Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/the-future-of-muscular-dystrophy-management-updates-for-duchenne-muscular-dystrophy/15317/

Released: 06/16/2023
Valid until: 06/16/2024
Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Future of Muscular Dystrophy Management: Updates for Duchenne Muscular Dystrophy

Announcer:
Welcome to CME on ReachMD. This activity, titled “The Future of Muscular Dystrophy Management: Updates for Duchenne Muscular Dystrophy” is brought to you by The France Foundation and is supported by an educational grant from Sarepta Therapeutics, Inc.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Cheeley:
Duchenne muscular dystrophy, or DMD, is considered a rare disease affecting 1 in 3,500 male births, but to the patients afflicted and to the families who love them, it's a painful, everyday experience. However, current advances in gene therapy are exciting. Helping clinicians interpret and utilize the outcomes of gene therapy clinical trials is critical to effective treatment and management of DMD, as is the coordination of multidisciplinary teams for the ongoing care of these patients.

I'm Dr. Mary Katherine Cheeley, and welcome to this episode titled: The Future of Muscular Dystrophy Management: Updates for Duchenne Muscular Dystrophy. I'd like to welcome my guests, Dr. Julie Parsons and Dr. Craig Zaidman, who will be sharing their insights on this disease. Dr. Parsons is a Pediatric Neurologist and the Co-Director of the Neuromuscular Clinic at the Children's Hospital in Aurora, Colorado. She holds the Haberfield Family Endowed Chair in Pediatric Neuromuscular Disorders, and is a Professor of Clinical Pediatrics and Neurology. Dr. Parsons, it's great to have you with us.

Dr. Parsons:
And I'm happy to be here. Thank you.

Dr. Cheeley:
Dr. Zaidman is a Pediatric Neurologist and a Professor of Neurology and Pediatrics at Washington University School of Medicine in St. Louis, Missouri. Dr. Zaidman, welcome to the program.

Dr. Zaidman:
Hi, thanks for having me.

Dr. Cheeley:
So let's dive right in By discussing the importance of earlier diagnosis of DMD. Dr. Parsons, how would you suspect a boy might have DMD?

Dr. Parsons:
So boys with Duchenne dystrophy come to us in a variety of different ways. Typically, a primary care provider will see a little boy because maybe they're a little bit more clumsy than parents would anticipate, they don't keep up when they're running, they're having a little trouble getting upstairs. Maybe they're toe walkers. Sometimes the boys come in because they have cognitive or learning delays. And actually, interestingly, we've had patients that have come in from gastroenterologists because a patient will come in with a little, medical issue or infection, they have routine laboratory studies done and they have elevated transaminases without evidence of liver

disease. So patients are sent to the gastroenterologist. And some of the kids have actually had liver biopsies. There's nothing wrong with their liver, but it's really that they have an elevation in their CK. So we've had boys referred that way.

Physical therapists will oftentimes refer the patients as well. Primary care providers in the past have referred kids with developmental delays to get a little bit of physical therapy to see if it helps, and then to see them back. And, so we've had referrals that way as well.

On physical exam for these boys, even early on, there usually is a head lag that persists, it's a little bit unusual. Also, the boys may have firm calves and firm forearms, and sometimes have a tongue that's a little bit large. So sometimes you can find some physical exam findings even on the younger boys.

So if a boy has a delay, it's fine to have a boy see the physical therapist, but a creatine kinase should be ordered. And the mantra if there's a delay, do a CK, should be tucked into the back of your head. So that if there's a boy who comes in with a gross motor delay or cognitive delay, doing a creatine kinase is cheap, it's quick. And if there's an elevation to 8,000, to 20,000, there's hardly any other diagnosis that will come to mind besides Duchenne dystrophy in these guys. So those patients should be referred to a neuromuscular center for genetic confirmation of their diagnosis.

The genetic testing is relatively easily available now. There are entities that do the genetic testing for free, the turnaround time is quick, and the genotype becomes very important in terms of how we treat these boys and what treatments we are able to offer them. So genotyping all of our boys is really important.

40 years ago, when I started, we did muscle biopsies and electrical studies on the kids. We don't need to do those anymore; we can really make a very firm definitive diagnosis just by doing genetic testing. We also think about, well, if we do genetic testing, is newborn screening around the corner? And as right now, there are no newborn screening programs that are established in the states outside of New York City, and there's a pilot program in North Carolina, but we don't have broad newborn screening for Duchenne dystrophy at this moment in time, although potentially that's something that we'll see in the future.

So thinking about the diagnosis, getting a CK, and then making an appropriate prompt referral to a neuromuscular center I think is my recommendation of the way to go.

Dr. Cheeley:
Now turning to you Dr. Zaidman, can you share with our listeners how your clinical trial experience and the evidence that comes from those trials applies to real-world patient management scenarios?

