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The Role of Pediatricians in Diagnosing and Treating Spinal Muscular Atrophy

Announcer Introduction

Welcome to ReachMD.

This medical industry feature, titled "The Role of Pediatricians in Diagnosing & Treating Spinal Muscular Atrophy," is sponsored by Novartis Gene Therapies. This program is intended for healthcare professionals.

Here's your host, Dr. Matt Birnholz.

Host Introduction

Spinal muscular atrophy, or SMA, is a rare, genetic neuromuscular disease caused by a lack of a functional *SMN1* gene, resulting in the progressive and irreversible loss of motor neurons. This affects muscle function, including breathing, swallowing and basic movement. With SMA affecting one in every 10,000 births worldwide, pediatricians will likely see a minimal number of cases of SMA over the course of their careers. Nevertheless, SMA is the leading genetic cause of infant death – and pediatricians can play a critical role in diagnosing and treating this disease.

This is ReachMD, and I'm Dr. Matt Birnholz. Joining me is Dr. Chamindra Konersman of Rady Children's Hospital in San Diego, and Dr. Kevin Strauss, of the Clinic for Special Children in Pennsylvania. Together, we'll be discussing the diagnostics and treatment priorities in SMA, the role pediatricians play toward meeting these priorities and one of the current treatment options.

Doctors, welcome to you both!

Dr. Konersman:
Thank you for having me.

Dr. Strauss:
Thank you. It's really an honor to be here.

Dr. Birnholz:
Let's begin with the foundational question — which is what is SMA specifically? Dr. Konersman, can you lead us off?

Dr. Konersman:
SMA is a rare, progressive, neurological condition, and if it's untreated, it results in progressive paralysis of the arms and legs, and in its most severe form, can cause difficulties with breathing, which will necessitate the need for ventilation, and if untreated, can cause death, typically, by age two in the babies. It is a genetic disease, and in that sense, patients with SMA are missing the *SMN1* gene, and that stands for survival motor neuron gene. Because of the missing gene, these nerves in the body don't have the necessary protein in order to function properly. That is what's causing the motor neurons to die slowly over time. SMA is a condition that needs to be captured and diagnosed as early as possible, because we have learned that early diagnosis actually improves outcomes. That is why I'm partnering with Novartis Gene Therapies today, to do this podcast so that we can raise awareness about SMA and its treatment options, and the fact that early diagnosis allows for better outcomes in these patients.

Dr. Birnholz:
Thanks for that overview. Why don't we turn to the diagnostic considerations for SMA now, and coming back to you for a moment, Dr. Konersman how are these patients diagnosed, and what are the current challenges in the diagnostic arena?

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Dr. Konersman:
The only way to diagnose SMA is to do a genetic test. The genetic test does need to be combined with a clinical examination, however, hopefully as these patients are being captured on the newborn screening panel, their examination looks nearly normal. When a physician gets called to diagnose a patient who possibly has SMA, what they're typically told is that they have a hypotonic infant who is weak and not able to attain their milestones, and they typically have motor milestone delay. For instance, they will not be able to roll, pick up their head, and they're not achieving their sitting independently like they should at the appropriate age. Most physicians who diagnose SMA are typically neurologists, although it can certainly be diagnosed by other physicians, including pediatricians. So raising awareness of this condition, so that even a pediatrician who sees a multitude of patients in their clinic needs to be able to recognize this condition right away. So, if it is, indeed, a SMA patient, I will consider it a medical emergency, and I move very rapidly to do the gene testing. The idea is to get a very rapid turnaround time of just a few days, so that you can diagnose these patients as early as possible. In 2018, SMA was added to the Recommended Uniform Screening Panel, also known as the RUSP. However, it's up to each state to abide by this recommendation and add SMA to the newborn screening panel. Currently, there are 33 states who screen for SMA through the newborn screening program. However, that leaves us with 17 states plus Washington, DC who are currently not screening their newborns.

Dr. Birnholz:
Dr. Strauss, let me turn to you now for your perspective on this. Because as I mentioned earlier SMA is a rare disease and pediatricians most likely are only going to see a minimal number of SMA cases over the course of their careers. So with that in mind, what role do or should they play in diagnosing and treating SMA?

