Reviews

Risdiplam for the Use of Spinal Muscular Atrophy

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Spinal muscular atrophy (SMA) is one of the leading causes of death in infants related to the degeneration of neurons. Currently, there are no curative treatment options for SMA, and many options available may not be feasible. This review presents the background, clinical studies, and indications for the use of Risdiplam in treating SMA. SMA causes a decrease in the production of survival motor neuron proteins (SMN) and current treatments target to increase the expression of SMN. Risdiplam is the first and only oral medication to be approved to treat SMA. As an SMN2 splicing modifier, it has provided stronger systemic therapies than previous intrathecal and gene replacement therapies. There have been many efforts to treat SMA with multidisciplinary approaches. These include intrathecal injections to gene replacement therapies. However, these have been faced with limitations such as reaching a good therapeutic dose in systemic tissues, route of administration, and price. Risdiplam is currently the only orally administered drug approved by the FDA for the treatment of SMA. It not only provides a good therapeutic window to systemic tissues but allows for a non-invasive approach in infants. Further investigation and comparison on the safety profile of Risdiplam due to its broader systemic effect should be considered with other available therapies.

INTRODUCTION: SMA TYPES AND EPIDEMIOLOGY

Spinal muscular atrophy (SMA), the leading genetic cause of infant death, is a neurodegenerative disease of the anterior horn of the spinal cord and lower brainstem neurons.[1,2] Loss of these motor neurons results in the characteristic non-progressive weakness of SMA.[3] Spinal muscular atrophy is inherited in an autosomal recessive pattern, resulting from most classically homozygous deletions of the survival motor neuron 1 (SMN1) on chromosome 5q13.2 in 92% of cases. The carrier frequency is 1/50, with an incidence of 1/12,000 and prevalence of 1/100,000.[4] There are various types of spinal muscular atrophy that are classified based on metrics of disease presentation, including the age of onset, highest motor function achieved, and age of death. Type 1 SMA, also known as Werdnig Hoffman Disease, is the most common and most severe, occurring in months 0-6 of life with an average age of death of less than two years old.[5] This accounts for approximately 50% of the cases of SMA. Type 2 and type 3, also known as Kugelberg Welander Disease, are milder forms diagnosed in early childhood but have longer life expectancies depending on the individual disease severity. Type 4 SMA is adult-onset in the 2nd or 3rd decade of life and is the highest functioning form of the disease.[6]

CLINICAL MANIFESTATIONS

Spinal muscular atrophy is classified as a motor neuron degenerative disease involving the anterior horn of the spinal

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cord and lower motor neurons. This is due most commonly to a homozygous deletion of SMN1 on chromosome 5q11.2-13.3, resulting in an absence or decrease in deep tendon reflexes, diffuse symmetrical proximal weakness of the lower limbs, and ultimately skeletal muscle atrophy.[7] While those diagnosed with SMA classically have alterations or deletions in the telomeric SMN1 gene. The centromeric SMN2 gene also plays a role in the phenotypic expression of the disease. SMN2 is almost genetically identical to SMN1 except for a single-point mutation. This mutation causes exon 7 to be skipped during pre-mRNA processing, causing the subsequent mRNA to be rapidly degraded, which leads to a lower functional protein yield.[8] There is currently no absolute genotype to phenotype correlation between the SMN genes and disease progression.[7] However, increased copy numbers of SMN2 are associated with the less severe clinical phenotypes due to its ability to function similarly to SMN1 when present in higher quantities. Low levels of the FL-SMN protein made by SMN2 are sufficient to ensure embryonic development and preventing the disease from becoming embryonically lethal.[9]

As previously discussed, phenotypic classifications of SMA are organized by the age of onset, the highest level of motor function, and age of death. Type 0, commonly recognized as a variant of type 1 SMA, is the most severe disease form with prenatal onset and death typically within one week of delivery. These patients present at birth with hypotonia, a weak cry, poor feeding, joint contractures, and diminished fetal movement in utero. Patients with type 0 SMA also require respiratory support at the time of birth.[7]

Type 1 SMA, also known as Werdnig Hoffman Disease, presents between birth and six months of age with limb weakness, weak cry, poor feeding, respiratory distress, and a splayed or "frog-leg" posture. Tongue fasciculations are also a common presentation. These patients commonly have a bell-shaped chest with paradoxical breathing, which is a pattern that shows flattening of the chest wall and protrusion of the abdomen with inspiration. The eye and facial muscles are typically spared along with patient cognition. The highest level of motor function achieved is sitting with support, and the patient often dies of respiratory distress at less than two years old.[7,8]

