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Increasing Awareness and Access to Spinal Muscular Atrophy Therapy

Announcer:

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Here's Dr. John Brandsema

Dr. Brandsema:

Hello, and welcome to CME on ReachMD regarding spinal muscular atrophy. My name is John

Brandsema. I'm the neuromuscular section head at the Children's Hospital of Philadelphia.

By way of introduction, spinal muscular atrophy, or SMA, is a broad range of disorders that all reference degeneration of the nerves, but the most common form known as 5q SMA is characterized primarily by degeneration of anterior horn cells in the spinal cord and the motor nuclei in the lower brain stem. There does not tend to be an involvement of the brain in this disorder, and most patients have normal intelligence.

The way that SMA disorders in their most common form tend to present is with diffuse, symmetric, proximal weakness that is more pronounced in the lower limbs than in the upper limbs. Deep tendon reflexes tend to be unobtainable or at most markedly decreased, and in the more severe forms, you also see bulbar involvement with progressive respiratory insufficiency and also difficulties with speech and swallowing. The incidence of the most common form is about 1 in 10,000 live births, and there is a range of severity depending on how old the patient is when they present with symptoms ranging from the most severe form presenting immediately at birth to the most common form presenting in infancy before patients reach the milestone of sitting, and then there are sitters and walkers with SMA.

The inheritance pattern is important to understand related to the genetics. In terms of the most common form, all patients have nonfunctional SMN 1 protein. This is normally due to a deletion of part or all of SMN 1 and including exon 7 within that gene, so both alleles will have nonfunctional SMN 1 genes, but the SMN 2 gene is also on the same chromosome, chromosome 5, uh, and is similar to SMN 1 with only a few key nucleotide differences. One of those nucleotide differences, exon 7, causes SMN 2 not to be able to make functional survival motor neuron or SMN protein as efficiently as SMN 1 does, and so, as a patient with SMA is dependent on the number of copies of SMN 2 that they have for SMN protein, each of those copies is able to make about 10% of the amount of SMN protein that the SMN 1 gene has, and it tends to be that those who have more copies of SMN 2 will present later in life with symptoms that are less severe and less rapidly progressive, whereas those who have fewer copies of SMN 2, uh, tend to present earlier on. However, this rule does get violated, and there are patients who have more copies that present more severely and vice versa like we do to other genetic modifiers. It's very important to understand the difference between the SMN 1 and SMN 2 genes when thinking about currently available therapies for SMA that target this SMN deficiency as the hallmark of the disease.

Let's next discuss the burden of disease in SMA. In the most severe form, patients present immediately at birth. This is, uh, traditionally in the past known as type 0 or now sometimes classified as the most severe form of type 1 SMA. Uh, most of these babies will require respiratory support immediately at birth, uh, and have significant limb weakness. Uh, this phenotype is unfortunately very

severe and is usually life-limiting within the first few months of age. This is also extremely rare. The most incident form of SMA, about 2/3 of cases, is type 1 SMA in the natural history, which is, uh, presentation of symptoms before 6 months of age or reaching the milestone of sitting, so the way these patients were defined is that they never achieve the ability to sit independently. Um, this form is rapidly progressive in most patients and, uh, almost universally leads to the need for respiratory support and nutrition support, uh, before 2 years of age. If these are not supported, they would have a high mortality within the first couple of years of life, uh, but with full breathing and respiratory support, there can be a much longer lifespan, into adulthood for some patients.

Type 2 SMA is defined by sitting but never walking or standing independently. Uh, these patients tend to present between 6 and 18 months of age, uh, and have a more slowly progressive weakness, uh, but still involving respiratory support and some element of nutritional deficiency or inability to, uh, fully eat on their own in most patients, although some avoid reaching this milestone. Survivorship is into adulthood for patients with, uh, good supportive care in most patients, uh, and, uh, to middle age in several patients with, uh, standard of care.

Type 3 SMA patients walk, uh, but may lose that ability over time, uh, due to the progressive nature of the disease. Uh, these patients, uh, sometimes do not have any need for respiratory support, although some may, and, uh, it has a normal life expectancy.

And then there's a type 4 SMA that presents in adulthood, again with normal lifespan and usually just limb weakness without any bulbar respiratory or issues with scoliosis.

In terms of the natural history of SMA, the approach has always been optimizing supportive care, and so this would be working with an interdisciplinary care team that includes rehab specialists, such as physical and occupational therapists, uh, as well as orthopedic specialists who, uh, maximize function in the limbs and minimize contracture and scoliosis, which can be limiting mechanically and also can affect respiration in patients who have respiratory insufficiency. In the most severe forms, involvement of a pulmonologist is key, uh, to both prophylactically try to avoid respiratory deterioration and also optimize respiratory support. Um, and there can also be GI manifestations of the disorder where, um, there are issues with motility and also reflux, um, that needs specialized management, uh, to optimize, uh, nutrition status and, uh, minimize symptoms.

In today's world we now have some targeted treatments that are available in the clinic and also some treatments that have been in research trials that may be on the horizon. The first medication that was approved for SMA is Nusinersen. Uh, Nusinersen was approved in December of 2016 for the treatment of all forms of SMA, and there have now been, uh, thousands of patients, uh, treated around the world with this approach. Uh, this approach works on the SMN 2 gene to increase SMN protein

expression by modifying the transcription and translation of that gene to make it more likely to make fully functional SMN protein. It does require intrathecal delivery, and there is a loading phase of 2 months, a building of 4 doses over 2 months followed by a maintenance dose every 4 months for life.