Dr. Strauss:
That's a great question. SMA is indeed a rare disorder, but among genetic disorders, it's actually relatively common. SMA is a paradigm of exactly the type of condition where pediatricians can really play a instrumental role in optimizing the diagnosis and therapy. They're often the first people to come in contact with a newborn child from the medical field. I just want to stress again, as Dr. Konersman had noted, the importance of timing for treatment of SMA. SMA is a progressive, neurodegenerative disease, and we have entered a new era where there are now three disease-modifying therapies available, all of which can have a profound impact on outcome, but the effectiveness of any one of them is critically dependent on the timing of dosing. I think the other really important thing to say about a pediatrician's role with a disease like SMA is that for SMA, like any genetic disorder, a child with a condition like this will very likely see multiple subspecialists. At minimum, they would typically have a pediatric neurologist following them, often physical therapy, possibly pulmonary or GI doctors, and the pediatrician's role is to integrate those services and keep the whole child in view, and make sure that all of the subspecialists are providing what would be the absolute best standard of care. When something like a treatment for a disease like SMA comes along, pediatricians really have to embrace that opportunity, and use it as an opportunity to educate themselves, and to partner with other pediatricians and advocacy groups to spread newborn screening, to spread education, so that we can really champion newborn screening nationwide and ultimately worldwide, and get these children treated as quickly as possible. Right now, the newborn screening programs for SMA are able to capture about 60-70% of all children born in the United States, but we still have a ways to go. Pediatricians should be able to recognize a floppy baby, where a baby who has absence of reflexes, or tongue fasciculations, or swallowing difficulties. Those are signs that there's been some irreversible motor neuron loss. For the child who receives a diagnosis through newborn screening programs, the pediatrician has a very important role to play in not only making a referral to a pediatric neurologist, but being engaged with the family, and making sure all their questions about available treatment options are being answered.

Moderator Mid-Tag
For those just tuning in, you're listening to ReachMD.

I'm Dr. Matt Birnholz, and today I'm speaking with Drs. Chamindra Konersman and Kevin Strauss about spinal muscular atrophy, or SMA.

Dr. Birnholz:
So, we've been focusing on the importance of diagnosing SMA as soon as possible. But I want to shift over to what happens after the family receives a diagnosis and what their options are? Dr. Konersman, let's start with you.

Dr. Konersman:
After a family receives the diagnosis of SMA, the family should talk to the treating physician as soon as possible. The treating physician, in certain states, could be the pediatrician, although more often it typically tends to be a neurologist or another health care professional that is well-versed in the SMA treatment and diagnosis. The next steps include knowing the treatment options, as Dr. Strauss had mentioned, and currently there are three FDA-approved drugs for the treatment of SMA.

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Dr. Birnholz:
And regarding those treatments for SMA, I understand that a one-time gene therapy is an option. What can you tell us about that, Dr. Konersman?

Dr. Konersman:
The one-time gene therapy is called ZOLGENSMA. It is also known as onasemnogene abeparvovec, and it was approved by the FDA in May of 2019, to treat children who are less than two years of age, who have a genetic diagnosis of SMA. It is a one-time gene therapy that is given through an IV infusion, and it fundamentally addresses the genetic root cause of the disease by replacing the missing *SMN1* gene. It provides the neurons with a working copy of that gene. And the idea is to stop the progression of SMA by allowing for greater strength in the muscles. ZOLGENSMA has transformed the clinical picture, by allowing for greater survival in the patients who are treated. ZOLGENSMA data demonstrates significant and clinically meaningful therapeutic benefit in patients with SMA. Clinical trials evaluated the safety and efficacy of a one-time IV infusion of ZOLGENSMA in patients with SMA Type 1, who showed symptoms of SMA, less than six months of age, and they also had two copies of *SMN2* backup gene, and had the *SMN1* gene deleted. A total of 22 patients with SMA Type 1 took part in the Phase 3 STRIVE clinical study. 20 of the 22 patients – so about 91% – were alive and did not need permanent breathing support at 14 and 18 months of age. 13 of the 22 patients – about 59% – could sit without support, for at least 30 seconds by the 18-month study visit. ZOLGENSMA has a clinically transformative impact on event-free survival, including increased motor function and achievement of motor milestone development that has not been seen before in the natural history of SMA patients. ZOLGENSMA resulted in the rapid improvement of CHOP INTEND score by the one-month mark, after receiving the infusion, as evidenced by the STRIVE study. In terms of the long-term data of ZOLGENSMA, we do have patients who were originally in the START Phase 1 study, who rolled over to the long-term study. 13 of the 15 patients rolled over to the long-term safety study, and we have data for four years after the infusion, and five years of age. It is important to remember that ZOLGENSMA is not a cure for SMA. It can stop the progression of the condition, and that is why it's important to treat as early as possible. There are risks associated with the treatment of ZOLGENSMA, which is why it is important for each patient and family to work with their treating physician to determine what treatment is right for them. They need to weigh the benefits and the risks, consider what medication is best for them. The most common side effect that occurred in patients treated with ZOLGENSMA were elevated liver enzymes, and vomiting. Treatment with ZOLGENSMA can cause acute serious liver injury. Liver enzymes are often elevated and can reflect acute serious liver injury in children who receive ZOLGENSMA.

