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

Evolutions in Duchenne Muscular Dystrophy: Treatment Implications for the Present and Future

Announcer:

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Dr. McDonald:

So I'd like to provide an overview, an introduction to the Duchenne muscular dystrophy gene and the dystrophin protein product. The dystrophin gene is the largest gene that has been identified in the human genome. It’s an extremely large gene that has 79 exons that span the gene. It’s located on the X chromosome. And this encodes for the dystrophin protein, which is extremely important outside of skeletal protein to maintain the integrity of muscle fibers. And when we have either an impairment or an absence of the dystrophin protein, essentially what we see is a progressive loss of muscle fibers over time and replacement of those muscle fibers with fat and connective tissue. So the dystrophin protein is extremely important. It's expressed in various tissues including skeletal muscle, cardiac muscle, and smooth muscle. It's also expressed with various dystrophin isoforms in the brain as well.

So the function of dystrophin is that it serves as a molecular shock absorber to protect muscle fibers. It will actually protect sarcolemmal membranes from injury and disruption during normal everyday contractile activity.

So you can see here on the figure that the dystrophin protein is located on the intracellular side of the sarcolemmal membrane; one side, the amino terminus binds on to the actin cytoskeleton. The other C terminus domain actually binds on to the dystrophin-associated protein complex, which spans the sarcolemmal membrane. And the dystrophin protein itself actually will fold and unfold during normal contractile activity and will actually serve as this molecular shock absorber to protect the sarcolemma membrane from injury and disruption during, again, routine muscle contractile activity.

So it's important to note that with a dystrophic myopathy or muscular dystrophy, the lack of the dystrophin protein will lead to progressive segmental necrosis and ongoing progressive muscle degeneration. And so in the figure on the left, when we have reduced amount of dystrophin or complete absence of dystrophin, that will lead to a mechanically weakened plasma membrane, which is prone to focal tears during normal contractile activity. And so it might start with a small tear up at the top, and that tear may actually extend. And with the disruption of the sarcolemmal membrane, you get a massive influx of extracellular calcium into the intracellular side of the sarcolemma membrane, and then subsequently inactivation of a variety of proteolytic enzymes, which will contribute to the pathogenesis and inflammatory cascade and the ultimate segmental necrosis of that muscle cell or muscle fiber.

And with this segmental necrosis in the muscle fibers, what you see on the right is actual leakage of creatine kinase from the intracellular side from the intracellular space into the extracellular side of the sarcolemmal membrane. And this will lead then to extremely high elevations in the creatine kinase enzyme. And ultimately, this will lead to a series of pathogenic processes, which will lead to inflammation and disruption of the sarcolemmal membrane.

So it's again important to note that the dystrophin-associated protein complex, the maintenance of that is essential for muscle fiber health and for preventing damage during normal muscle contractile activity.

So with the dystrophinopathy, we see that the primary gene mutation will lead to an absence or reduction in the dystrophin protein. Then we see an inflammatory cascade, an immune response that occurs, which leads to muscle fiber injury and degeneration; the muscle fiber will undergo cycles of degeneration and regeneration, and eventually, the muscle fiber is replaced by fat and connective tissue.

So the therapeutic strategies that are used for Duchenne muscular dystrophy will target various events. The primary therapeutic strategies are to actually replace the dystrophin protein or actually increase levels of dystrophin protein. This can be done with either STOP codon readthrough approaches, exon skipping approaches, or gene transfer therapies or gene therapy. In addition, there has been standard of care development of treatment of Duchenne patients with corticosteroids, which ultimately act through the NF-kappa B pathway inhibiting NF-kappa B activation.

And then there are other approaches which are emerging in our strategy to treat Duchenne muscular dystrophy and Becker muscular dystrophy with treatments or combination strategies. These can be antifibrotic therapeutic approaches and immunomodulatory therapeutic approaches; there can be strategies that actually target the mitochondria and will work through improved biogenesis. And then are emerging strategies that will actually downregulate the contractility, the fast-twitch muscle fibers, the type 2 muscle fibers, which can actually lead to protection of those type 2 muscle fibers, which are the first fibers to actually show a degeneration as the disease progresses with Duchenne muscular dystrophy and Becker muscular dystrophy.

