Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/neurofrontiers/navigating-treatment-choices-for-dmd-key-factors-to-consider/26388/

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

Navigating Treatment Choices for DMD: Key Factors to Consider

Announcer:
Welcome to *NeuroFrontiers* on ReachMD. On this episode, we'll discuss available therapies for Duchenne muscular dystrophy with Dr. Nancy Kuntz. Not only is Dr. Kuntz an attending physician at the Ann and Robert H. Lurie Children's Hospital of Chicago and Medical Director of the Mazza Foundation Neuromuscular Program, but she also presented a session on this exact topic at the 2024 American Association of Neuromuscular and Electrodiagnostic Medicine Annual Meeting. Let's hear from her now.

Dr. Kuntz:
At this year's AANEM meeting in Savannah, Georgia, a colleague, Dr. Craig Zaidman, and I are going to hold a session entitled *Navigating Through the Available Therapies for Duchenne: How Do You Choose?* And what's inspired this session is that there are finally some disease-targeted therapies in addition to the standard of care for Duchenne. These are all new. There are some that have been FDA approved that I'll outline for people here briefly, but there are also a lot of them in the pipeline undergoing clinical treatment trials. And it's very important that everyone who cares for boys with Duchenne muscular dystrophy is aware of all this progress.

The process of choosing a treatment for an individual boy with Duchenne muscular dystrophy can be quite complicated. You have to start with making sure that you're doing the basics and providing some form of corticosteroids. Even though it's not completely clear that there's only a single way to do that, there are different treatment regimens and dosing schedules for using prednisone or prednisolone. There's also use of a fluorinated corticosteroid, deflazacort, that has some long-term benefit in function. So the basics would be including a stable corticosteroid regimen and then making sure that there are preventative cardiac medications and pulmonology follow-up for the boys.

But once that's done, much of the other disease-targeted therapies that are new in treatment of Duchenne muscular dystrophy are mutation-specific. So there's a whole group of them that are exon skipping by making slight, additional deletions in the mutated dystrophin gene to bring it back into reading frame to produce smaller amounts of shorter dystrophin. What scientists did is they started off with the exons because only a single exon can be skipped with these strategies. They started off with skipping exon 51, which reaches the largest fraction of all the boys with different kinds of dystrophin mutations. For example, there are over 300 different mutations, and only about 15 percent of those are benefitted by skipping exon 51 and then being brought back into reading frame. That is done with an agent right now called eteplirsen. It requires weekly IV therapy.

In addition to that, one of the new, exciting treatments has been gene replacement therapy. The complexity with using gene replacement therapy for Duchenne muscular dystrophy is that the dystrophin gene is one of the largest in the body. There are over 79 exons in the dystrophin gene, and this makes it three times as large as the capacity of the largest vector that has been identified to date to provide gene replacement. Therefore, there are five different scientific groups around the world working on different kinds of micro-dystrophin where they select different portions of this very large gene, replicate that into a micro-dystrophin, and then package that into a viral vector; there's only one that's currently FDA approved, and that's delandistrogene moxeparvovec. That has been approved for boys with Duchenne four years of age and older. And this is a one-time therapy with an IV infusion of many, many copies, 10 to the 14th times the weight in kilograms, and it requires intensive monitoring over three months as well as additional corticosteroid therapy beginning 24 hours before and going on for another three months after the infusion.

There have been a few individuals who have had immune reactions to this, and therefore, with this particular gene replacement agent, if the dystrophin deletion that the boy includes exon 8 and/or 9, they're excluded from being eligible for this treatment because that appears to be what has triggered the previous severe immune reactions. In addition, there's a small fraction of boys who have existing immunity to the adeno-associated viral vector used to deliver this, and therefore, they cannot receive it. There are other clinical trials

ongoing with different promotors, which direct the agent to different organ systems and different transgenes, again picking different parts of the dystrophin gene and different, adeno-associated viral serotypes, for their vector. We'll have to wait and see how all of those do. So far, we have eight years of experience through the clinical trials with the single agent that's been FDA approved, the delandistrogene moxeparvovec, and it looks very promising. There has been clear benefit and no diminution of the impact. People are always very excited about things like potential for CRISPR/Cas9 gene editing, and that may be very pertinent to different forms of the mutation in dystrophin, but that has not yet been brought to clinical trial in Duchenne.

Announcer:
That was Dr. Nancy Kuntz discussing her session at the 2024 American Association of Neuromuscular and Electrodiagnostic Medicine Annual Meeting that focused on therapies for Duchenne muscular dystrophy. 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!