Dr. Zaidman:
Sure, I'd be happy to do that. Probably what you're alluding to is the excitement regarding some of the newer therapies in Duchenne muscular dystrophy. You know, in the last few years we've had really a relative explosion, I guess you could say, because of the antisense oligonucleotides, which are available for patients with Duchenne who have specific genetic mutations that are amenable to that. And then most recently, the excitement regarding gene transfer therapies, including shortened versions of shortened versions of dystrophin, or what we call micro-dystrophin, which is administered through a harmless virus in order to help the muscle produce a version of the protein that it's currently missing.

Regarding the clinical trial experience with gene transfer therapy, one important thing to note is that unlike the ASOs, or the antisense oligonucleotides, which are weekly intravenous infusions, these gene transfer therapies, it's a one-time intravenous infusion. And once it's given, it’s in you; it can't be removed. It requires weekly laboratory monitoring and changes to the baseline dosing of steroids.

The experience thus far has been, I think, favorable based on the available clinical trial data. The gene transfer therapy products are usually well tolerated, they often cause nausea. There have been some serious side effects, including concerns about toxicity to the heart or inflammation or myocarditis in the heart. There has been concern in some cases of boys developing antibody responses in the muscle or what we call immune-mediated myositis.

In terms of the efficacy or the benefit of the gene transfer therapy, I think it's looking favorable, but there's limited data available. The comparison of the boys in the open label trial, and here we're talking about ambulatory boys, primarily ages 4 through 8, at least in the Sarepta product, are that they show improvement on their North Star Ambulatory Assessment by about 2 to 3 points. And that's compared to a historical cohort of untreated boys with Duchenne muscular dystrophy, untreated with the gene transfer therapy, I should say, those boys in the control cohort were on steroids.

And similar results have been reported through other pharmaceutical products. There's one from Pfizer, for instance, that I'm thinking of. And that's been administered to boys ages 4 through 12.

So I think that the preliminary or early data is favorable. But there are ongoing studies, including placebo-controlled studies to better

understand the impact of these medications. And it's going to take some time to determine who the optimal candidate for these medications are, in terms of age and functional status.

Dr. Cheeley:
For those just joining us, this is CME on ReachMD. I'm Dr. Mary Katherine Cheeley, and joining me to talk about the latest developments related to screening, diagnosis, and patient monitoring, and gene therapy of patients with DMD are Dr. Zaidman and Dr. Parsons.

Let's jump back to you, Dr. Parsons, what unmet needs might be addressed with gene therapy in relation to our currently approved treatment for patients with DMD?

Dr. Parsons:
So right now, at the present time, our standard of care is using steroid medication, which is a symptomatic type treatment for dystrophy. Of course, there are all kinds of side effects that are associated with chronic use of steroids that are unpleasant, although the use of steroids certainly has helped our guys to retain strength a little bit longer and to be ambulatory for a longer period of time.

More recently, as Dr. Zaidman said, there are some other treatments that are genotype specific for patients that include exon skipping agents. Those agents are administered via I.V. on a weekly basis. So it takes a fair amount of time and is a fair amount of commitment to being treated with these agents. And there are four currently that have been approved. This is certainly another line of treatment.

With the gene transfer therapy, the idea would be that you actually would be able to substitute that little mini dystrophin that is missing in these patients to try to help stabilize the dystrophin protein and to mitigate some of the symptoms of Duchenne dystrophy. There is some thought, although the gene transfer product is specific for certain tissues, that because Duchenne dystrophy also affects other organ systems, for instance, cognitive, there's cognitive issues with these guys as well as cardiac, muscle weakness, and cardiomyopathies that develop over time, that maybe if we had a gene transfer product, that we would be able to target more organs than just the muscle.

I think, Dr. Zaidman, in the trials that you were involved with, are all kids with dystrophy eligible for gene transfer?

Dr. Zaidman:
No. So the candidacy for our current therapeutics, as you mentioned, Julie, are those ASO therapies, you do have to have a particular genotype in order to be a candidate. For the gene transfer therapy, of course, those types of medications are still in clinical trials, but the candidacy for those clinical trials includes several unique features. One feature is that a patient has to undergo antibody testing to see if that person makes antibodies against the viral vector. If the person makes antibodies against the viral vector, then if this product were administered, they are more likely to destroy it and potentially could have some consequences of that immune response.

In addition, to my knowledge, there are genetic candidacy requirements also for these categories of micro-dystrophin gene transfer therapy. And that is to avoid or minimize the possibility that a patient who's now making this new micro-dystrophin protein will not generate an antibody response against the protein.

So those are the two main inclusion criteria from a lab point of view. Of course, each clinical trial also has had its own inclusion criteria regarding age and level of function. There have been boys as young as 3 and into the teenage years that have been dosed with a gene transfer product for mini or micro-dystrophin, of the majority of the boys on whom the outcomes have been compared are ambulatory boys, usually between 4 and 8, or 4 and 12. And that's been where the primary focus has been in terms of the outcomes assessment of these clinical trials so far.