So glucocorticoids have become the standard of care for treatment of Duchenne muscular dystrophy patients. This has really dated back to the 1980s where prednisone and prednisolone were studied in Duchenne muscular dystrophy clinical trials. These were randomized placebo-controlled clinical trials, which demonstrated some advantages to prednisone treatment, in terms of a variety of muscle outcome measure parameters, strength, timed function tests, and so forth. And treatment with prednisone and these other glucocorticoids have actually been demonstrated to have a long-term impact on progression to clinically meaningful disease progression milestones.

With regard to deflazacort, this was FDA approved specifically for Duchenne muscular dystrophy patients in 2017. And it now has a label for the treatment of Duchenne muscular dystrophy in patients 2 years of age and older. Deflazacort may have some advantages to prednisone in terms of efficacy when patients have been treated for longer periods of time. There may also be some advantages in terms of weight gain with regard to deflazacort over prednisone. There does appear to be more cataract formation with deflazacort. And the growth of patients appears to be stunted with both the FISA court and prednisone.

Vamorolone is a newly approved dissociative steroid that is considered by the FDA to be a different class of corticosteroid. It also has been approved specifically for the treatment of Duchenne muscular dystrophy in patients ages 2 years of age and older. Vamorolone may have some advantages in comparison to both deflazacort and prednisone in terms of linear growth and also bone fragility and a risk of fractures and loss of bone mineral density over time.

And then there are emerging small molecule therapeutic approaches to Duchenne muscular dystrophy, which are really quite exciting. The Edgewise-5506 compound is currently being evaluated in both Becker muscular dystrophy patients and Duchenne muscular dystrophy patients. This actually targets the fast-twitch type 2 muscle fibers are the fast-twitch muscle fibers, and actually because of some reduction in contractility of those fast-twitch type 2 muscle fibers, the EDG-5506 compound actually seems to possibly prevent the contraction-induced damage in dystrophic muscle, particularly those fast-twitch type 2 muscle fibers. And it's currently undergoing clinical trials in both phase 2 and phase 3 clinical trials in Becker muscular dystrophy and phase 2 clinical trials in Duchenne muscular dystrophy patients.

Givinostat is a HDAC inhibitor or a histone deacetylase inhibitor that promotes the expression in muscle tissue of muscle cell regeneration genes. So it works through what are referred to as epigenetic pathways that will actually enhance the regeneration of muscle fibers. It also seems to reduce inflammation in muscle tissue but also it may also have an effect through the TGF-beta pathway at improving the fibrosis that occurs in muscle tissue and it may have some positive effects in terms of the fatty deposition or fatty replacement in muscle tissue. A phase 3 trial has been completed in with givinostat in Duchenne muscular dystrophy patients and there were positive results in that clinical trial with regard to the primary prespecified clinical endpoint for stair climbing. And there were also statistically significant positive impacts on the North Star Ambulatory Assessment as well as positive effects on skeletal muscle MRI fatty infiltration into the muscle fiber. So givinostat is really quite promising and is being considered for approval by the FDA.

I'd like to now move into cell-based therapy approaches, and specifically, the CAP-1002 product which is being developed by Capricor. This is a cell therapy that consists of allogeneic cardiosphere-derived cells. And these are a unique population of cells that contain cardiac progenitor cells. These are actually derived from heart specimens that were destined to be transplanted into patients, but for

whatever reason were ultimately not utilized. And so that heart tissue then is used to actually grow out the cardiosphere-derived cells. The cells themselves with this therapy are infused intravenously. And the cells actually seem to go to the pulmonary vasculature, where they then secrete what are called exosomes. These are membrane laden vesicles, which have a cargo that seems to have an impact on micro RNAs and ultimately have a variety of positive benefits on skeletal muscle tissue, as well as cardiac tissue as well, decreasing inflammation. They can have positive effects on muscle degeneration. They seem to promote muscle regeneration in patients that have received intravenous infusions. And there currently has been a positive phase 2 trial of CAP-1002 in Duchenne patients who were largely not ambulatory. There were positive benefits on the performance of upper limb measure and upper limb deterioration. And there were also positive benefits looking at left ventricular ejection fraction by cardiac MRI. And there's currently a phase 3 trial investigating the efficacy of CAP-1002 in patients aged 10 and above who are in the late ambulatory stage as well as the nonambulatory stage of Duchenne muscular dystrophy.