Type 2 SMA, an intermediate form, presents between 6 and 18 months with proximal weakness of lower limbs, absent reflexes, minipolymyoclonus in distal limbs, and tongue atrophy with fasciculations. In addition, scoliosis is a common manifestation of the disease, which contributes to restrictive lung complications. Like type 1, the facial muscles and eyes are often spared, but these patients have a higher level of motor function and can often sit without support by age nine months. In most patients with Type 2 SMA, death occurs before age 25. However, some may live longer than this anticipated age.[8]

Type 3 SMA, also known as Kugleberg-Welander disease, is an even milder form with presentation older than 18 months and often further into childhood. These patients present with difficulty climbing stairs and frequent falls, both of which are attributed to the characteristic proximal muscle weakness. These patients can often walk independently, but this skill may be lost with disease progression. Most patients with this phenotype of SMA have a normal lifespan.[7,8]

The last type of SMA is Type 4, or adult-onset SMA. These patients have very mild muscular symptoms and can walk independently throughout the disease course. The lifespan of a patient with type 4 SMA is also a normal adult life span.[7,8]

Other non-5q spinal muscular atrophy variants exist, including X-linked Spinal and Bulbar Muscular Atrophy, Hexosaminidase A deficiency, Monomelic Muscular Atrophy, and Fazio Londe disease. X-linked Spinal and Bulbar Muscular Atrophy, also known as Kennedy disease, is a progressive lower motor neuron disease in older men due to a CAG trinucleotide repeat in the androgen receptor gene. This additionally presents with gynecomastia, testicular atrophy, and reduced fertility in addition to the muscular symptoms. Hexosaminidase A deficiency presents with proximal muscle weakness, dystonia, and cerebellar dysfunction due to GM2 ganglioside accumulation. Monomelic muscular atrophy is cervical muscle weakness, presenting in the first month of life with neck flexion and neck extension weakness. Lastly, Fazio Londe presents with proximal muscle weakness in addition to hearing loss, cranial nerve involvement, and upper motor neuron symptoms.[6]

DIAGNOSIS

Currently, the standard tool for diagnosing SMA is molecular testing. This confirms 95% of suspected cases but will not diagnose compound heterozygotes or those with frameshift, nonsense, or missense mutations. SMN2 copy numbers are also determined to help predict the phenotypic severity of the disease, although the correlation is not absolute. If there is a high index of suspicion and testing molecular testing is negative, an SMN1 dosage analysis and gene sequencing should be performed to analyze the possibility of the patient having a rarer genetic cause of the disease.[10]

Other types of testing less commonly employed include electromyography and muscle biopsies. Electromyography, or EMG, would classically show signs of denervation. This would consist of positive sharp waves, fibrillation, and occasional fasciculations. It would also show high amplitude waves, longer durations, and decreased muscle recruitment. This type of testing is only considered if patients are negative for both the classic deletion and other mutational testing. Muscle biopsy is no longer performed, even in patients with atypical testing or negative genetic testing. However, historically it showed atrophic fibers within islands of hypertrophic fibers.[10] Post-mortem autopsy often shows loss of motor neurons in the anterior horn, as anticipated based on the clinical symptomology of the disease.[11,12]

COMPLICATIONS

Complications of SMA vary based on disease type and progression. Some of the most notable involve feeding problems, including limited mouth opening, chewing difficulties (38%), choking (30.6%), and dysphagia. These are particularly apparent in SMA Type 2 patients over 20 years old. This increases the patient risk for aspiration pneumonia (9.3%) and can result in patients becoming underweight

(33.3%) in a study involving individuals with diagnosed Type 2 and 3 SMA.[13]

Another important complication of SMA involves its effect on the respiratory system. Bulbar dysfunction is a common feature in particularly Type 2 SMA, which leads to poor respiratory effort due to respiratory muscle weakness. Hypoventilation and restrictive lung disease, often secondary to scoliosis in type 2 and 3 SMA, also contribute to the respiratory distress common in nearly all types of SMA.[10] This is often ameliorated with respiratory toilet, non-invasive ventilation, and antibiotics to prevent infection secondary to aspiration.

