Transcript Details
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Spinal Muscular Atrophy (SMA) in Adults: Perspectives on a Treatment Choice and the Importance of Monitoring Motor Function

ReachMD Announcer:
Welcome to ReachMD. This medical industry feature, titled “Spinal Muscular Atrophy in Adults: Perspectives on a Treatment Choice and the Importance of Monitoring Motor Function,” is sponsored by Biogen. Here’s your host, Dr Laurey Brown.

Dr Brown:
Welcome to our program on treating adult patients with later-onset SMA. I’m Dr Laurey Brown, a physical therapist, and joining me in this program is Dr. Vamshi Rao, a neurologist who I collaborate with frequently. Dr Rao and I have worked with several individuals with SMA of all ages. Today, we’ll first discuss the importance of regular monitoring, and review motor scales for SMA patients. Next, Dr Rao will go over the considerations for treating adults and clinical trial data for SPINRAZA in later-onset SMA. Finally, we’ll discuss some real-world evidence of SPINRAZA use in adults, and outcomes in a hypothetical SPINRAZA patient.

Before we begin, I’d like to disclose that all participants are receiving compensation from Biogen. Let’s get started.

Primary rehabilitation goals are set based on the level of motor function that a patient has at the time of assessment.[1,2] These goals may change as a patient’s ongoing needs and concerns shift over time.[1] For non-sitters, the goals are optimizing their functional ability and outcomes.[2] Physical and occupational therapy can help these patients with head control as well as postural control and alignment.[2] For sitters, the main objectives are to maintain or improve function, positioning, and mobility.[2] Regular stretching is helpful for these patients, and light weight-bearing orthoses may help with assisted or supportive standing or assisted ambulation in patients with sufficient strength. Mobile arm supports can help improve upper extremity function.[1,2] For walkers, the main objectives are maintaining, restoring, or improving function and mobility, in addition to improving the ability to walk for longer.[2] Orthotics may support functional walking, whereas a wheelchair or scooter can add mobility for longer-distance transportation.[1]

There are several standardized scales used to assess function in SMA. These are categorized according to patient age or motor function. The HINE assesses motor milestones in patients between the ages of 2 months and 24 months.[3-5] CHOP INTEND is used to measure motor skills in infants or children with infant-level motor function.[5-7] The HFMSE was designed to assess motor function in later-onset SMA.[8,9] ULM, and RULM, capture functional capabilities in non-ambulatory patients with SMA.[10,11] The 6-Minute Walk Test is a measure of exercise capacity and motor function in ambulatory patients.[12,13] This is not an exhaustive list of scales that are designed to monitor disease progression and improvement. So the scales that we choose for our patients are selected based on if they are required by payers, patient burden, ease of administration, reliability, and sensitivity to changes.[14] Let’s take a look at how we assess motor ability in clinical practice by examining a hypothetical patient case.

Here’s our patient, David, who was 21 years old in 2016. Let’s review his clinical presentation before he received any drug treatment. He was diagnosed with Type 2 later-onset SMA when he was 18 months old. At the time, there was no treatment available. He was unable to walk independently and used a wheelchair at home and work. He had trouble with physical transitions, like going from sitting to lying down or rolling in bed. He also noticed a progressive decline in his upper limb function, leading to trouble with daily activities, such as lifting his morning coffee mug. David’s presentation is representative of patients I see in the clinic. Since David has later onset SMA and is unable to walk independently, we would use HFMSE and RULM to measure motor ability. Let’s look at exactly what these two scales measure.

The HFMSE is used to evaluate overall motor function in later-onset SMA.[8,15] 33 items are grouped into seven categories sitting, rolling,

transitioning to crawling, standing or stopping, transitioning to kneeling, squatting or jumping and climbing stairs.[8,15] Each item is scored from 0 to 2, where 0 represents no response and 2 represents a complete response.[8,15] The total score is the sum of all points from each item and ranges from 0 to 66.[8,15] A change of ≥3 points may be considered clinically meaningful.[16] The HFMSE is often used as an outcome measure in SMA clinical trials.[8]

