Transcript Details
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Gene Therapy in SMA Care

Announcer:
Welcome to ReachMD.

This medical industry feature, titled “Gene Therapy in SMA Care,” is sponsored by Novartis Gene Therapies. This program is intended for healthcare professionals. Here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
Spinal Muscular Atrophy, or SMA, is among the most common rare diseases in the world, affecting 1 in every 10,000 births. It's crucial to diagnose and treat SMA as early as possible, given the progressive nature of the disease. Each patient's journey with the disease is unique, and based on a number of characteristics including age of diagnosis and disease type, healthcare providers should consider the need to diagnose and treat SMA as urgent.

This is ReachMD, and I'm your host, Dr. Jennifer Caudle. And joining me is Dr. Sandra Reyna, Vice President of Global Medical Affairs, Head Therapeutic Area at Novartis Gene Therapies. Together, we'll discuss SMA and the urgency to treat the often-devastating disease early on. We'll also discuss Zolgensma, onasemnogene abeparvovec-xioi, a gene therapy that addresses the genetic root cause of the disease with a one-time dose, and its potentially transformative impact on babies and young children diagnosed with SMA.

Zolgensma is indicated for children under 2 years of age and has a box warning for serious liver injury and acute liver failure. We'll cover important safety information throughout this podcast and the full prescribing information is provided.

Welcome Dr. Reyna. Please introduce yourself and we can dive in with a foundational question, what is SMA?

Dr. Reyna:
Thank you for having me. As a former practicing pediatric neurologist, this is a topic that is especially important to me. I am a clinician and researcher, and I have been involved in this field for over 20 years now. At this time, I'm very much focused in working in the industry, and I have been for the last 7 years. This has allowed me to really expand on my clinical practice when it comes to putting into place what I've known for patients and what I understand about the disease, and I'll apply that knowledge into now developing and being part of a program that allows for therapies to come forward for clinical and treatment care.

The disease that I work with, which is spinal muscular atrophy its been very, very dear to my heart, as I've been working so closely with these families for like I said almost 20 years now, and understand a lot of what the natural, you know, cause of disease is. And not only that, but also what is the natural course that this disease follows.

So I can tell you that SMA is a rare and often devastating genetic disease. SMA is caused by a lack of a functional *survival motor neuron 1* also known as *SMN1* gene. This results in the progressive and irreversible loss of motor neurons, which affects muscle function, including breathing, swallowing, and basic movement.

SMA is a leading genetic cause of infant death, and if left untreated, it can lead to progressive muscle weakness, paralysis, and in one of its most severe forms, permanent ventilation, or death in 90% of cases by the age of 2.

In its most severe forms, SMA progresses quickly, and once motor neurons have been lost, they cannot be recovered. It’s for this reason that healthcare professionals genuinely consider the diagnosis and treatment of SMA as medical urgency and emergency. It’s imperative to begin treatment, including proactive supportive care, as early as possible. We have an SMN backup gene which is known as the *SMN2* gene. And this gene produces a faulty and weak protein, but it still allows these children to survive. So therefore, the SMN protein that the *SMN2* gene produces is present, but in a very, very small amount.

It is important to treat SMA as early as possible.

Dr. Caudle:
Thanks for that overview. So how can doctors and these patient's families ensure that babies are getting diagnosed as early as possible?

Dr. Reyna:
You know, diagnosing and treating SMA quickly is crucial to stopping progression of the disease.

Unfortunately, many clinicians may not initially recognize the early signs of SMA, or may misattribute them to typical developmental delays, telling parents to wait and see how things are progressing. This can lead to delays in diagnosis and treatment.

One of the simplest ways to detect the disease is via a routine newborn screening exam. The aim of newborn screening is to detect treatable conditions in infants that are not clinically evident during the newborn period in order to intervene as early as possible. The detection of disease through newborn screening allows for timely access to treatment and effective care, resulting in improved clinical outcomes. For some children it can mean detecting and treating the disease before symptoms first appear.