Gastrointestinal symptoms can also complicate the diagnosis of spinal muscular atrophy. This can involve constipation due to poor abdominal muscle tone, leading to bowel impactions in the non-ambulatory and gastroesophageal reflux disease (GERD). While uncommon in the forms that cause early death, depression and other psychiatric issues can complicate those cases surviving into adolescence.[14]

CURRENT TREATMENT OF SPINAL MUSCULAR ATROPHY

Current guidelines for the treatment of SMA involve a multidisciplinary approach focused on improving the function of multiple systems and tissue types.[15] This autosomal recessive disease leads to the apoptosis of lower motor neurons, mainly the anterior horn cells. The damaging effects on alpha motor neurons lead to the clinical symptoms of this disease, such as muscle and bulbar weakness, atrophy, and hypotonia that cause numerous downstream effects. Orthopedic management of scoliosis, positive airway pressure for respiratory support, and nutritional support improve clinical outcomes but do not target the protein deficiency causing disease.[16] Beyond the nutritional, orthopedic, and respiratory support, several innovative approaches developed recently targeting the protein deficiency that leads to this historically lethal disease. The treatment depends on the clinical phenotype and the classification of disease severity from one of the five forms of the disease: SMA type 0, type 1 (Werdnig-Hoffman), type 2, type 3, and type 4. The severity of the disease ranges from the most severe SMA type 1 to the mildest SMA type 4 and is inversely related to the number of SMN gene copies. SMA type 1 typically leads to death within the first two years of life. With other SMA types, children may survive to adulthood with delayed motor milestones and other serious difficulties. The older the onset of the disease, the better the disease prognosis.

The underlying genetic defect leading to spinal muscular atrophy is a decrease in the survival motor neuron protein (SMN) production caused by either a deletion or mutation in the SMN1 gene. This protein is expressed in cells throughout the body, such as skeletal muscle, cardiac muscle, and bone. Another SMN gene, SMN2, produces some SMN protein, but the amount is insufficient to accommodate for loss caused by the SMN1 gene deletion.[17] Generally, people have two copies of the SMN1 gene and the number of copies of the SMN2 gene varies, with some having up to 8 (NIH). In about 96% of patients, there is a homozygous deletion of both exon 7 and 8 from the SMN2 gene on chromosome 5q or just exon 7, leading to drastically diminished SMN protein.[15] The amount of SMN2 gene copies a person has is inversely correlated with disease severity and is a target for treatment. Therefore, patients with multiple copies of the SMN2 gene tend to have less severe clinical disease. Many of the drugs developed to target the more severe forms of SMA, such as SMA1 because without treatment SMA type 1 has a life expectancy of under two years of age due to rapidly progressive respiratory collapse. These patients present clinically before six months of age as "floppy babies" due to deterioration of anterior motor neurons. SMA type 2 is the most common type of spinal muscular atrophy and is the focus of many treatments. Early initiation of treatment, especially pre-symptomatic treatment, is the only definitive factor linked with treatment success.[18]

NUSINERSEN

Nusinersen (Spinraza) is an antisense oligonucleotide drug injected intrathecally into patients with SMA and gained FDA approval in 2016. Before 2016, SMA therapies were mainly just supportive measures to improve quality of life and did not preserve alpha motor neurons or improve muscle weakness. Hence, the development of nusinersen was fascinating. Nusinersen's mechanism of action involves modulating the pre-mRNA splicing of SMN2 protein, leading to greater production of SMN2 protein. Nusinersen is the first drug approved for SMA treatment in pediatric and adult patients and has shown promising results in clinical trials.[19] In a double-blind, placebo-controlled study of 121 SMA type 1 patients, a statistically significant difference between untreated and early treated patients for a time of death or time to permanent ventilation was demonstrated, supporting the correlation between the earlier onset of treatment and treatment efficacy. Motor outcomes were also improved in the early treatment group (93%) compared to only 13 of 29 patients who had motor improvement in the later treatment group (after 13.1 weeks of symptoms).[19] The trial was ended after 13 months due to the significant increase in motor milestone response shown with Nusinersen compared to sham treatment. Because Nusinersen is administered intrathecally, its effects are limited to the CNS motor neurons and do not affect the levels of SMN in other systemic tissues. The limitations to intrathecal administration of Nusinersen can be a problem for patients with scoliosis, spinal disc fusion, or other spinal deformities, which are common in patients with SMA type 2. Lumbar puncture in these patients can be profoundly difficult to achieve. To overcome these difficulties, image-guided intrathecal administration is recommended in these patients.

