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Advances in DMD Care: Evaluating a Gene Therapy's Efficacy and Safety

Dr. Turck:

Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. John Brandsema about the recent FDA approval of the first gene therapy for patients with Duchenne muscular dystrophy who are 4 to 5 years old. Dr. Brandsema is a pediatric neurologist and the Neuromuscular Section Head at the Children's Hospital of Philadelphia, where one of the clinical trials for this new therapy took place. Dr. Brandsema, thanks for being here today.

Dr. Brandsema:

It's a pleasure. Thanks for having me.

Dr. Turck:

Well to start us off, Dr. Brandsema, would you give us a brief background on Duchenne and why it's so challenging to treat?

Dr. Brandsema:

Duchenne muscular dystrophy is our most common muscular dystrophy of childhood, with an incidence of about 1 in 3,500 to 1 in 5,000 live births in males depending on the source you read; and the reason that it's challenging to treat are multiple. One is that it's a very severe progressive form of muscular dystrophy, so we tend to see loss of ambulation in the early teens, on average around 12 years of age, with significant involvement of cardiac and respiratory muscles in the teens to young adulthood. It often becomes life limiting in the early 20s; although with best supportive care, we can have a lifespan into the 30s or sometimes even 40s for patients with more targeted interventions.

The other challenge is that it's a spectrum of severity, and so not everybody has exactly the same experience of the disease. There are some that lose their ambulation as early as 6 years of age, and there's others that are still ambulatory much later in life with the same gene dystrophin being mutated. One thing we struggled with for a long time is that we haven't had specific treatments that target the disease itself. The best thing we could do was corticosteroid therapy, which comes with a range of its own side effects because we have to use quite a high dose of either prednisone or deflazacort. But it's obviously not curative, so we're all hopeful about some of the next-generation treatments that are starting to come into the clinic that we may be able to impact the disease much more specifically and have better outcomes for patients living with the disorder.

Dr. Turck:

Well, speaking of that, let's zero in on this new gene therapy. How is it used to treat patients? And who's eligible for this treatment?

Dr. Brandsema:

The gene transfer that has been approved for Duchenne muscular dystrophy is called delandistrogene moxeparvovec. It's a real mouthful. But the problem with dystrophin is it's a very large gene, and so we can't give the entire gene back. We have to give a manufactured version that is smaller—referred to as either micro-dystrophin or mini-dystrophin depending on who's making it—and these constructs have what are felt to be the most important pieces of the protein that get developed so that the dystrophin is localized well to the muscle membrane and also has its function maintained in terms of stabilizing contraction and interaction with other important proteins at the sarcolemma membrane.

So who is eligible? Right now it's a very exciting time for the community because the label was expanded recently. It was initially for 4-

and 5-year-olds based upon the index trial approved in 2023, but now in 2024 has been expanded to be for all individuals living with Duchenne muscular dystrophy with the one exception of those who have an exon mutation of 8 or 9 inclusive in their dystrophin mutation because those individuals were found in the research trials to be more prone to having significant side effects and reactions to the treatment, and therefore, they have been excluded from treatment up until this point.

The way that the treatment is given is via a viral vector. It's called rh74. And so the other way that you can be excluded from being eligible is if you have a positive titer to those rh74 antibodies, which happens just from spontaneous exposure in the community to individuals cumulatively over the lifespan. And that's uncommon to have these antibodies, but if you have a titer above a certain cutoff, you also cannot receive treatment because it's neither safe nor efficacious to do so.

Dr. Turck:

Now what can you tell us about the clinical trial in which your department participated? What were the key efficacy findings at your site and for the overall study?

Dr. Brandsema:

The trial was a very large endeavor that was international so there were many sites involved around the world and in this country. The goal was to dose initially younger individuals in the trial called EMBARK. And then there was not just a non-ambulatory older cohort but also ambulatory older cohort that was enrolled in a different study called ENVISION, which is less far along. So the data from the EMBARK study clearly showed on muscle biopsy that there was robust expression of these micro-dystrophin constructs at three months post dosing, and this surrogate biomarker is one of the strongest pieces of data that has led to approval for several of the new Duchenne-targeted therapeutics. It's this expression on muscle biopsy that tends to be given a lot of weight by the regulatory authorities.