Here is the data from the Lancet publication, the recent publication which demonstrated the CAP-1002 actually resulted in a significant slowing of upper limb deterioration using the performance of upper limb measure. The data on the right shows the forest plots, showing a tendency towards improvement, statistically significant improvement in a variety of performance of upper limb indices shown there on the right. Obviously, this was a fairly small study, and there's now a phase 3 trial which is evaluating the effects of CAP-1002 on upper limb deterioration in patients with Duchenne muscular dystrophy.

I'd like to turn our attention now to gene-targeted therapies, focusing initially on exon skipping approaches to treat Duchenne muscular dystrophy. This exon skipping approach can treat up to 30 to 40 percent of all Duchenne muscular dystrophy patients. And in the example here, this would be a patient with an exon 51 skip-amenable mutation. So we have, with normal translation of the dystrophin protein, the ribosome comes down and assembles a full-length normal dystrophin protein, and this would be in the normal translation that occurs. And in this instance here, in the next example, with an exon 48 to 50 deletion, the ribosome comes up and reaches the portion of the gene where there is now an out-of-frame mutation, the ribosome really stops assembling the normal protein. And so there's really this disruption of the reading frame that occurs. And so what we have then is a shortened protein shown on the right, which is unstable, and essentially disintegrates. And the individual ultimately then has a near-complete absence of the dystrophin protein on muscle biopsy occurring with this out-of-frame mutation with a deletion here in this example of exon 48 to 50.

And then in this next example, the PMO drug actually essentially binds on to exon 51, it actually allows for the translation and assemblage of the protein to occur. So we have restoration then of the normal reading frame by skipping of exon 51. And essentially, what we have then is a production of a shortened dystrophin protein, but a functional dystrophin protein, nonetheless. So this is the classic example here of an exon skipping strategy.

There are a variety of exon skipping therapies, both first generation and later generation exon skipping therapies that are in the therapeutic pipeline. There have been four products that have been FDA approved to this date. These have all been approved using an accelerated approval pathway based on production of low levels of dystrophin protein that are reasonably likely to predict clinical benefit. And these four drugs have been approved, targeting exon 51 skipping, exon 53 skipping, and exon 45 skipping.

And then there are a new generation of exon skipping drugs, which have a variety of strategies to either get more of the exon skipping drug into the intracellular side of the sarcolemmal membrane. Other strategies have been utilized, for instance, for endosomal escape, to allow more of the exon skipping drug to be available to target the cell nucleus.

And these are all in various phases of clinical development and clinical trial. But we're hoping that these next-generation exon skipping strategies will actually produce significantly higher levels of dystrophin protein than we see with the current FDA approved exon skipping strategies.

And there is a registry data that is currently being collected on these patients that are being treated with commercially available exon skipping drugs. This is the depiction of the EVOLVE phase 4 registry study that's being conducted by Sarepta Therapeutics. A number of patients have been enrolled in this trial who are in the process of receiving eteplirsen for skipping of exon 51, golodirsen for skipping of exon 53, and casimersen for skipping of exon 45. And the data on the right actually shows the Kaplan-Meier survival curves for a proportion of patients remaining ambulatory who had been treated with eteplirsen. And here, you can see that in patients receiving eteplirsen, the median age at loss of ambulation is actually in excess of 15 years of age, 15.3 years of age, which is really quite consistent with the past clinical trial results which were reported by Sarepta, which ultimately led to the FDA approval of eteplirsen. So the registry data, again, is looking very favorable in terms of these exon skipping drugs having a significant clinical benefit in terms of disease progression and age to loss of ambulation in Duchenne muscular dystrophy.

Dr. Proud:

Now let's transition to a discussion of gene transfer therapies. The strategy is to utilize a miniaturized but fully functional dystrophin. And

the way that this is designed is to capture what are felt to be the most critical portions of the DMD gene in this circumstance and include those in the viral vector for delivery.