ZOLGENSMA.

Zolgensma (Onasemnogene adeparvovec), previously known as AVXS-101, is a gene replacement therapy approved in 2019 to treat patients with SMA under two years of age. Zolgensma uses a self-complementary adeno-associated virus capsid to transport a functional copy of the SMN gene to cells in the central nervous system.[20] Unlike Nusinersen, Zolgensma can penetrate the blood-brain bar-

rier and therefore may be delivered by a single intravenous injection.[20] The efficiency of this drug being only a one-dose treatment and the promising results of clinical trials so far is possibly reflected in its price, at one time being close to 2 million dollars. In a Phase 1 study of 15 infants with SMA type 1, all patients were alive and not using permanent ventilation at two years following a single IV injection of Zolgensma. 92% of these patients could sit unassisted, 17% could stand unassisted, and 17% could walk unassisted.[21] Patients also demonstrated increased respiratory function and ability to feed themselves independently.[21] Again, the earlier the treatment was initiated, the better the results.

RISDIPLAM

Risdiplam is the only orally administered drug approved for the treatment of SMA. It was FDA approved in 2020 for use in patients two months of age and older, and it functions as an SMN2 gene splicing modifier leading to higher levels of SMN protein. Oral administration is a significant advantage of this drug because it can affect systemic tissues involved in the multisystem pathogenesis of this disease.[22] In different mouse models, Risdiplam was found to increase survival by increasing the SMN2 mRNA in a dose-dependent manner.[22] There are currently four phase 2 trials testing the safety and efficacy of Risdiplam for use in different SMA types.[22] Compared to the natural progression of the disease, event-free survival time was significantly increased in infants treated with Risdiplam for 12 months.[22] Within four weeks of treatment initiation, Risdiplam lead to a greater than a 2-fold increase from baseline levels of SMN protein, and these results were sustained for at least a year.

RISDIPLAM DRUG INFORMATION

Evrysdi is an SMN2 splicing modifier composed of Risdiplam that is recommended to be taken orally at the same time daily following meals. It is recommended that the drug be taken immediately after it is drawn into the oral syringe. Patients should drink water following administration of the drug, and if it is not fully swallowed or vomiting occurs, another dose is not recommended to accommodate the lost dose. The most common side effects of this drug are fever, diarrhea, and rash in 10% of patients diagnosed with later-onset SMA. In infantile-onset SMA, the side effects experienced were those observed in later-onset SMA, with the addition of approximately 10% having upper respiratory tract infection, constipation, pneumonia, and vomiting. Less common side effects of Risdiplam in later-onset SMA include mouth and aphthous ulcers, arthralgias, and urinary tract infections. This drug is to be avoided in patients with hepatic impairment and is not recommended in pregnant women due to animal data suggesting a risk of fetal harm. In some animal studies, Risdiplam was found to have adverse effects on reproductive organs. Therefore, it is recommended that pregnancy testing be carried out for females of reproductive potential before initiating this drug (Evrysdi prescribing info).