In terms of efficacy, the primary outcome measure was the North Star Ambulatory Assessment at a year, and unfortunately, there was not a difference between the treated group and the placebo group seen in the initial cutoff of the EMBARK study. This was felt to be partially due to imbalance of randomization; randomizing by age and not by functional status at baseline in the earlier phases of the work was a concern, and there was a tendency towards more severely affected individuals being in the placebo group in the initial phase II arm of the study, which is what led many to believe that there could have been an effect on the efficacy outcome there. But when you look at secondary outcome measures like the time to rise from the floor, the 4-stair climb, and the 10-meter run, these all did show clinically meaningful differences with significance compared to the placebo group.

Dr. Turck:

For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. John Brandsema about a gene therapy for patients with Duchenne muscular dystrophy.

So, Dr. Brandsema, if we continue examining the clinical trial data that led to the approval of this therapy, what else can you tell us about the main adverse effects or consequences and how many people experience these effects?

Dr. Brandsema:

Safety is a very long conversation when it comes to gene therapy. I think one thing to be aware of is that it cannot be reversed. Once you give it, it is in the body, and we have to deal with the consequences if something arises. The issues tend to be immune mediated, and we have waves of problems that tend to arise in rare patients. Most get through it okay, but the first thing is we have to give extra steroid during the time of treatment for at least a couple of months afterwards. The people being dosed are on a higher dose of steroid than would be their baseline treatment for Duchenne, and we tend to see a wave initially of flu-like symptoms with some individuals, even vomiting and other things immediately after the infusion within the first couple of days. Then within a week, there are immune-mediated reactions from the innate immune system where we tend to see complement-driven problems, things like thrombotic microangiopathy. There has been myocarditis reported in that phase. And some individuals require escalation of their immune treatment related to that.

And then we have another wave at about the 3-month mark and 2 months to 4 months where we see the adaptive immune system start to have flares in some individuals that, again, lead to myocarditis. Another reaction that's common in that period is hepatitis or myositis, where individuals have worsening of their muscle weakness compared to their baseline with the dystrophy and sometimes also have the first involvement of respiratory muscles and swallowing muscles that previously were okay for them with this reaction, which again requires escalation of immune therapy.

So all of these reactions are uncommon, but if they happen, they can be quite significant and require adjustment of treatment and also for some people, prolonged stays in the hospital related to that.

Dr. Turck:

And what impact do you think this new therapy will have on the quality of life of patients with Duchenne?

Dr. Brandsema:

Quality of life is significantly impaired in people living with Duchenne muscular dystrophy. Anything we can do to alter the trajectory of relentless loss that these people experience in terms of both their skeletal muscle function and eventually other systems being involved, such as the cardiorespiratory system, would make a significant difference in their experience of the disease, and we need to do better than what we're able to do right now for sure. We give steroids at the expense of a significant side effect profile for a very modest impact on the disease of only a year or two slower milestones. This is why these more targeted treatments have such promise.

It seems from the long-term follow-up of the individuals that were dosed early on in phase I and II of the research protocol of the construct that's currently available in the clinic that it is not curative. I mean, of course there is a stabilization, which is what we're hoping for in the progression of the disease, but there is still progression of weakness over time. Whether this is related to incomplete full transduction of all of the muscle, whether there could be some sort of loss of effect over time related to protein expression of the transgene when it's in the muscle, other immune-mediated factors are playing into it, or whatever it is needs to be clarified with further work and research, but it is clear that this disease is not something that we have beaten by any point yet.

We have many other treatments that are being worked on for this disease, and hopefully, in this combination treatment approach along with early treatment with early diagnosis being something that people are hoping to advocate for with techniques such as newborn screening, we may be able to get closer to having people have a more functional life living with Duchenne.

Dr. Turck:

Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. John Brandsema, for joining me to discuss the latest advances in gene therapy for patients with Duchenne muscular dystrophy. Dr. Brandsema, it was great speaking with you today.

Dr. Brandsema:

Again, it was a pleasure. Thank you.

Dr. Turck:

For ReachMD, I'm Dr. Charles Turck. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.