Now let's take a look at RULM. The RULM captures a wide spectrum of functional capabilities in both ambulatory and non-ambulatory patients with SMA.[11] There are 19 assessments utilizing 7 everyday items and test the ability of the patient to write, tear paper, drop coins, lift cups and small weights, push buttons and manipulate lids on containers.[11] The total score ranges from 0 to 37.[11] A change of ≥2 points may be considered clinically meaningful.[16]

Let's revisit David. Upon performing the HFMSE and RULM assessments, we find that his untreated baseline HFMSE score is 18 and RULM score is 20. Later in the presentation, we will see how these scores may change after treatment, and what this means for David. In terms of management, it's important to remember that David's care team could span different specialties, so communicating David's motor ability to interdisciplinary team members is important and consistent with the standard of care for SMA.[4,5] For David's physical therapy program, I would recommend strengthening focused on core and upper extremity activation multiple times per week.[2] The SMA standard of care guidelines recommend standing for about 60 minutes, multiple times a week.[2] For David, this would likely look like standing with the use of a supported stander. There should also be some sort of aerobic exercise multiple times per week, alternating with strengthening days.[2] And of course, consistency is key and seeing David routinely to watch out for changes in his motor ability is really important.

That brings us to the end of Part 1. Next, we'll review clinical trial data in later-onset SMA.

Dr Rao:
Welcome to Part 2 of our program. I'm Dr Vamshi Rao. The therapeutic landscape for SMA has evolved considerably over the last few years. Thanks to widespread adoption of newborn screening, many patients are being diagnosed earlier and are able to seek treatment sooner.[1] As adolescents with SMA transition into adulthood, around age 13, we introduce them to adult care, where the focus shifts from a family unit model to an individual model. Transition should ideally occur between the ages of 18 and 21, at which point the patient may feel empowered to participate in their own care.[2]

In terms of treatment goals and considerations for adults with SMA, we want to maintain mobility for as long as possible. So, we develop a comprehensive plan, integrating drug treatment with physical therapy, that fits with the patient's goals. This may help the patients maintain the motor milestones that they are able to achieve.[3] We'll dive into SPINRAZA clinical data next, but first, let's review some important safety information.

ReachMD Announcer:
INDICATION
SPINRAZA®, also known as nusinersen, is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.[4]

SELECTED IMPORTANT SAFETY INFORMATION
Coagulation abnormalities and thrombocytopenia, including acute severe thrombocytopenia, have been observed after administration of some antisense oligonucleotides. Patients may be at increased risk of bleeding complications. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 24 of 146 SPINRAZA-treated patients (16%) with high, normal, or unknown platelet count at baseline developed a platelet level below the lower limit of normal, compared to 10 of 72 sham-controlled patients (14%). Two SPINRAZA-treated patients developed platelet counts less than 50,000 cells per microliter, with the lowest level of 10,000 cells per microliter recorded on study day 28. Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. SPINRAZA is present in and excreted by the kidney. In the sham-controlled studies for patients with infantile-onset and later-onset SMA, 71 of 123 SPINRAZA-treated patients (58%) had elevated urine protein, compared to 22 of 65 sham-controlled patients (34%).[4]

Dr Rao:
SPINRAZA is an intrathecal injection administered by, or under the direction of, healthcare professionals experienced in performing lumbar punctures. The recommended dosage is 12 mg, or 5 mL, per administration.[4] Treatment with SPINRAZA begins with 4 loading doses. The first 3 doses are administered at 14-day intervals. The fourth dose should be administered 30 days after the third dose. After the starting dose period, a dose should be administered once every 4 months.[4]

The SPINRAZA clinical trial program includes efficacy and safety data from over 7 years of clinical trial data and more than 15 real-world studies.[4-14] The SPINRAZA clinical program included four studies in infants, which includes the ENDEAR study and the ongoing NURTURE study.[4-6] SPINRAZA has also been studied in later-onset SMA. CHERISH and CS2/CS12 evaluated SPINRAZA in children aged 2-16 years.[4,8,9] Let's take a closer look at the CHERISH trial.