MECHANISM OF ACTION, PHARMACOKINETICS/ PHARMACODYNAMICS

The mechanism of action of Risdiplam is designed to increase the survival of the SMN2 protein levels systemically by including exon 7 into SMN2 mRNA transcripts. RG7800 is a small molecule SMN2 splicing modifier that led to the development of Risdiplam.[17] It was administered to patients with Type 2 and 3 SMA in the MOONFISH clinical trial, and dosing was subsequently suspended due to adverse retinal side effects. Following the RG7800 clinical trial results, Risdiplam was developed with increased specificity toward SMN2 exon 7 splicing and showed a much more favorable pharmacokinetic and pharmacodynamic profile.[17] In animal studies, the total plasma concentration of Risdiplam was representative of the total tissue concentration of Risdiplam. In mice and monkeys, the total drug levels of Risdiplam in plasma, brain, and muscle were similar up to 39 weeks of administration.[17] In brain tissue concentrations of 189 animals, the brain stem and cortex demonstrated very similar Risdiplam concentrations with an average cortex/ brain stem concentration of 1.10 (Poirier et al., 2018). Risdiplam and RG7800 are luckily not substrates for multi-drug resistant protein 1, which would normally restrict their entry into the brain via ATP-dependent efflux of the drug from cells. This allows these small molecule splicing modifiers to penetrate the blood-brain barrier with ease. Radioactivity was measured following administration of 14C- Risdiplam and peak concentrations were measured at 2 hours. The highest concentrations of radioactivity tissue/ plasma ratios were measured in the kidney cortex (9.1), liver (7.2), lung (7.1), spleen (8.0), pancreas (4.7), kidney medulla (4.1), heart (2.4), trachea (2.7), mucosa of the small intestine (3.4), large intestine (1.5), and rectum (4.1) (Poirier et al., 2018). In SMA mouse models, the levels of SMN protein levels increased in a dose-dependent manner with 0.1 mg/kg/ day, increasing SMN2 in the brain by 28% and in muscle by 32%. With a 1 mg/kg/day dose, the SMN2 levels in the brain increased by 206% and in muscle 210%.[17] Other favorable effects of Risdiplam in mice were improved motor function, survival, and increased body weight (Poirier et al., 2018). These animal studies can favorably predict the pharmacologic efficacy in human subjects because of the way unbound Risdiplam has been shown to distribute at the site of action.[17] Risdiplam has been demonstrated to freely distribute blood into the CNS and other tissues in animals and is expected to do the same in human subjects.[17] The high passive permeability of both RG7800 and Risdiplam can be attributed to their inability to act as substrates for MDR1, which would otherwise restrict their permeability into brain tissue, as stated earlier.[17] Because both humans and monkeys are closely related in terms of efflux transporters. It is reasonable to believe that human CSF levels of Risdiplam will be like those observed in monkeys (Poirier et al., 2018). Risdiplam is an exciting newly developed drug for treating spinal muscular atrophy and clinical trials on animals suggest the results will be similar in patients.

CLINICAL STUDIES: SAFETY AND EFFICACY

SMN PROTEIN LEVELS BEFORE AND AFTER RISDIPLAM TREATMENT

One study analyzed the SMN protein level in the blood of healthy individuals versus those who received treatment with Risdiplam for SMA Type 1-3.[23] SMN protein levels in whole blood of healthy adults (18-60 years old) from a single ascending dose study and Japanese bridging study were quantified and compared with those from subjects in the FIREFISH (SMA type 1, 3.3 months- 7 months old), SUNFISH (SMA Type 2, 2-24 years old) and JEWELFISH (nonnaïve SMA, 13-52 years old) trials before and after treatment. The varying copy numbers of SMN2 in patients with SMA were also quantified and recorded.[23]

Overall, individuals with SMA Types 1-3 did have lower SMN protein levels in the blood than healthy adults. However, the amount of protein present did not seem to correlate with the amount of copy numbers for SMN2. Of note, subjects with Type 1 SMA did have lower baseline levels of SMN protein compared to younger patients with Type 2 and 3 SMA. After four weeks of treatment with Risdiplam, the SMN protein levels present in the blood of those with SMA increased to amounts equivalent to or higher than that of healthy adults. Additionally, this increase was persistent in individuals who continued to receive Risdiplam long-term (this study contained data for up to one year of receiving the treatment).[23] The highest increase in SMN protein levels was seen in infants with SMN type 1.[23]

SINGLE ESCALATING DOSE STUDY OF RISDIPLAM

A phase 1 randomized, double-blind, placebo-controlled (RDBPC) study showed the safety of Risdiplam in healthy individuals. This single ascending dose (SAD) study compared oral Risdiplam (0.6 mg-18.0 mg) to a placebo amongst a group of healthy adult males ages 18-45 years old. No moderate-severe adverse events (AEs), withdrawal from the trial related to AEs or mortality were reported during this study. Two drug-related AEs as determined by the investigator were pollakiuria in the placebo group (n=1, 16.7%) and headache in the 18.0 mg Risdiplam cohort (n=1, 16.7%). Other frequently reported A.E.s included: headache (n=4), diarrhea (n= 2), abdominal pain (n=3) and nasopharyngitis (n=2). All episodes of these symptoms were short-lasting and without significant consequence. Throughout the study, there was no ophthalmologic toxicity, major changes in vital signs or electrocardiogram readings of the participants. The oral Risdiplam solution was reported to be well tolerated in both the fed and fasted state, with no significant interaction with the CYP3A inhibitor itraconazole when taken in the fed state.[24]