You can see the components of the dystrophin gene in its entirety here. But because this gene is the longest piece of DNA in the human genome, it unfortunately will not fit into the adeno-associated viral vector in its entirety. As such, the goal is to include these critical regions as components to make a transgene that will fit into this AAV vector and allow for production of a miniaturized dystrophin protein.

This miniaturized version of micro or mini dystrophin is then delivered via an adeno-associated viral vector. Currently, this is being administered intravenously into the patient and allows for delivery of this transgene into muscular cells. The adeno-associated viral vector then is able to release this transgene into the muscle cell nucleus, where it can form an episome and circularize to allow for production of protein via transcription and translation. And the goal ultimately is for that protein, in this case dystrophin, to be able to go to the muscle cell membrane, stabilize that muscle cell membrane, and allow for that structural stability to be able to optimize strength for the long term.

There are several gene transfer therapies that are being investigated for the treatment of Duchenne muscular dystrophy. Here we see that these often start as a phase 1/2 clinical trial, advance to the phase 3 clinical trial program. Ultimately, we hope for full FDA approval. We have one FDA approved treatment for Duchenne muscular dystrophy as a gene transfer therapy, which is delandistrogene moxeparvovec, and this was achieved via an accelerated approval pathway in 2023.

In the clinical trial programs investigating gene transfer therapies, it's important to assess outcomes and a variety of different measures. We can look at the dystrophin protein production, we can look at the vector genomes per nucleus, we can look at a variety of different biological markers that tell us that the delivery of the transgene was successful. But then obviously, we're going to want to look at functional endpoints as well. And the North Star Ambulatory Assessment score is a functional endpoint that allows for quantification and scoring of motor function in Duchenne muscular dystrophy. This is a well-validated scoring system that has been investigated in Duchenne muscular dystrophy patients.

We can see here some natural history data that has been collected over time in a variety of different patients with DMD at different ages. And what we know is that early on, under 6 years of age, we see a trend towards improvement or increasing in this NSAA score. However, our boys with Duchenne muscular dystrophy tend to peak in their motor function on this NSAA score at age 6.3 years. Subsequently, they decline over time as they lose function and progress in their weakness.

This NSAA score is composed of 17 different items, and a patient will receive a score of 0 if they're unable to perform a task, a 2 if they are able to perform a task in a typical fashion, but they will receive a 1 if they perform the task but in an atypical fashion or with a modification. You can see that the tasks that are assessed go from easiest to most difficult. We asked the boys to stand or walk, and then we successively increase the skill level, ultimately ending with asking them to stand on their heels or even hop.

Delandistrogene moxeparvovec has been investigated in numerous clinical trials. EMBARK was the phase 3 clinical trial that was a randomized multicenter, double-blind, placebo-crossover study evaluating the safety and efficacy of delandistrogene moxeparvovec in boys ages 4 to 7 years old; 125 boys were randomized to either receive a single IV infusion of delandistrogene moxeparvovec in phase 1 of the study, or a single IV infusion of placebo. They were monitored over 52 weeks. And then those that received the IV infusion of placebo would go on to receive active product or delandistrogene moxeparvovec, and those that received delandistrogene moxeparvovec in part 1 would receive an IV infusion of placebo in part 2.

If we think about the North Star Ambulatory Assessment score, we can consider some of the limitations of assessments that we utilize, whether it's in clinical trial or whether it's in our clinical practice. There are limitations to every assessment that we may pursue. And one of those limitations may be the degree with which change happens, the duration over which change happens, and the disease state that we are evaluating. We know that the North Star, as we've previously discussed, changes over the course of a boy's age as he grows, as he progresses along in his journey with Duchenne muscular dystrophy. The challenge that we've come to recognize with the North Star Ambulatory Assessment score is that score of 1, because that score of 1 represents any challenge or modification at performing the given task on the North Star. And so we can see that a boy may perform a task with a modification very quickly or very slowly, but that score will still be a 1 regardless of the degree of challenge or the quality of movement. This is where some of our other assessments like time to rise and 10-meter walk/run may in fact be more sensitive at being able to discern immediate changes in motor function. We have to keep these in mind as we assess these differences in clinical practice and with regard to clinical trial outcomes.