CHERISH was a Phase 3, randomized, double-blind, sham-controlled trial designed to evaluate the efficacy and safety of SPINRAZA in individuals with later-onset SMA.[4,8] 126 individuals with Type 2 or 3 SMA were included in this study.[8] 84 trial participants were treated with SPINRAZA and 42 underwent a sham-control procedure.[8] 12 mg of SPINRAZA was administered intrathecally on days 1, 29, and 85, and a maintenance dose was administered on day 274.[8] The primary endpoint was least-squares mean change from baseline in the HFMSE total score at month 15. Patients treated with SPINRAZA demonstrated a 3.9-point mean increase from a baseline score of 22.4, and sham control patients had a 1.0-point mean decrease in HFMSE score from a baseline score of 19.9.[4]

The secondary endpoint looked at the clinically meaningful change in HFMSE scores, which translates to an increase of 3 or more points in the HFMSE score. At 15 months, twice as many patients treated with SPINRAZA achieved a clinically meaningful change in HFMSE score from baseline.[4] These data show that SPINRAZA treatment improved motor outcomes in later-onset SMA. The most common adverse reactions that occurred in at least 20% of SPINRAZA-treated patients and at least 5% more frequently than in control patients were fever, headache, vomiting, and back pain.[4]

That brings us to the end of Part 2.

ReachMD Announcer:
Laboratory testing and monitoring to assess safety should be conducted. Perform a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing at baseline and prior to each dose of SPINRAZA and as clinically needed.[4] Severe hyponatremia was reported in an infant treated with SPINRAZA requiring salt supplementation for 14 months. Cases of rash were reported in patients treated with SPINRAZA. SPINRAZA may cause a reduction in growth as measured by height when administered to infants, as suggested by observations from the controlled study. It is unknown whether any effect of SPINRAZA on growth would be reversible with cessation of treatment. The most common adverse reactions (greater than or equal to 20% of SPINRAZA-treated patients and greater than or equal to 5% more frequently than in control patients) that occurred in the infantile-onset controlled study were lower respiratory infection and constipation. Serious adverse reactions of atelectasis were more frequent in SPINRAZA-treated patients (18%) than in control patients (10%). Because patients in this controlled study were infants, adverse reactions that are verbally reported could not be assessed. The most common adverse reactions that occurred in the later-onset controlled study were pyrexia, headache, vomiting, and back pain. Post-lumbar puncture syndrome has also been observed after the administration of SPINRAZA.[4]

Please see full prescribing information via the link provided for additional important safety information.

Dr Brown:
In Part 3 of our program, let's review the real-world evidence for SPINRAZA treatment in adults with SMA. Beyond the clinical program, real-world evidence for SPINRAZA in teens and adults is growing and has expanded to include more than 15 independent, observational studies.[1-17] These studies have looked at outcomes of SPINRAZA treatment in adults ranging from 16 to 72 years.[1-17] Keep in mind that you should inform patients and caregivers that SPINRAZA can increase the risk of bleeding and could cause renal toxicity, and of the importance of obtaining blood laboratory testing and urine testing at baseline and prior to each dose. More recently, Coratti and colleagues performed the most comprehensive critical review and meta-analysis of SPINRAZA efficacy.[17]

This review was a meta-analysis assessing the motor function benefit upon SPINRAZA treatment.[17] Using PRISMA guidelines, publications containing structured assessments of SPINRAZA efficacy in later-onset SMA patient cohorts were identified. 30 full-text articles were selected and analyzed, of which 15 studies were in adults treated with SPINRAZA, while 10 papers included data from untreated adults.[17] Subgroup analyses were further conducted to understand the influence of age, SMA type, and motor function on the pooled results of the treated population.[17]

Dr Rao, could you take us through some limitations and results from the study?

Dr Rao:
Sure. Limitations were that not all studies included details on similar variables; therefore, detailed statistical analysis or meta-analysis could not be performed for all variables.[17] Some studies had a small number of participants, leading to increased variability, high heterogeneity, and broad confidence intervals, so a direct comparison with studies in untreated patients cannot be made.[17] Overall, the

meta-analysis found that the benefit of SPINRAZA treatment was statistically significant.[17] HFMSE scores showed a pooled mean change from baseline of 2.27.[17] For RULM, the pooled mean change from baseline was 1.11, and for the six minute walk test, the pooled mean change from baseline was 19.8 meters.[17]