Overall, in this single ascending dose study, the 18.0 mg dose of oral Risdiplam was found to cause a 41% maximum placebo corrected increase in SMN2 full length (SMN2FL) expression.[24] In these healthy participants, the SMN protein concentration was found to be unchanged, likely related to the majority of SMN1 full length (SMNFL) mRNA being expressed at a higher amount when compared to SMN2FL.[25] However, these results support the idea that in an individual with SMA, these increased SMN2FL mRNA expression would lead to increased SMN protein concentration.[26]

FIREFISH TRIALS

PART 1

The goal of the exploratory first part of the FIREFISH trials was to establish the safety, tolerability, pharmacokinetics, and pharmacodynamics of varying doses of Risdiplam in infants 1-7 months old with Type 1 SMA and two SMN2 gene copies. After eight months of treatment with Risdiplam, the results showed an increase in 93% of the subject's Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score by ⩾ 4 points (with an average increase of 16 points). Additionally, there was an overall increase of Hammersmith Infant Neurological Examination Module 2 (HINE-2) milestones reached in the 14 participants. The milestones are as follows: rolling to their side or from prone position to supine(29%), horizontal or upward kicking (50%), sitting with or without support (43%), full head control (43%).[27]

Part 1 also assessed the number of infants that survived and didn't require permanent ventilation (defined as event-free survival), needed a tracheostomy or lost their ability to swallow. An interim analysis showed there was a 90.5% (19/21) event-free survival rate. None of the infants that survived required tracheostomies, permanent ventilation or were unable to swallow.[28]

The same trend, which was appreciated after eight months of Risdiplam treatment in terms of the motor development of the subjects, continued at a 16-month analysis. Eighty-two percent (14/17) of infants in the high dose cohort reached a CHOP-INTEND score of 40 after 15 months of Risdiplam treatment. Twelve percent (2/17) of infants in the high dose cohort also reached one of the first HINE-2 walking assessment milestones of bouncing. Additionally, no individual required permanent ventilation or the need for a tracheostomy.[29]

By the end of Part 1, there were no drug-related adverse events which led to the withdrawal of infants from the study after, on average, 19 months of treatment with Risdiplam. [30]

PART 2

The second part of the FIREFISH trials was the confirmatory portion that assessed the safety and efficacy of the dose of Risdiplam selected from part 1. The main endpoint for efficacy was established as the infants' ability to sit up without support for 5 seconds after 12 months of treatment. This was assessed using the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development, third edition (BSID-III). Additional, endpoints were also established and assessed.[30]

The conclusions of part 2 were that 29% (12/41, $p<0.0001$) of infants who received 12 months of treatment with Risdiplam were able to sit up unsupported for at least 5 seconds. This is a development that infants with untreated Type 1 SMA do not accomplish.[31] Overall, 78% (32/41) of infants responded to Risdiplam using the HINE-2 tool for measurement.[32] In terms of head control, 76% of infants

were able to reach this milestone. Of the 41 participants, 61% were able to achieve some form of the sitting milestone. Standing was achieved by 22% of the infants, while 2% achieved the walking milestone. Overall, 90% (37/41) of infants attained a four score increase of their CHOP-INTEND score by the end of 12 months of treatment.[32] A CHOP-INTEND score ⩾ 40 was attained in 56 % (23/41) of infants. This is in stark contrast to the usual down-trending CHOP- INTEND score in untreated Type 1 SMA infants over time.[33] Additional endpoints which were assessed included the ability of the subjects to swallow and orally feed. By the end of the 23 months, 95% of the surviving infants (36/38) were still able to swallow while 89% (34/38) were able to orally feed.[32]This is a positive finding, as, within the cohort of untreated infants with Type 1 SMA, those older than 12 months required support with feeding.[33]

Three infants succumbed to Type 1 SMA complications, but these deaths were determined not to be from Risdiplam.[32] Over the 12 months course of treatment, 49% (20/41) of the infants didn't require hospitalizations. Furthermore, the survival rate of infants in the trial was 93% (38/41), and the event-free survival rate was 85 % (35/41) after 12 months of treatment.