Dr. Veerapandiyan:

So we will be talking about some of the other gene therapy programs for Duchenne muscular dystrophy. This is from Pfizer, the product

is called fordadistrogene movaparvovec. We'll talk about a phase 1 study. This is an open-label study; they have enrolled boys aged 6 to 12 that was stratified by age also 6 to 7 year old and then 8 to 12 years old. And the primary outcome measure was safety and microdystrophin expression. And they also looked at the functional assessment using North Star Ambulatory Assessment. In this study, there was robust micro dystrophin expression. And if you look at the NSAA scores are 2 years by age group, comparing that with the predicted controls taken from cTAP model, for age 6 to 7 years, there was 2.5 points increase in the mean change, whereas for aged 8 to 12 years, there was 2.3 points increase in NSAA. So there was short-term functional improvements in this study was noted.

So this next program is from Regenxbio, RGX-202. It's also phase 1/2 study. Here we have dosed five boys so far. They had two different dose levels. There's 1e14 gc/kg, and there's then 2e14 gc/kg. The outcome measures were safety and also the microdystrophin expression. This is data from the first three boys that were dosed at the dose level 1, which is 1e14 gc/kg, and the age at dosing here, as you could see, the first patient is 4.4, and the second patient is 10.5 years at age of dosing, and the third patient at 6.6 year old at dosing. And you could see the weight at dosing. And if you look at the microdystrophin expression, again, there is robust microdystrophin expression ranging between 11.1 percent of normal to 83.4 percent of normal. And also there's a reduction in the CK levels, serum creatinine kinase levels at week 10 from baseline.

So here you could see the muscle biopsy images of one of the patients that were dosed in this program. As you could see at baseline, there was no dystrophin expression, and at week 12, you can see there's microdystrophin expression in these red linings or the muscle cell lining, so there is microdystrophin expression and there's also these microdystrophin is targeted to the sarcolemma and the muscle cell. And so far, there has been no serious adverse events in these boys. And the RGX-202 has been well tolerated. And we have also dosed two more boys in the high-dose cohort, which is 2e14 cohort. And that has been well tolerated totally so far. And the follow-up period varies between 3 weeks and 9 months post administration.

Alright, so moving on to risks associated with gene transfer therapy. When I talk to my patients about the gene transfer therapy risks, I usually talk about the risk profile that we know about that particular product, whatever product that you're talking about, and then I can expand it to include risks that we know from the whole gene therapy programs in Duchenne muscular dystrophy. I also expand it further to include any sort of AAV-based gene therapy programs, what we have learned from the clinical trials in terms of risks. These are mainly immune related. If you look at the system-wide differentiation of these risks, if you look at it from a hepatic standpoint, acute liver injury or elevated liver enzymes have been noted in these patients and they are usually self-resolved or they need additional corticosteroids that they are already on as part of the gene therapy protocol. From a gastrointestinal standpoint, the most common side effect being nausea and vomiting that's been seen within first few days after the infusion. And complement activation has also been noted in these boys after gene transfer therapy. And of the more serious complement activation causing hemolytic uremic syndrome, or atypical hemolytic uremic syndrome has been noted in some of the other programs in Duchenne muscular dystrophy. From a cardiac standpoint, myocarditis and elevated troponin have been noted. And one of the most rare that has been seen in boy-specific genetic change for increased risk of having this specific side effect called immune-mediated myositis. And from what we have known so far, boys with deletion of exons, including 8 or 9, are at high risk of having this immune-mediated myositis. And that's why it's an exclusion in the currently approved delandistrogene moxeparvovec. And these boys are also excluded from the clinical trials because of this side effect that we have noticed so far. And we're still continuing to learn what's causing this.

So now that we have so many therapies available for Duchenne muscular dystrophy, and the pipeline is still growing with a lot of therapies in the clinical trials. We know none of these therapies are a cure; they're not going to halt the progression of the disease or they're not going to reverse the progression of the disease. We know most of these therapies are actually slowing down the progression. So in the future, it's going to be combination therapy, combining multiple different options. Maybe combining genetic targeted therapy with non-genetic targeted therapies will be the potential to improve the patient outcomes and also slowing down the progression of the disease in the future.

