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Keys to Slowing Disease Progression in SMA

Announcer:
Welcome to *NeuroFrontiers* on ReachMD. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is NeuroFrontiers on ReachMD. I'm Dr. Charles Turck. And joining me to discuss how we can slow disease progression and maintain motor function in patients with spinal muscular atrophy, or SMA for short, is Dr. John Brandsema. He's the Neuromuscular Section Head at the Children's Hospital of Philadelphia, and an Associate Professor of Clinical Neurology at the Perelman School of Medicine at the University of Pennsylvania. Dr. Brandsema, thanks for being here today.

Dr. Brandsema:
It's a real pleasure to join you. Thanks so much for the opportunity.

Dr. Turck:
So, if we start with some background, Dr. Brandsema, would you tell us a little bit about the pathophysiologic processes underlying SMA?

Dr. Brandsema:
I'd be happy to. SMA is a monogenic disorder. It's autosomal recessive, and inheritance of both parents are usually carriers. And the problem is usually a homozygous deletion of the SMN1 gene, and so someone's missing both copies of that survival motor neuron-1 gene. We do have a homologue, or backup gene in the body. It's called SMN2, it's on the same chromosome, chromosome 5. But SMN2 isn't able to make SMN protein as effectively as SMN1 is. Only about 10 percent or 15 percent efficiency. And because of that, people who are missing their SMN1 gene are reliant on that SMN2 gene for their SMN protein, which is in every cell of the body, but especially motor neurons are very vulnerable if they're deficient in SMN. We have our population of motor neurons for life when we're first born, we can't make more of them or divide motor neurons. And so, as those motor neurons start to die off with this disease, we'll see the progressive loss of function, that is the hallmark.

We have four different types of SMA; three of them which present in childhood. The type 1 SMA is unfortunately the most common, about 60 percent of cases, which will have very severe early onset of their disease and it's actually the most common genetic form of infant death SMA. The type 1 patients will never achieve sitting as a milestone. In type 2 SMA they can sit but never walk. And in type 3 SMA, defined by the natural history they're able to walk at some point in their life but may eventually lose that skill over the lifespan because the hallmark of SMA is that while you may have initial development, you will reach a plateau where the disease is overwhelming what the body is able to do developmentally. And then there's a relentless decline phase from that point on. The rarest form of SMA, type 4 SMA, presents in adulthood, and it's less than 2 percent of cases.

The other point I want to be sure to emphasize is that that double deletion is in about 95 percent of cases of SMN1 but the other 5 percent or so is a point mutation or some other genetic change, which makes the SMN 1 gene nonfunctional and is missed by screening techniques that look for double deletion as the diagnosis.

Dr. Turck:
With that in mind, what treatment options are currently available to help slow disease progression and maintain motor function? And how do these options differ from one another?

Dr. Brandsema:

It's been a truly transformational time over the past five to six years since our first targeted treatment was approved in late 2016 for spinal muscular atrophy. We now have three targeted treatments that are available in the United States for genetic treatment of this disorder. And those three treatments are different in terms of how they work with the mechanism, but all have the common end result of increasing the amount of that deficient SMN protein that I was mentioning earlier.

And so, the first option that might be considered in terms of having its own unique mechanism of action is onasemnogene abeparvovec, which is also referred to as gene transfer. So, this is a one-time intravenous infusion that is given to those under 2 years of age in this country, although in other parts of the world, there's other indications that may be given also. And after you get this I.V. infusion of an SMN transgene through a viral vector you transduce the motor neurons in various other cells of the body that are deficient in SMN. But with this functional SMN gene that has its own ability to express, it does not integrate into the person's DNA, it's its own self-expressing transgene within the cell. And this is meant to be durable, hopefully, for the life of the person. We know that once you lose a motor neuron, you can't get it back, and it's no way to divide motor neurons. You have your population for life when you're first born. So having the stabilization of being able to make this SMN protein is really important for maintenance of the motor neuron health. And we hope that it's going to be a durable expression throughout the lifespan. This is a one-time infusion and treatment.

Safety-wise there are significant safety issues that come up, but they are rare. The most common safety issue that will happen is an inflammation related to an immune reaction to either the virus itself as it's being introduced to the body, or more commonly, the transgene as it starts to express. And so, what we'll tend to see is hepatitis or inflammation of the liver which makes it required that everybody gets steroid therapy at the time of their treatment for at least 2 months after treatment to try to minimize the chances of this reaction happening. But some do end up on steroids for a longer period of time if they're having persistent signs of inflammation in their body.

The other two therapies that are available are both SMN2 modulators. So, they work on that homologue or backup gene that I mentioned in terms of the pathophysiology. Nusinersen was first approved. It is required to be delivered intrathecally, so you have to actually give it to the CSF space through a lumbar puncture. And this is given serially over time. So, you start with a loading phase of four doses over two months. So, after you finish that two-month four-dose regimen, you'll then go into a maintenance phase of a dose every four months. So that's three doses a year, and that's for the life of the individual. You can imagine that, especially in children they may require procedural support for a lumbar puncture where they are getting repetitive sedations or anesthesia. Which, if somebody also has respiratory involvement, or even if they don't, has a cumulative risk to it over time that needs to be considered in terms of the balance here.