The most common serious adverse events were mainly respiratory, including pneumonia (32%), bronchiolitis (5%), respiratory failure (5%) as well as hypotonia (5%). The most common non-life-threatening adverse events were also respiratory, with the most frequent being upper respiratory infection (46 %), followed by pneumonia (39%) as well as nasopharyngitis (12%), and rhinitis (12%). Pyrexia occurred in 39% of the subjects, and GI adverse events included constipation (20%) and diarrhea (10%). A maculopapular rash was observed in 10% of the infants but cleared up as treatment continued. There were no adverse ophthalmologic effects associated with Risdiplam treatment reported.[32]

SUNFISH TRIALS

PART 1

The exploratory first part of the SUNFISH trials set out to establish safety, tolerability, pharmacokinetics, the pharmacodynamics of Risdiplam, as well as establishing an adequate dose to be used for part 2. In this multicenter, double-blind, placebo-controlled study, participants from the ages of 2-25 years old with Type 2 and Type 3 SMA were assessed for changes in motor function during one year of treatment with Risdiplam. The average age of individuals in the study was eight years old.[34] The participants had varying levels of functionality and physical manifestations of SMA (such as scoliosis) at the beginning of the study.[35] Amongst the 35 subjects who received Risdiplam, 14.3 % (5 subjects) were ambulatory, while 85.7% (30 subjects) were non-ambulatory.[34] Fourteen of the participants received the dose that would be used in part two from the inception of the study while 21 participants received the part two-dose later on.[34]

The Motor Function Measure 32 (MFM32) was used to assess motor capabilities at the beginning and throughout the study. The average MFM32 score at the initiation of the trial was 37.5. After treatment with Risdiplam for 12 months, 70% of participants (21/30) achieved a ⩾ 1 score increase, while 63.3% (19/30) had a ⩾ 3-point increase. This score increase was more drastic in the 2–11-year-old cohort, with 76.5% of this group saw a ⩾ 3-point increase of the MFM32 score than the 46.2% of the 12–24-year-old group that saw a ⩾3 score increase. Additionally, a persistent elevation in SMN protein level was observed in participants who received the part two-dose after 12 months of treatment. This increase was, on average, > 2 times increase from the subjects' baseline.[34]

There were no deaths or adverse events which led to withdrawal from the trial. Of the 51 participants, 90.2% (46) experienced at least one adverse event throughout the trial. The following numbers are based on ⩾ 5 patients reporting the AE, where n= the number of events. Several of the AEs were respiratory and are as follows: nasopharyngitis (9), upper respiratory tract inflammation (8), upper respiratory tract infections (8), pharyngitis (6 events), respiratory tract infection (6), bronchitis (5), influenza (5). Others included pyrexia (17), cough (15), vomiting (14), oropharyngeal pain (9), rash (7), headache (7), pain in extremities (6), and abdominal pain (6). Many of these were linked to SMA and not Risdiplam. Six of the patients. (11.8%) reported severe adverse events and are listed as follows, where n= number of events. Nausea (2), vomiting (2), upper respiratory tract infection (2), atrial fibrillation (1), chronic respiratory failure (1), pneumonia (1), gastroenteritis (1), femur fracture (1). However, none of these severe events were linked to Risdiplam use and did resolve over time. Throughout the trial, there were no significant ophthalmologic effects reported which were linked to Risdiplam. Overall, Risdiplam was well tolerated by the patients at all the doses tested in the trial.[34]

PART 2

The second part of the SUNFISH trials was a randomized, placebo-controlled, double-blind study involving patients ages 2-25 years old. This confirmatory portion of the study assessed the safety and efficacy of the dose of Risdiplam selected from part 1. The primary endpoint was defined as a change in the patient's MFM32 score from baseline after 12 months of treatment with Risdiplam. The secondary endpoints were as follows: change in the subject's revised upper limb module (RULM), Hammersmith functional motor score-expanded (HFMSE), SMA Independence Scale (SMAIS) scores from baseline in addition to the percentage of patients who achieved stabilization or improvement of the MFM32 score after one year of Risdiplam treatment.[36]

Overall, the primary endpoint was met in a significantly greater number of patients receiving Risdiplam than those receiving placebo. Similarly, a significantly greater number of patients receiving Risdiplam had a stabilization or improvement of their MFM32 score than those receiving placebo. There was also a significant improvement from the baseline of the RULM score after 12 months of Risdiplam treatment. Additionally, SMA patients ⩾ 12 years old, and their caregivers reported increased independence using the SMAIS. The SMAIS measures independence using items such as the ability of an individual to brush teeth, eat food using utensils, and write with a pen.[36]