In 2018, newborn screening for SMA was added to the Recommended Uniform Screening Panel, also known as RUSP, a federal list of often devastating disorders that require intervention as early as possible and have treatment options available. It is currently being adopted on a state-by-state basis.

Raising awareness of SMA and encouraging newborn screening for the disease are crucial to facilitate identification, diagnosis, treatment, and supportive care as early as possible.

Dr. Caudle:
So once a child is diagnosed with SMA, it's critical that they are treated as soon as possible. I understand that there's a one-time gene therapy treatment option that is available to children under 2 years of age. What can you tell us about that?

Dr. Reyna:
Oh my goodness, yes, there are now three FDA approved treatments available for the disease. As a clinician who has been working with SMA patients for decades, this is remarkable. As recently as 10 years ago, we often told parents of children diagnosed with SMA that there was nothing we could do to stop the disease's progression.

One of the approved treatments is Zolgensma, which was approved by the U.S. FDA in 2019, in May for children less than 2 years old with SMA. Zolgensma is the only gene therapy for SMA and is designed to address the genetic root cause of the disease by replacing the function of the missing or non-working *SMN1* gene with a single one-time dose. A new working copy of the gene is delivered to the patient cells, stopping SMA progression by telling motor neuron cells to make more of the important SMN protein. Zolgensma is a transformative gene therapy and represents a completely new class of SMA treatment. It's an essential treatment option, not only designed to provide a long-term benefit, but has one-time administration, a key differentiator from other SMA treatments. It's also the only gene therapy for SMA that continuously delivers functional SMN protein in motor neurons throughout the body.

You know, there are risks associated with Zolgensma, which is why it's important for each patient and family to work with their physicians to determine what treatment is right for them, weighing in both the potential benefits and potential risks.

Zolgensma has a box warning for serious liver injury and acute liver failure and patients with pre-existing liver impairment may be at higher risk. Cases of acute liver failure with fatal outcomes have been reported. Liver function needs to be assessed at baseline and for at least 3 months after infusion.

And you will need to administer an oral systemic corticosteroid before and after Zolgensma infusion. Platelet count and troponin I levels need to be assessed at baseline and monitored for at least 3 months after infusion.

The most common side effect that occurred in patients treated with Zolgensma were elevated liver enzymes and vomiting.

I would like to remind the audience to listen to additional important safety information at the end of this episode, and to see the accompanying full prescribing information including box warning, and you can visit www.zolgensma-hcp.com.

Dr. Caudle:
Dr. Reyna, you mentioned there are three treatments available for SMA. It's great that patients have options. Can you share a bit more about what physicians might consider when choosing a treatment? And can you share a bit more detail about Zolgensma? What patient populations have been studied? And what milestones are we seeing children with SMA achieve after its one-time use?

Dr. Reyna:

Thank you. I will definitely take that question one step at a time.

There are a number of elements to take into consideration when, recommending a treatment, including the route of administration. Zolgensma is given in a single dose through in an intravenous infusion for about an hour, and then the patients usually go home.

As mentioned earlier, patients will need to receive an oral corticosteroid before and post infusion. In post treatment, they will take the oral for at least 2 months after, depending on their liver function assessments. Baseline and monitoring labs for at least 3 months after infusion are required.

Other SMA treatment require chronic repeat dosing.

Another key element many physicians use as a parameter for selecting treatment is available data. Zolgensma has demonstrated significant and clinically meaningful therapeutic benefit in presymptomatic and symptomatic patients with SMA, including a prolonged event-free survival and achievement of motor milestones unseen in natural history of the disease. And to date, sustained for more than 5 years post-dosing.

Zolgensma continued to provide durable efficacy over 5 years after treatment in an ongoing long-term follow-up study of a Phase 1 START trial. All 10 patients from the START high-dose cohort who enrolled in a long-term follow-up were alive and free of permanent ventilation as of June 2020.