Otherwise, it generally tends to be very well tolerated in terms of safety. There is a concern in the category this is in, which is antisense oligonucleotide therapy, of renal injury. And so, we do monitor for urine proteins and also for another effect, which have been seen with the group, which is low platelets, which did happen in the research trials with nusinersen in a small number of cases, but was not ever causing a significant bleeding event and tended to resolve with repetitive exposure to nusinersen. And this is what we've seen in the real-world experience as well. It's important to monitor for these things to look for low platelets and to look for renal inflammation. But in terms of having to intervene clinically related to a result that's very, very uncommon.

And then the last option I'll mention is risdiplam, which was the last approved more recently. It is a small molecule that also works on the messenger RNA. It's a pre-messenger RNA from the SMN2 gene to increase SMN expression by the SMN2 gene similar to nusinersen. The way that risdiplam is administered is via a suspension, and so the person can swallow it if they're able to swallow or you can give it through a G-tube. And it's a daily therapy, so you are obligated to give it around the same time of day for the life of the person living with SMA, and that will again increase the amounts of SMN protein.

Safety-wise, there has been some concerns about effect on epithelial tissues, and some rash and some GI upset in some individuals. But that tends to resolve with sustained exposure in most of the people who have that issue; at least in the research trials, that's been the experience. And there's also a concern about its effect on reproduction in women taking risdiplam. It's known to be teratogenic in the first trimester. So, if you have SMA and become pregnant, it's recommended not to take risdiplam with your pregnancy if that's possibly avoidable in the first trimester. In the male case, if you're taking risdiplam there was a concern in the animal model for decreased sperm production in the animals that were exposed to risdiplam. And it's not clear whether there's a human correlate to that yet, there's still ongoing study but it's recommended to counsel a male of reproductive age that they may have an effect on fertility if they take risdiplam.

So, the bottom line of all of this is that we have these three treatment options that are available for somebody who is under 2 years of age, they may choose between all three of those options with the family. And then if you're above 2 years of age in the United States, you're choosing between the two SMN2 modulators, either risdiplam or nusinersen. All of these things, when they are given, have a tremendous effect in terms of efficacy.

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 slowing disease progression and maintaining motor function in spinal muscular atrophy, or SMA.

Now when it comes to selecting the best treatment option for our patients, Dr. Brandsema, are there any other considerations we should keep in mind?

Dr. Brandsema:
All of us as providers, I believe, have the goal of having the person living with disease themselves make the decision, or if it's not developmentally appropriate to do so, if it's a child or somebody with cognitive impairment having their caregivers be well informed enough to be able to make that decision on their behalf. And also, to involve all of the stakeholders that might be involved in that decision.

We have the advantage of having three highly efficacious options in this space if you're under 2 years of age. And two efficacious and well-tolerated treatments if you're above 2 years of age in the United States living with SMA. And so, it's really about the individual circumstances of the person, how you might approach what might be the right option for them to decide.

The first option is no treatment, which is sometimes decided upon by some individuals who have been living with SMA for a long time, or perhaps those who have a high copy number and identified early on, you may choose to watch closely for the first period of their life and then start to intervene when you might see a symptom. That is an approach that's suggested by some in terms of treatment guidelines.

But other things to consider specific to the treatments are the differences in tolerability. As I mentioned, while it's rare, there are significant safety issues that arise in people who have been treated with gene transfer, that it's very important for the decision-makers to be well aware of when they're deciding upon that treatment approach.

Dr. Turck:
And before we close, Dr. Brandsema, do you have any final thoughts or takeaways you'd like to share with our audience?

Dr. Brandsema:
I'd really like to emphasize two key points for anybody listening that's involved in the care of people with SMA or people living with the disease. The first is that we want to make this diagnosis as soon as possible and get somebody to the right kind of care as soon as possible. So we really need to establish care with a team that's familiar with the disease so that we can navigate the various options for intervention both in terms of best standard of care with all of the multisystemic issues that come up related to the disease, but also the targeted treatments and what might be the right approach to use for that person.

But the other key point to recognize is that it is a lifelong disease to live with SMA whether you're treated or not, and so we need to stay engaged with that SMA care team throughout the lifespan. This is because we both want to optimize standard of care and make sure that somebody's as functional as possible but also look for potential long-term side effects of any potential treatment that we've given or other issues that might be coming up related to the new phenotypes that are emerging of SMA on treatment. We just are learning about this now as we've had these treatments only for a short period of time relatively in the clinic. And it's a long life with SMA that we're facing if we treat an infant. So, we need to keep that care optimized.

And we're still doing a lot of work to try to do even better. This is not curative, any of the treatments although some people are very close to normal function that are treated. They still have manifestations of their disease over time. And so, we need to do better. And we're working on various things and research trials to further improve function in people living with SMA.

Dr. Turck:
All of those key takeaways in mind, I want to thank my guest, Dr. John Brandsema, for joining me to discuss strategies for slowing disease progression and maintaining motor function in spinal muscular atrophy. Dr. Brandsema, it was great having you on the program.

Dr. Brandsema:
Thanks again.

Announcer:
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