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Spinal Muscular Atrophy Care: Optimizing Therapeutic Decision Making

Announcer:
You're listening to *Neurofrontiers* on ReachMD, and this episode is brought to you by Biogen Inc. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and joining me to share strategies for therapeutic decision-making to support sustained functional gains in patients with spinal muscular atrophy, or SMA for short, is Dr. John Brandsema. He's 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 pleasure. Thanks for having me.

Dr. Turck:
Well, so let's start with some context. Would you walk us through the pathophysiology of SMA and how our therapeutic strategies have evolved over the years?

Dr. Brandsema:
SMA is a genetic autosomal recessive disease, so it's caused by a deficiency of the survival motor neuron, or SMN1 gene. Usually, patients have both copies deleted—very rarely, mutated—but the end result is that the SMN1 gene is not able to make SMN protein. We do have a homolog gene on the same chromosome, SMN2, but that doesn't make SMN protein as well, and so you're only able to make about 10 or 15 percent of what SMN1 is able to make. The more copies of SMN2 you have, the more of a mild phenotype you'll present with. But unfortunately, the most common form of SMA is the most severe, where about two thirds of patients will present with very severe symptoms in infancy. And the deficiency of SMN leads to the loss of motor neurons, which are very important for function, not only of the skeletal muscles, but also, in severe cases, the bulbar musculature. So things like speech and swallowing become affected, and breathing as well becomes an issue over time.

Dr. Turck:
Now, looking at the available treatment options, we have three FDA-approved therapies for SMA. So how do you differentiate them in terms of pharmacology, efficacy, safety, and route of administration?

Dr. Brandsema:
The first approved was back in late 2016: we had nusinersen, which is an antisense oligonucleotide. The way that that medication works is it increases production by that SMN2 gene of the SMN protein so that you're correcting the deficiency. It's delivered intrathecally, so you need to do a lumbar puncture. There's a loading phase of four doses over two months, and then you go into a maintenance phase of three doses a year for life. And usually, it's very well tolerated. The main complications can be related to the lumbar puncture itself, with things like post-lumbar puncture headache or, very rarely, CNS infection.

But the lab abnormalities we have to watch for related to the antisense are low platelets and renal injury, looking for urine protein. So we do these tests, as well as coagulation parameters, with each dose to ensure that that's not developing. Over time, the global experience with this has been very, very good, with very minimal, if any, reports of any significant issues related to those lab abnormalities.

We then had gene transfer come into the clinic in 2019, so onasemnogene abeparvovec is a single intravenous delivery of a version of SMN, essentially the SMN1 gene, through a viral vector. This needs to be given, at least in this country, very young, so we have a label up to two years of age, after which it's no longer available to patients in the United States. And it's a single dose, hoping that you will transduce a lot of motor neurons with this SMN homolog that then creates SMN protein for its sustained health. But the durability is still in question, because it's a very new therapy, and it's not that any person has lived a long time after receiving it, so we're still learning about whether this is something that we can see sustained effect from.

And then the last option that came into the clinic was risdiplam, which is an oral version of an SMN2 modulator. So it again increases the expression of SMN protein by the SMN2 gene. And that can be either swallowed or, in those who can't swallow, delivered via G-tube. That tends to be very well tolerated. There's been a few patients with GI side effects related to it, in terms of diarrhea or stomach upset. And there's also a question about whether there's an impact on male fertility. Based on animal studies, there were some issues with sperm production in the animals, and so we do counsel male patients about sperm preservation options, if possible. In females, it is known to be teratogenic in the first trimester, and so we have to be careful around pregnancy with its use. But otherwise, it's very well tolerated in most patients, and is a good option that now also has a tablet form available, which is convenient for patients since we've been using the suspension for years before that. But the tablet cannot be given through G-tube.

Dr. Turck:
And what real-world evidence is there on the long-term efficacy of SMA treatments, particularly in regard to motor function preservation or gains?

Dr. Brandsema:
What we tend to see is, of course, the earlier started, the better with a disease that is defined by loss of a tissue that we can't get back. Of course, motor neurons, once they're gone, are gone, and we can't regenerate them. So those who are treated very early—now that we have universal newborn screening in place in this country—it's really made a huge impact, because we're able to treat babies right away after birth if they are affected, which is giving them a better chance at preservation of their motor neuron pool.

Now, there is a subpopulation that is still quite severely affected early on, and even if we don't see symptoms in the infants, they still can have evidence of motor neuron loss if we do things like electrophysiology, a nerve conduction study, for example. And those patients don't tend to do quite as well, even though we give them the replenishment of their SMN.

But if somebody's already been symptomatic with their SMA for a while before they start treatment, they may see a slight improvement, but most of them, what we're aiming for is stabilization. And this is what's been shown in real-world studies now. I mean, we have almost a decade of experience with nusinersen, and risdiplam studies are starting to come up now in the real-world too, where what we tend to see is—instead of the relentless loss that was the hallmark of this disease in the past—what we're seeing is stability over time in the motor function outcome measures.

