kg dosing. And this was statistically significant compared to placebo. The trial met the first 4 sequential secondary endpoints, the time to stand velocity of a vamorolone at 2 mg/kg per day versus placebo, a 6-minute walk test at both 6 mg/kg per day and 2 mg/kg per day dosing, and the time to walk or run 10-meter velocity at the 6 mg/kg per day dosing of vamorolone, and which was statistically significant when compared to placebo.

In addition, clinical safety and biomarker endpoints were also assessed. The height percentile declined in prednisone treated patients, whereas in vamorolone patients, it did not. Bone turnover markers declined with prednisone, but not with vamorolone, which was statistically significant. These bone turnover markers were osteocalcin, P1NP, and CTX-1.

When reporting treatment emergent adverse events, there were 79.3% of patients in the placebo group reporting a treatment emergent adverse event – at least one – 83.9% in the prednisone group, and 83.3% in the vamorolone-treated group.

Now, I would like to ask Dr. Nancy Kuntz about the findings and how are these relevant to the unmet needs of patients with DMD?

Dr. Kuntz:
Well, it's clear that the overall numbers and percentages of adverse events was not really different in any of the treatment groups in a setting where the boys who received vamorolone compared to placebo had the clear and statistically significant effectiveness of the treatment. If you look at very specific things like slowing of linear growth and increased turnover of bone minerals there was an important and statistically decreased occurrence in the vamorolone group, and that's very impressive.

Dr. Hamid:
Dr. Monduy?

Dr. Monduy:
Yes, I think it's very exciting to see this data and, looking at the efficacy, how it compares to prednisone and with better side effect profile in terms of the linear growth and the decreased bone turnover markers.

Dr. Hamid:
Dr. Kuntz, would you like to ask the second question?

Dr. Kuntz:
Sure. There was a meta-analysis subsequently done by Elhalag and his colleagues that really validated and extended the vamorolone phase 2b study that we just discussed led by Guglieri. This new meta-analysis included studies by collaborative groups led by Eric Hoffman, Edward Smith, Jean Mah, as well as the one by Michela Guglieri.

Dr. Monduy, could you discuss this meta-analysis and highlight any additional information it provides?

Dr. Monduy:
Of course. So, this meta-analysis included patients on vamorolone, patients on placebo, and patients on glucocorticoids. And if we look at the data that they concluded from their pooled analysis in terms of efficacy, when we compare vamorolone to placebo there was a statistically significant difference in terms of improvement with increased time to stand velocity, time to run/walk the 10-meter velocity, and time to climb 4-stair velocity in the vamorolone-treated patients, as compared to placebo. When we compare it to prednisone, there was a statistically significant association between the vamorolone group and increased time to run/walk 10 meters velocity compared with the glucocorticoid group, but no difference in time to climb or time to stand velocities. And then, looking at safety profile, there was a statistically significant association between the vamorolone group and increased high percentile for age compared with the glucocorticoid group. But there was no statistically significant difference between vamorolone and glucocorticoids in terms of BMI or weight.

Dr. Hamid, what is your perspective on this?

Dr. Hamid:
I think this sheds some important light on the efficacy and safety of vamorolone.

Dr. Monduy:
Dr. Kuntz?

Dr. Kuntz:
This increases our confidence that the safety profile of the early studies which were very, very positive continue to be positive. It gives us options for something that is safe and equally effective, or better in some circumstances, which has fewer side effects, is a clear improvement.

Dr. Hamid:
For those just tuning in, we're listening to CME on ReachMD. I'm Dr. Omer Abdul Hamid and I'm here today with Dr. Migvis Monduy and Nancy Kuntz. Our focus of today's talk is the emergence of a novel cortical steroid for the management of patients with Duchenne muscular dystrophy, or DMD.

Dr. Hamid:
Now, let's go through a case. Dr. Kuntz, in this example you have a patient, Tim, who is 7 years old and was diagnosed with DMD at age 5. He has been on prednisone since his original diagnosis. Now, at age 5, his height was 42 inches and within the 50th percentile, but by age 7, his height is 46 inches and is within the 10th percentile.

His BMI also increased over the last 2 years from the 50th percentile to the 75th. Tim's time to run/walk velocity has also deteriorated over the intervening 2 years. How might you approach the decision to switch from prednisone to another agent?

Dr. Kuntz:
He has excess weight gain and slowing of his linear growth from 50th down to 10th percentile. He's also experiencing some motor declines which are not uncommon at his age. Beyond the age of 6 we begin to see the peak and then a decline in the motor outcomes for boys with Duchenne. But here I think that we have an option and I would consider switching to vamorolone to promote normal linear growth while still providing the anti-inflammatory benefit to the muscle. And because he's 7 years old and is already beginning to show some slowing of his motor skills I would suggest beginning the vamorolone at 6 mg/kg per day to try to give him a robust response. We did see it in the studies, some dose-related differences between the 2 mg/kg per day and 6 mg/kg per day doses of vamorolone, so I would begin here wanting some good impact on this boy with the motor decline at the 6 mg/kg per day dose and observe.

His exact weight was not mentioned, just his BMI, but at this age and height and BMI, he's probably somewhere between 25 and 30 kilograms, and so at 6 mg/kg per day, his daily dose would be somewhere between 150 and 180 mg of vamorolone. That does increase on a per kilo basis up to 50 kilos because the maximum recommended dose of vamorolone per day is capped at 300 milligrams for anybody 50 kilos or heavier. And then I would observe and see how he does. If weight gain remains a problem, or there any other unanticipated side effects, I would consider down-titrating to 4 mg/kg per day, or if needed, lower to 2 mg/kg per day.

Dr. Monduy:
So, I agree that switching to vamorolone is a good option, so that we don't have to compromise by having to decrease the dose of the glucocorticoid because the patient's already having decreased linear growth, and then compromising efficacy. So, switching to vamorolone is a good alternative.

Dr. Hamid:
It seems to me like patients that have side effects from other corticosteroids might be good candidates for this medicine, as well as patients that may have had an inadequate response from what we deemed necessary from corticosteroids.

Now let's address some of the key aspects of our discussion today. Dr. Monduy, I'll start off with you.

Dr. Monduy:
In their conclusion, Elhalag and colleagues stated that, "Our analysis results reveal that vamorolone treatment was associated with improvements in some motor outcomes like time to run/walk velocity and increased height percentile for age compared with the glucocorticoid group. Our analysis suggests that vamorolone can be used in the treatment of patients with DMD, as it is more effective and safer than corticosteroids."

So, I would like to know your perspectives overall and thoughts on this suggestion.

Dr. Kuntz:
The structure, as we know, of vamorolone is novel, and it lacks the 11-beta hydroxy moiety within the molecule that changes it's impact on the 11-beta hydroxysteroid dehydrogenase enzymes, and it makes it an antagonist rather than an agonist of mineralocorticoids. And I think some of that's going to relate to some of these side effects, and we had pointed out the decrease in bone turnover. But continued observation to see how that impacts the health of the bones, the mineralization, the rate of vertebral fractures, and even side effects in terms of fluid retention and hypertension and ultimate contribution toward cardiac outcomes.

Dr. Hamid:
I agree with everybdoy. It seems like we have another agent here that is as efficacious, if not more efficacious, and with less side effects.

That's all the time we have today, so I wanted to thank our audience for listening and thank you to Drs. Migvis Monduy and Nancy Kuntz for joining me and sharing your insights. It was great speaking with the both of you today. Thank you again.

Dr. Monduy:
Thank you. Thank you both.

Dr. Kuntz:

It was a pleasure. Thank you, goodbye.

Announcer:
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