Most recently, final results from both the 2 and 3 *SMN2* gene copy cohorts of the completed Phase 3 SPR1NT trial, which followed the treatment of 29 presymptomatic patients. It demonstrated that whether they have 2 or 3 copies of the *SMN2* gene, most presymptomatic children with SMA treated with one-time Zolgensma were able to achieve age-appropriate motor milestones including sitting independently, standing, and walking.

The purpose of SPR1NT study was to evaluate the efficacy and safety of Zolgensma in patients younger than 6 weeks of age showing no symptoms of SMA. In this study, the Bayley-III scale was used to determine children's motor skills compared to what is expected of a typical developing child.

There were 14 patients in the 2-copy cohort. A hundred percent, or 14 of the 14, patients could sit independently [for] 30 seconds or more or, which was the primary endpoint, 79%, 11 of the 14, of the patients achieved this milestone within an age-appropriate time period, according to the World Health Organization multicenter growth reference study, or WHO, which established windows of achievement for the development of motor milestones. 71% of the patients, or 10 of the 14, stood without assistance for more than 10 seconds. According to the WHO scale, 5 of the 10 patients achieved this milestone within age-appropriate time period; 71% of the patients, or 10 out of the 14, walked without assistance, which is five steps or more according to the WHO scale, 6 of the 10 patients achieved this milestone within age-appropriate time period.

A hundred percent of patients, 14 out of 14, reached CHOP-INTEND score of 58 or higher at any visit up to 18 months of age. And 93%, 13 of the 14, achieved a score of 60 points or higher, keeping in mind that this scale has a total of 64 points.

Ninety-three percent, 13 of the 14, of patients were able to maintain weight. This is greater than or equal to the 3rd percentile for age and gender as defined by WHO, without need of non-oral or mechanical feeding support at all visits up to 18 months of age. The study duration for this cohort was until 18 months of age.

Then we can describe now the 3-copy baby cohort. A hundred percent of the patients, 15 of the 15, stood without assistance for 3 seconds or more as measured again by the Bayley scale, which was the primary endpoint; 93%, 14 of the 15, of the patients achieved this milestone within age-appropriate time period; 93% of the patients, 14 of the 15, patients walked without assistance as measured by the Bayley scale; 11 of the 14 patients achieved this milestone within age-appropriate time period; 93% of the patients, 14 of the 15, of the patients stood with assistance, which is 10 seconds or more according to the WHO scale. 11 of the 14 achieved this milestone within an age-appropriate time period. The study duration for this cohort was until 24 months of age.

Now both groups were alive and free of permanent ventilation at the end of the study. This data really represents a significant contrast to the natural history of SMA. Novartis Gene Therapies continues to monitor product safety including a long-term, about 15 years, of safety follow-up studies in patients treated with Zolgensma. To date, more than 3,000 patients have been treated with Zolgensma worldwide across clinical trials, managed access programs, and in the commercial setting.

Dr. Caudle:
Thanks, Dr. Reyna. We understand that living with SMA can be a lifelong burden for patients and their families. After one-time treatment with Zolgensma, is there a need for continued therapy?

Dr. Reyna:

Very good question. Each patient's journey is unique. And it is important to define what success might look like for each individual patient as their underlying disease characteristics and timing of diagnosis and treatment elements is critical to treatment outcomes. And this can vary hugely.

So I can tell you, from my own experience, the difference that I was able to see, when I would diagnose a patient early in life, literally right after birth, and start any form of treatment, whether that was standard of care, whether that was prescribing whatever medication was available at the time that I was seeing patients, and there was a very huge difference between those who were diagnosed and identified early and started planning on their treatment versus those who came to me after symptoms had already set in.

There is a window of opportunity that should be important to stress when these patients are there in front of you. How are they presenting? What are the signs? What is the immediate management that these children have to have as part of the standard of care plus now available therapies?