And also, importantly, in those who do have respiratory involvement or bulbar involvement, that it's at least stabilized in most individuals, maybe not, again, an improvement, but a stabilization. And this is a tremendous therapeutic impact relative to the natural history, which is loss over time.

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 the management of spinal muscular atrophy, or SMA.

So now that we've reviewed available treatment options, Dr. Brandsema, what else can you tell us about how you approach therapeutic decisions based on age, SMA type, and disease stage?

Dr. Brandsema:
The hallmark of any decision is always ensuring that the family and the patient themselves, if they're developmentally able to, are informed and are making a decision that's right for them. I mean, we can have an opinion as the care team, but ultimately, the person living with the disease and their caregivers are the ones that are making the decision about what is the right path forward. And so having

three different options in the under two-year-of-age group is a luxury.

There are some situations where decisions start to become made a little bit more black or white. For example, if somebody is seropositive for the antibodies that are used to deliver the gene therapy, the AAV9 antibody, then they cannot receive onasemnogene abeparvovec, and that's taken off the table, and we have to talk about one of the SMN2 modulators.

There also may be some people who really have issue with the lumbar puncture procedure for nusinersen, whether it be that they have a bleeding diathesis or they have very significant spinal anatomy issues. Now, we did get around that when that was our only option at the beginning, but now that there's risdiplam also, that sometimes is something that leans a little bit more towards that option.

It starts to become an issue of, when are you meeting the person relative to their experience of SMA? Is it a newborn screen or even a prenatal diagnosis, which is starting to happen more and more nowadays? Or is it a symptomatic diagnosis when the person's already been experiencing motor neuron loss? And if so, what is the burden of disease that they're already facing? And what might be the potential benefit of various interventions relative to their age and also their functional status?

So this is a tremendous area of inquiry. And even the standard of care of SMA is needing to be reframed, because we had an understanding of what the optimal management of what this disease was in terms of multidisciplinary care in the natural history. But that is no longer the reality for any person living with SMA, because most are on some form of SMN repletion now. Not all, but most. And therefore we need to start to think about things like orthopedic management, pulmonary management, endocrine management, and all of these other aspects of the care through a new lens of living in an age of SMN repletion.

Dr. Turck:
Now, you've touched on involving patients, caregivers, and families and putting them front and center in the therapeutic decision-making process. If we focus on expectation setting for just a moment, what are some ways we can discuss with them treatment goals, especially when navigating the difference between motor stabilization and improvement?

Dr. Brandsema:
One consideration is when you're meeting the person, again, relative to the disease presentation. So in a prenatal consult, sometimes we're discussing the timing of delivery and getting people on therapy as soon as possible postnatally.

Once we have a newborn screening diagnosis, that can sometimes be the most stressful, because this is a new family with a baby that seems totally normal most of the time to everybody involved, and then we're giving them this news that they have this disease that's potentially life-threatening within two years of life in the natural history, and we have to make a decision about what treatment to use. But this is new to the family a lot of the time, and it's a lot to talk through all of the different nuances of the various treatment options and what the risk–benefit profile might be. So that often takes multiple visits and a lot of patience, and some families, given that they're already in a postpartum state that is stressful to begin with, need more time and support to get through that.

If you're meeting a symptomatic individual, the family is already worried about their child and some sort of symptom that they're having, and so having a diagnosis sometimes at least gives them something to focus on. And then also, now we have a treatment option that can really change the trajectory of how that person's going to experience the disease, which is pretty rare in the neuromuscular clinic, although it's becoming more and more of a reality with our genetically targeted therapies coming into the world.

Dr. Turck:
And last, Dr. Brandsema, how are multidisciplinary teams enhancing outcomes, and what practical strategies support collaboration and continuity in the management of SMA?

Dr. Brandsema:
The real goal would be that the person living with SMA has a care team that is clear in terms of people who are interested and expert in managing the disease and communicate with each other.

So for our team, at least, what we strive for is having clinic settings where we're all in the same place so we can talk to each other in real time relative to a concern that's coming up, whether it be the timing of a surgery or an adjustment in diet or whatever it may be something that we're trying to modulate to give people the best possible outcome.

Now, that's not always available to every patient in terms of local resources, and so sometimes you have to do a bit of a patchwork and pull it together yourself in terms of finding what kind of resources you might have that are still accessible to you. But I hope that every person with SMA feels like they have a care team in place that has the disease expertise to be able to help them navigate, because it is a complex disorder. It requires input from many different specialties to be able to optimize function and outcomes and best quality of life. And these treatments also are complex to deliver and need a team with expertise doing it, and so hopefully that is becoming more and more of a reality across everybody living with the disease, in our country at least. When you look globally, it becomes even more complicated. But the goal would be living the best possible life with SMA and having the people on your team to do that for you.

Dr. Turck:
Well, with those final thoughts, I want to thank my guest, Dr. John Brandsema, for joining me to discuss how we can make effective decisions and care plans for patients with spinal muscular atrophy. Dr. Brandsema, it was great speaking with you today.

Dr. Brandsema:
Sure, it's a pleasure. Thank you.

Announcer:
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