If you look at the currently available FDA-approved therapies, let's look at some of the pros and cons. As we all know, steroids are the main line of treatment for these boys. If you look at the pros, of course, it's applicable for all patients with Duchenne muscular dystrophy. We know that it prolongs the time to loss of ambulation. It reduces the requirement of scoliosis surgery; it also improves the cardiopulmonary function or slowing down the progression of the disease from a cardiac and pulmonary standpoint. Whereas, if we're looking at the cons, the side effect profile that comes with the steroids. Of course, long-term steroid use can cause weight gain, changes in their behavior, there's osteoporosis, osteopenia, pubertal suppression, cataracts, etc.

Then the next group of therapies we're going to look at that are currently available include the exon skipping agents. Of course, we have the dystrophin expression data from these exon skipping agents. We also know they may prolong the time to loss of ambulation. It can also help with stabilizing the disease process. Whereas if you look at the cons, these are actually intravenous infusions that are given once a week, so it requires more frequent clinic visits or even home infusions but more frequent IV sticks. And it is not applicable for all

the patients with Duchenne muscular dystrophy. It's only applicable to a subset of patients with specific genetic change that they would be eligible for these therapies. And it also requires monitoring of renal function because of the theoretical risk of exon skipping agents affecting the kidneys.

And then we have the gene transfer therapy. The advantage obviously, is the dystrophin expression, and we know it slows down the progression of the disease or improves the function outcome with the limited data that we have already. And it is also a single intravenous administration. It's applicable for most of the boys except the genetic exclusion that we talked about. The currently approved therapy is contraindicated for boys that have exon deletion involving exons 8 and 9. Whereas, if you look at the cons, at least in this point of time, the delandistrogene moxeparvovec, it's only approved for age 4 and 5 year old. And then we talked about the whole gamut of immune-related side effects. And they're also a subset of boys who may have pre-existing antibodies to the vectors that's being used in the gene therapy programs.

So to conclude, a summary of therapies for Duchenne muscular dystrophy, there are several approved therapies for Duchenne muscular dystrophy, including glucocorticoids, exon skipping agents, and gene transfer therapy. And there are many therapeutics in the pipeline, including small molecules, cell-based treatments, more exon skipping agents, second generation exon skipping agents, or PPMOs, and gene transfer therapy. It is extremely important to set expectations and goals when you treat these patients and decide on the treatment what they need. And future research will investigate the impact of combination therapies in these patients with Duchenne muscular dystrophy.

Dr. Proud:

Here we have Alex who is a 6-year-old boy diagnosed with Duchenne muscular dystrophy. He underwent gene transfer therapy at age 5. And after gene transfer therapy, he improved in his ability to rise from a seated position on the floor. His walking was much faster. But he still fatigues after a long day of activity and has some difficulty going up and down stairs. His parents want to optimize his long-term outcomes, and so they asked their neuromuscular team what other interventions might be beneficial for him.

Dr. McDonald:

Yeah, I think this is a great example that really begins to get us thinking about the possibility of combination therapies for patients with Duchenne muscular dystrophy. I think it's exciting that this patient, Alex, is a 6-year-old male, has been able to benefit from an AAV gene therapy approach. And we actually see gene therapy creating very exciting benefits in terms of ability to rise from the floor, ambulate, and walk in a much more functional and normal pattern. But here, we can see that because this patient, again, was not treated as a newborn, has probably already lost significant portions of muscle fibers. We're hoping that the gene therapy will actually lead to long-term durability and preservation of muscle fibers. This patient is still having some fatigue after a long day of activity and some difficulty going up and down stairs. So I think we need to really think about the potential for combination therapy in this patient. I think one of the first things I would do would be to evaluate his specific genetic mutation for the possibility of adding on an exon skipping drug and determine if he has an exon skip-amenable mutation. I think that would be one of the first thoughts that I might have. In addition, with a dystrophin restoration strategy, such as AAV gene therapy, I think there's a real possibility that this may lead to benefits in terms of being steroid sparing. So this patient could potentially be treated with an alternative steroid regimen that might produce less side effects and less toxicity. So perhaps, a high-dose weekend steroid regimen or perhaps considering transition of this patient to a daily regimen of vamorolone which might have benefits in terms of his longitudinal growth, as well as bone fragility.