For patients in the untreated cohorts, the pooled mean change from baseline was −1.00, indicating a significant reduction of the mean HFMSE score from baseline.[17] For RULM, the pooled mean change from baseline was 0.47, and for the 6MWT, the pooled mean change from baseline was –8.29.[17]

Dr Brown:
Thank you, Dr Rao. Real-world studies provide us with more information for treating diverse patient types, since clinical trials cannot capture the full spectrum of individuals with SMA. Real-world studies can fill that gap.[18]

Dr Rao:
Absolutely. Also, disease registries are crucial because they help ensure that real-world data are collected properly. One of the largest SMA registries is the Biogen-sponsored International SMA Consortium Registry, which follows patients of all ages across the US, the UK, and Italy.[18] Having access to additional data is valuable, because we can get a better understanding of how SPINRAZA works in different types of individuals with SMA. Safety was not critically evaluated in this publication, but we know that common side effects of SPINRAZA include pyrexia, headache, vomiting, and back pain, and that post-lumbar puncture syndrome has also been observed after administration of SPINRAZA. Let's revisit David, the patient we introduced in Part 1.

Here is David, now 22 years old, treated with SPINRAZA for about 15 months. He has increased overall muscle strength, which helps him transition from sitting to lying down or rolling in bed. He also has improved ability to hold his morning coffee mug.In terms of his scores, he has a 3-point increase from his baseline in the HFMSE scale. His RULM score increased by 2 points from baseline. His side effects include headache and back pain. David's results align well with the outcomes of participants in published studies and patients I've treated in my practice.[19,20] We see that David has expressed an interest in switching therapies.

A conversation about treatment choice involves shared decision-making. So, if David was my patient, I would help him understand the safety and efficacy of all treatment options. We would talk about why he wants to switch and manage his expectations regarding outcomes. We would come up with a treatment plan based on his goals.[21-23] I would also help David realize the importance of continuous treatment evaluations.[24] Finally, I would remind David that SMA treatments are not a cure, so he will likely be on therapy for a long time.[25]

After discussing with his neurologist, David tried another treatment, but after a few months, decided it wasn't the right fit for him and switched back to SPINRAZA. Some patients have been on a different journey, and have made unique, individualized choices. I have had a few patients like David, who have changed therapies, then switched back to SPINRAZA. You can access the SPINRAZA Prescribing information via the link provided for guidance on how to approach delayed and missed doses. Dr Brown, how would you monitor patients like David who have restarted SPINRAZA?

Dr Brown:
When patients like David switch back to SPINRAZA, we like to monitor motor function and range of motion, looking for either gains or losses of functional ability and to identify what we need to focus on improving. So I would check his range of motion and use Hammersmith and RULM to test his strength. I would think about how well David can function overall, how easily he transitions in and out of his equipment at home, and how he manages transportation. If he is not fully comfortable with managing his SMA care, I would help advocate for him to instruct others in his life on how to assist him. While standardized assessments are helpful for tracking objective changes, to help gain an accurate picture of change, we also assess the patient's subjective reports. Adult patients present an additional challenge for performing follow-up assessments as they typically have jobs and busy schedules. So when possible, we schedule patients for their assessments on the same day as their dose to limit the burden of care and to optimize care delivery. At the end of the day, the choice of therapy is a joint decision between the patient and their care team, keeping in mind the patient's treatment goals.

Let's close our program today by looking at a real patient who switched therapies, and then came back to SPINRAZA. Dr Rao, will you introduce us to Ryan?

Dr Rao:
Here is Ryan, an actual individual living with Type 2 SMA, who was treated with SPINRAZA. While being treated with SPINRAZA, Ryan was curious to try another treatment. After a few months, he realized that it wasn't right for him and decided to go back to SPINRAZA. I've certainly treated patients who have switched therapies, and all such conversations involve shared decision-making with the patient.

That brings us to the end of our program.

Dr Brown:
We hope you enjoyed our discussion today.

Dr Rao:
Thank you for joining us today.

ReachMD Announcer:
This program was brought to you by Biogen. Please see the SPINRAZA full Prescribing Information at the link provided. Additionally, for more educational videos about SPINRAZA, please visit SPINRAZAhcp.com. Visit ReachMD.com/IndustryFeature if you'd like to watch today's presentation again. This is ReachMD. Be Part of the Knowledge.

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