Dr. Birnholz:
Thanks, Dr. Konersman. And for our listeners, I'll add that Zolgensma has a boxed warning for acute serious liver injury and patients with pre-existing liver impairment may be at higher risk. Liver function needs to be assessed at baseline and for at least 3 months after infusion; and physicians need to administer an oral systemic corticosteroid before and after Zolgensma infusion. In addition, there is a warning for thrombocytopenia and elevated levels of Troponin-I. Platelet count and troponin-I levels need to be assessed at baseline and monitored for at least 3 months after infusion. And I'd like to remind our audience to listen to additional important safety information at the end of this episode, and to see the accompanying Full Prescribing Information, including the Boxed Warning.

So, Dr. Strauss, coming back to you, what are your thoughts on the subject of gene therapy?

Dr. Strauss:
I do think that one of the things that really is quite astonishing to me about gene therapy in particular is the fact that we can touch a child once – a single IV infusion. Touch that child once during their lifetime with that therapy, and it can transform the arc of their life and reduce suffering for the entire family hopefully over the course of the lifetime. I've often said to people that these therapies are of the level of significance of the discovery of penicillin. They really are a complete change, a new exemplar in medicine that has given us the ability to reach into and change the natural course of a disease that, just up until a few years ago, was associated with catastrophic outcomes. I've cared for many children with SMA, and never imagined that in the course of my career, something like gene therapy or some of these other recent therapies would come along, nor could I have imagined that they would be as effective as they apparently are. We still don't know the durability of effect, but we have no reason to believe, at this point, that that effect is going to wane over time.

Dr. Birnholz:
On that note, Dr. Strauss, in addition to the need for an oral corticosteroid and the monitoring mentioned previously, what should pediatricians and pediatric neurologists know about treating someone who has received a gene therapy for SMA?

Dr. Strauss:
If we look at clinical trials, access programs, and now dosing of gene therapy post-commercialization, we know that more than 700 children with SMA have received gene therapy. I think that in my experience treating children with SMA, whether they've had gene therapy or not, it's very important to recognize that each child is unique. And so, an important part of the pediatrician's job is to – is to

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really survey the needs of each individual child and family, and to strive to meet those needs. And often with SMA, that might include making sure the child has proper growth and feeding support, – making sure that they have a good pediatric pulmonologist and have any ventilatory equipment that they might need at home. Sometimes children who are treated later will need help with walking, and they'll require physical therapy. Gene therapy, administered early in life, particularly at what we would call the pre-symptomatic stage, has profound benefits for children. Many of these children who would have never rolled over, are now walking. And we'll hopefully be able to look back ten years from now and – and recognize that that remains true. But we'll have to follow the data. I've been a practicing pediatrician, treating children with serious genetic and neurogenetic disorders for 20 years now, and in my practice, I feel myself to be privileged to see the advent of these therapies for SMA – gene therapy in particular. And that's why I partnered with Novartis Gene Therapies to raise awareness about SMA – about its diagnosis and treatment.

Dr. Birnholz:
Great insights Dr. Strauss, thank you. Now lastly, Dr. Konersman, coming back to the big picture on SMA, what do you most want our listeners to take away from today's discussion?

Dr. Konersman:
Again, early treatment offers better outcomes, so it is best to treat these patients as early as possible, ideally before they even develop symptoms. Lastly, pediatricians and neurologists need to be aware of the newborn screening program regulations for their state. If you are not sure about where your state stands in terms of the newborn screening program, or you want more information on SMA, the best resource is "Cure SMA" organization, available at www.curesma.org.

Dr. Birnholz:
Well with that, I very much want to thank my guests, Dr. Chamindra Konersman and Dr. Kevin Strauss, for helping us better understand SMA, the importance of diagnosing and treating it quickly, and the current treatment landscape for this disease. I'll remind our audience to please keep listening for additional important safety information, and to see the accompanying Full Prescribing Information.

Doctors, it was fantastic speaking with you both today.

Thanks so much.

Dr. Konersman:
Thank you for inviting me.

Dr. Strauss:
Thank you. It was a real pleasure speaking with you today.

Announcer:
Let's learn more about the Important Safety Information for Zolgensma.

Indication
ZOLGENSMA is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1* (*SMN1*) gene.

The safety and effectiveness of repeat administration or the use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated with ZOLGENSMA.

Important Safety Information
BOXED WARNING: Acute Serious Liver Injury
Acute serious liver injury and elevated aminotransferases can occur with ZOLGENSMA. Patients with pre-existing liver impairment may be at higher risk. Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer a systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion.

WARNINGS AND PRECAUTIONS
Thrombocytopenia
Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed at different time points after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

Elevated Troponin-I
Transient increases in cardiac troponin-I levels were observed following ZOLGENSMA infusion. Monitor troponin-I before ZOLGENSMA

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infusion and on a regular basis for at least 3 months afterwards.

ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence ≥5%) in clinical studies were elevated aminotransferases and vomiting.

Please see the accompanying Full Prescribing Information also available at www.Zolgensma.com.

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