You know, there is currently no data-driven evidence for, or against add-on therapy following treatment with Zolgensma. And it potentially presents greater burden to the patient and the healthcare system as a whole. I recognize there are questions amongst some of the SMA community to understand the best possible treatment outcomes for every patient.

Each child is different. And what's best for the child depends on what the pediatrician or pediatric neurologist determines is necessary. Some patients will require a combination of supportive devices and therapies after treatment, which can include respiratory support by mechanical equipment like BiPAP, or a feeding tube, an assistive walking device or wheelchair, physical therapy, occupational therapy, or other therapies to ensure muscle development.

So therefore, in my own experience, I can tell you that treating patients early is critical. I have seen it firsthand, and it makes a difference in the world. Every motor milestone gained for this child is a huge gain compared to what their life would be without any treatment.

Dr. Caudle:
Thanks Dr. Reyna. And lastly, coming back to the big picture on SMA, what do you most want our listeners to take away from today's discussion?

Dr. Reyna:
Thank you for asking that. I'd like to return to the point we made earlier. It's so important to keep in mind. It is imperative to diagnose SMA as quickly as possible. The sooner a patient is diagnosed, the sooner their physicians can begin to formulate a treatment plan.

But as clinicians, we also need to recognize the signs of SMA as quickly as possible. So hypotonia or muscle weakness, labored breathing or difficult breathing, poor head control, and difficulty swallowing, are all warning signs to be aware of.

For patients that have been diagnosed, there are transformative therapy options, like Zolgensma, that are designed to provide a long-term benefit. The results we've seen from the one-time gene therapy are remarkably impactful. In fact, children treated pre-symptomatically with Zolgensma achieved standing and walking, some were even able to achieve motor development indistinguishable from their healthy peers without SMA. Of course, results and outcomes vary among children based on several factors, including how far their SMA symptoms have progressed prior to receiving treatment.

Dr. Caudle:
That's a great comment for us to think on, as we come to the end of today's program. I'd like to thank my guest for helping us better understand SMA, the importance of diagnosing and treating it quickly, and the potential clinical benefit of Zolgensma. As with any treatment, there are potential risks associated with Zolgensma. And patients will be monitored for at least 3 months after dosing. Dr. Reyna, it was great speaking with you today.

Dr. Reyna:
Thank you so very much for having me.

Dr. Caudle:
Please stay tuned to hear some important safety information.

Announcer:
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.

Limitations of Use
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: Serious Liver Injury and Acute Liver Failure

Cases of acute liver failure with fatal outcomes have been reported. Acute serious liver injury, acute liver failure, and elevated aminotransferases can also occur with ZOLGENSMA. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing. Administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion, and at other times as clinically indicated. If acute serious liver injury or acute liver failure is suspected, promptly consult a pediatric gastroenterologist or hepatologist.

WARNINGS AND PRECAUTIONS

Systemic Immune Response

Patients with underlying active infection, either acute or chronic uncontrolled, could be at an increased risk of serious systemic immune response. Administer ZOLGENSMA to patients who are clinically stable in their overall health status (e.g., hydration and nutritional status, absence of infection). Postpone ZOLGENSMA in patients with infections until the infection has resolved and the patient is clinically stable.

Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were typically observed within the first two weeks after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA) were reported to occur generally within the first two weeks after ZOLGENSMA infusion. TMA can result in life-threatening or fatal outcomes. Obtain baseline creatinine and complete blood count before ZOLGENSMA infusion. Following infusion, monitor platelet counts closely as well as other signs and symptoms of TMA. Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage as clinically indicated.

Elevated Troponin-I

Increases in cardiac troponin-I levels were observed following ZOLGENSMA infusion. Monitor troponin-I before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards. Consider consultation with a cardiologist if troponin elevations are accompanied by clinical signs or symptoms.

ADVERSE REACTIONS

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

Announcer:

This program was sponsored by Novartis Gene Therapies. If you missed any part of this discussion, visit reach-m-d-dot-com-slash-industry-feature. This is ReachMD. Be part of the knowledge.