And then finally, I think as a recently studied small molecule that may have additional benefit in a combination regimen, I think a medication such givinostat, which is an HDAC inhibitor, which appears to have additional benefits in terms of decreasing inflammation, enhancing muscle regeneration, and reducing and improving the fat fraction on skeletal muscle MRI and perhaps reducing fibrosis as well as fatty infiltration, may have additional benefits.

So I would be thinking in terms of a combination approach for this patient, in addition to the standard of care steroids and the AAV therapy, which might include addition of another agent such as a HDAC inhibitor.

Dr. Proud:

As I have these conversations with families of boys just like Alex, I think about the potential for me to optimize long-term outcomes in the boys that I'm caring for. Might we be able to utilize different mechanisms of action of therapies to provide that long-term optimized care and to provide more durability of improved muscle function and strength. I would take a look at Alex's molecular testing to see whether or not he might benefit from other currently approved therapies. I may consider whether Alex would qualify for an interventional clinical trial. I would discuss with his family the potential risks and benefits of pursuing any additional therapies. And then collectively, we could make a decision on the next best step for Alex, given his specific clinical circumstances.

Depending on Alex's mutation, we may find that he would be amenable to an exon skipping technology. And these technologies work differently than the gene transfer therapy that he's already had. It would serve to create a different type of a partial length dystrophin protein that could additionally improve his strength and optimize his long-term function with regard to his motor skills, his cardiac function, and his pulmonary function. And so if he would be potentially amenable to an exon skipping therapy, I would consider adding that therapy after his gene transfer therapy.

Dr. Veerapandiyan:

So Alex received gene transfer therapy at age 5. And it seems like he still has some weakness and fatigue. And he's also on corticosteroids, I would assume, since he has Duchenne muscular dystrophy. So this kind of goes back to one of the comments that I made that we know none of the therapies that we have available is a cure. And the future is going to be combination therapy, combination of whatever options that you're going to choose the genetic targeted versus downstream therapy.

So take for Alex, I will probably look at first the steroid that he's on and see if there is any option there to change the dosing or switch to a different type of steroids to see if that would help. And if he has a genetic change that's amenable for one of the exon skipping agents, maybe that's also something you could consider to add on commercially. And then I would also look at any other non-genetic targeted or downstream therapies that are currently available, either commercially approved or in the clinical trials. At least if you think about it, I don't think there's anything commercially approved therapy that's available, but there are clinical trials that are aiming at non-genetic targeted therapies, maybe that's something we could consider. And like Capricor or Edgewise, I know that Edgewise is doing a program on the post-gene therapy patients. That's something that we could look into also.

Dr. Proud:

It's important to have discussions about goals of treatment with any of our patients with Duchenne muscular dystrophy. We must consider that the goal of treatment might change as our boys go through their different phases of their journey with Duchenne. In our boys who are younger and still ambulatory, our goal might be to prevent or prolong their loss of ambulation, to potentially impact their respiratory system such that maybe they don't need invasive or non-invasive ventilation one day, and perhaps we could actually prevent or prolong the time to where they may see cardiac dysfunction.

In our boys who have already lost ambulation, it may not be realistic that we return them to an ambulatory phase, but they still have excellent strength in their arms and their hands, and so we'd like to preserve this. Maybe they are not yet on non-invasive ventilatory support overnight, and if we could prolong that, that would be an impressive outcome as well. And perhaps we've been able to stabilize their cardiac function, which is also a success in this phase of their disease.

Likewise, in the later non-ambulatory older boys, they may have been non-ambulatory now for well over 10 years, they may have some respiratory dysfunction and some cardiac dysfunction, but they may still have the use of their hands to be able to participate in activities that they enjoy, like texting, communicating with friends, playing video games, working on the computer, and it would be fantastic for us to be able to continue to give them that strength in their hands to be able to accomplish those tasks. In addition, if we could prevent them from progressing even further in their respiratory dysfunction, perhaps they may not need invasive ventilatory support. And if we could keep their cardiac function where it currently is with their current medical management, that would also be considered success as well.

So each of these different phases of the journey in Duchenne is going to impact the goals of treatment that we discuss with our patients and with their families.

Announcer:

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