The other approved therapy since just May of 2019, uh, is onasemnogene abeparvovec, which is a gene transfer therapy. Uh, this uses a BioVector delivered intravenously in the approved form to patients with SMA under 2 years of age as per the label in the United States, um, and this approach seeks to, uh, deliver a functional SMN gene that has been self-modified to promote itself, um, and express SMN protein in the nucleus of the cell. The gene does not integrate into the genome of the host. It is independent in the nucleus of the cell and self-expressing for SMN protein, and so those cells that are transfected will express SMN protein, which correct the deficiency. Um, the virus is particularly trophic for motor neurons, and so it does tend to target the roots of the nerves, which is the main pathologic area in SMA, and, um, the motor neurons are nondivided, so the hope is that those that have transfected will have expression for the lifetime of the cells.

Um, both approaches are also, uh, costly medications and require, um, a significant amount of advocacy in terms of peer-to-peer review and authorization within the United States access to care. Determining the cost of the access of these treatments has many facets to it, but in terms of the individual cost of the medication itself, in terms of Nusinersen, the price tag in the United States is roughly \$125,000 a dose, uh, which translates to almost a million dollars in the first year and almost half a million dollars in subsequent years for life, um, related to the medication, um, also considering the cost of administration relative to the procedure and, um, the effects on the life of the patient and family in terms of returning to care, um, that frequently. Um, in terms of gene transfer therapy, the current, uh, price tag is just over \$2 million for the single administration of an IV dose of that medication, um, and there is also associated monitoring that's quite intensive for the first couple of months, uh, related to that treatment, but in most care contexts, this is done outpatient at the current time.

Other than those 2 approved therapies, there are also other approaches that seek to modify SMN 2 gene expression, uh, known as Risdiplam and Branaplam, that are in research trials. Both of these are oral agents that are delivered via swallowing or G-tube suspensions that increase SMN expression by modifying the transcriptions, uh, of the, uh, the SMN 2 gene. And then there are approaches that also seek to optimize the function beyond the nerve and motor neuron or the genetics of the disease. The one approach that was tried recently is, uh, troponin activation known as Reldesemtiv. Um, this approach seeks to optimize muscle contraction in response to the signal from the nerve and has been through a phase II study. Um, there is also an ongoing trial at the moment, uh, using myostatin inhibition as an approach to optimize muscle function.

Uh, once we have a patient identified pre-symptomatically, we now have to make a decision between the 2 available approaches, Nusinersen and gene transfer or onasemnogene abeparvovec, for patients in terms of what might be the optimal approach to deliver it at this time. There are many factors to consider in terms of the clinically available as well as those that are still in research trials, uh, medications. Um, the research trials themselves are restricted to a very specific population, um, in terms of the inclusion criteria, um, looking for a relatively functional group of patients who were still symptomatic in the pivotal trial, such as the type 1 onset ENDEAR study of Nusinersen, um, or STRIVE study in, uh, gene transfer, um... Uh, but there were also pre-symptomatic arms as well as, uh, arms with, uh, patients who were presenting later with less severe symptoms. Um, the struggle is that the data for the pre-symptomatic patients is still actively being collected, um, and the data in older patients is still actively being collected at this time. And also, uh, there is very minimal data in populations that are more severely affected or denervated on how they might, uh, be expected to respond to these treatments, and so this became a concern early on in the use of Nusinersen treatment, um, related to, um, whether, um, there would be, um, a detectable response in such patients in terms of efficacy, um, but also whether there might be differences in the tolerability of the medication in patients since they have been researched. Um, in terms of tolerability, both available approaches now tend to be relatively well-tolerated. Nusinersen in the research trials in the, um, more severe, uh, phenotype of the type 1 onset SMA, um, did show some concerns for, um, respiratory infection increase as well as constipation, um, and, uh, there is safety monitoring required related to a possibility for thrombocytopenia as well as renal injury, uh, needing the monitoring of urine protein.

In terms of gene transfer therapy, the main, uh, concern is, uh, liver injury with elevated transaminases requiring the use of steroids, uh, around the time of dosing, um, and also, there has been some thrombocytopenia seen in those patients as well. Um, neither of these approaches, Nusinersen nor gene transfer, have any significant bleeding events related to the thrombocytopenia in the research trials, and there will likely be other, um, safety issues, um, identified related to the other approaches that are still actively in research trials, um, but it's very important to remember for patients that are treated pre-symptomatically or those who are symptomatic when they start dosing that none of these approaches are a complete cure for the disease, and it's still very important to maintain a connection with the specialized care center that continues to use optimized interdisciplinary care to maximize function and monitor for potential complications of, uh, living with SMA.

In conclusion, we're really currently in a novel age in terms of the approaches to SMA care where we have exciting opportunities to dramatically impact the phenotype of SMA for the first time. Uh, some questions that still arise are what the role of SMN protein in tissues outside the motor neuron may be, whether other areas of the body that are SMN-deficient may show manifestations of that over time as

we are correcting the primary effect of the phenotype in terms of degeneration of motor neurons, um, and this is something that will require further research in the future. It's also possible that combination approaches may be explored in terms of using, uh, different targeted treatments, both genetically as well as phenotype-driven, to truly optimize the function of an individual depending on when they first develop symptoms, if they ever did, if they were identified pre-symptomatically as living with SMA and also, um, how those symptoms change over time.

But it's important to remember that this is a severe disease and does tend to have many aspects that impact the lives of people living with this significantly as well as their caregivers, um, and the interdisciplinary care teams that we are a part of in the clinic are part of the support that these, uh, families and patients require, um, but there are many other organizations that are out there to, uh, provide resources, support, networking and education and advocacy related to this disease, and you can look at the resources provided on the slides for further information, both for providers as well as for those affected by SMA in the community.

Thank you very much for listening. I'm Dr. John Brandsema for CME on ReachMD.

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