Dr. Parsons:
So if we do have one of these gene transfer products that happens to be approved, it's not necessarily a blanket treatment for all boys with Duchenne dystrophy, is that correct?

Dr. Zaidman:
Absolutely. Each child has to be individually determined both based on their level of function, probably their age, and also their genotype and their laboratory findings at baseline. I'll mention also that gene transfer therapy is not a one and done. When you receive this therapy, it follows that there is quite intensive safety and laboratory monitoring required, there are additional steroids that need to be given during the weeks that immediately follow the gene transfer therapy. And having a close relationship with your treating physician and a deep understanding of the risks and benefits to this type of medication is really important. You know, once you give a gene transfer therapy to a person, you can't take it back again. This is not the sort of drug that can be start and stopped.

So assessing candidacy and having a good discussion about the risks and benefits of these types of medications is a real critical part of the therapeutic plan.

Dr. Cheeley:
So it sounds like there's so many different steps in this process. And I'd love to get the perspective of both of you guys. How can we ensure that we incorporate both the patient, if the child is old enough, and the caregiver perspectives into the clinical decision-making for gene therapy?

Dr. Zaidman:
I'll start if that's okay. I'm very excited about the possibility that we can have these discussions with families. And I think it's important to mention that as of the recording, there is not currently an FDA approved gene transfer therapy available for Duchenne muscular dystrophy, but we will have these types of opportunities to discuss with our families. I think assessing the risk-benefit of this type of therapy is really crucial to the understanding and decision-making for these families, and listening to their expectations.

Micro-dystrophin gene transfer therapy is not a cure, it is, I hope, going to change the course of the disease for boys with Duchenne muscular dystrophy. But to be fair, at this point, we really just don't know what its impact is going to be. It does not replace the native protein. It is a version, in fact, a very small version of the protein these boys are missing. And so having a conversation with each family regarding what the potential benefits would be, and what the risks are, is a crucial part of the decision-making process.

Dr. Parsons:
I absolutely agree. And I think when we sit down and have the opportunities to sit down with patients and families to discuss gene transfer therapy, we really do review the data that we have available from clinical trials, which as Dr. Zaidman said, is limited in terms of the number and the duration of effect and all. But we need to, I think, be very transparent in terms of also the safety issues that have occurred in patients who have been treated previously, including the risk of death. This is not a benign treatment. So we have the opportunity to have amazing changes in altering the course of the disorder over a boy's lifetime. We're hopeful for that. But it's not without significant risk. And we really need to have families and patients understand to decide if this is a treatment that they feel that they want to undertake. So we do need to listen to the families about their concerns, about their expectations, about their questions, and really to have a dialogue about this prior to delivering the agent.

And I don't want to forget to mention that we do have care guidelines and care considerations for the treatment of patients with Duchenne dystrophy that are comprehensive care guidelines. And those aren't going to change even in the light of having potentially this additional therapy available. So we know that outcomes for boys and their families with Duchenne dystrophy are enhanced or are benefited by just following the care guidelines. So it's really important to stay grounded in terms of having a multidisciplinary team provide care for the patients and families. And then to remember the moms and the sisters who may be carriers of dystrophinopathy. So moms who are carriers maybe have a 10 to 15% risk of having a cardiomyopathy, the sisters too. So we need to think about the entire family when we're taking care of these boys, even in light of these new exciting novel therapies that we will see coming in the next few years.

Dr. Zaidman:
Dr. Parsons, I totally agree with you about the importance of continued multidisciplinary care for boys with Duchenne muscular dystrophy even after, hopefully we will be prescribing this gene transfer therapy. It's my anticipation that the boys will still need a close ongoing care relationship with, of course, their neuromuscular doctor, but they're also going to continue to see a pulmonologist, they're going to continue to need to have their heart monitored, and with close follow-up with a cardiologist. And I'm anticipating continuing our cardiac protective medications.

Routine physical therapy and stretching, as well as splints or orthotics where appropriate is going to be a continued important part of the preventative care that we provide. And we will still need to continue to follow these boys' growth very closely, both because I anticipate an ongoing role for steroids in their care, as well as ongoing monitoring to make sure that they develop appropriately, go through puberty appropriately, that their height and bone health remains as optimal as we can achieve.

So even after, hopefully, we are changing lives with gene transfer therapy, it's so important for our families and caregivers to understand that the multidisciplinary care is still going to be an incredibly important part of trying to help these boys be all they can be.

Dr. Parsons:
I couldn't agree more.

Dr. Cheeley:
This has been such a great discussion today. I would love to thank my guests, Dr. Craig Zaidman and Dr. Julie Parsons, for speaking with me and sharing some of their key insights on this disease and how to treat these families. Dr. Zaidman, Dr. Parsons, it was a pleasure speaking with you both you.

Dr. Parsons:

Thank you.

Dr. Zaidman:
Thank you.

Announcer:
You have been listening to CME on ReachMD. This activity is brought to you by The France Foundation and is supported by an educational grant from Sarepta Therapeutics, Inc.

To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.