There were no major drug-related AEs that led to the

withdrawal of any patients from the study. Most of these events were related to the disease process of SMA itself. The adverse events amongst patients receiving Risdiplam are as follow where n=% of patients affected: upper respiratory infection (31.7%), nasopharyngitis (25.8%), pyrexia (20.8%), cough (14.2%), headache (20.0%), diarrhea (16.7%), vomiting (14.2%). The serious adverse events amongst patients who received Risdiplam are as follows: pneumonia (7.5), influenza (1.7%), pyrexia (1.7%), bacteremia (1.7%), gastroenteritis (1.7%).[36]

JEWELFISH TRIALS

The JEWELFISH trials were carried out to determine the pharmacokinetics, pharmacodynamics, safety, and efficacy of Risdiplam in non-naïve SMA patients 6 months -60 years old. In this multicenter, open-label study, all of the participants had previously received either RG7800 (RO6885247), nusinersen (SPERANZA), olesoxime or onasemnogene abeparvovec-xioi (ZOLGENSMA) before this study.[37] The average age of the participants was 20 years old, with 50% having Type 2 SMA (6 subjects) and 50% having Type 3 SMA (6 subjects). Nine participants were non-ambulatory (75%), while three subjects (25%) were ambulatory. The average MFM32 score at the initiation of the study was 48.44.[38]

Over 12 months of treatment, there was a persistent increase (on average more than 2 times that measured at baseline) in SMN protein levels amongst the Type 2 and Type 3 SMA patients. Additionally, post- Risdiplam treatment, the level of SMN protein detected in the blood was comparable to that seen in the SUNFISH Part 1 trial.[38]

Overall, there were no serious adverse events that led to the withdrawal of any participants. There were 10 patients, amongst which 41 mild-moderate adverse events were reported, the most frequent of which are as follows.[38] Two patients reported nasopharyngitis (5 events), 2 patients reported pyrexia (3 events), and 2 patients reported headaches (3 events). There were no adverse ophthalmologic events reported which were linked to Risdiplam. Overall, Risdiplam was well tolerated in the participants.

RAINBOWFISH TRIALS

The RAINBOWFISH trial is an ongoing study to determine the effects of Risdiplam on pre-symptomatic SMA infants from the ages of birth- 42 months who have genetically confirmed cases of SMA. At baseline, these infants must not exhibit symptoms contributable to SMA. Analysis of the participant's ability to sit unsupported for five seconds (as determined by the Bayley Scales of Infant Development -111) will be performed after 10 infants with at least 2 SMN2 copies and a compound muscle action potential (CMAP) of ⩾ 1.5 mV have received Risdiplam for 12 months.[39] Other endpoints such as survival, need for permanent ventilation, ability to swallow independently, CHOP-INTEND motor function score, development of SMA symptoms, and SMN protein level in the blood, amongst others, will also be measured.[39]

CONCLUSION

FUTURE DIRECTIONS: OUTCOMES OF SYSTEMIC EFFECTS OF RISDIPLAM

Spinal Muscular Atrophy, the current leading cause of infantile genetic death, is a disease of the anterior spinal horns that largely causes proximal muscular weakness amongst other complications that are both direct and indirect causes of, most classically, genetic deletion. The genetic deficit is caused by deletions or other alterations in SMN1, which is often partially compensated for by another similar, but less effective gene, SMN2. Many targets of drug research to improve outcomes in patients with SMA involve augmentation of SMN2 to compensate for the SMN1, and Risdiplam is one of the most recent drugs aimed at furthering this research and patient outcomes.

Risdiplam, an SMN2 splicing modifier, is currently the only orally administered drug approved by the FDA to treat Spinal Muscular Atrophy in patients under two years old. While most drugs, including Nusinersen (Spiraza), for instance, have historically been administered intrathecally, Risdiplam has proven the benefits of systemic administration of the drug as evidenced by information gathered through rodent research and various clinical trials. It has shown great penetrance through the blood-brain barrier with no restricted permeability noted, which can commonly concern drugs targeting the CNS administered systemically. The target of Risdiplam, SMN2, is most commonly known to have a presence in the CNS tissue and has important roles in other tissues of the body, including the organs and musculature itself. Administering Risdiplam systemically allows the gene-splicing modifier to take action at a greater number of sites than the brain and spinal cord alone. Many attributes to its success significantly improve quality of life, symptomology, and even event-free survival time.

While systemic administration benefits the amount of tissue it can penetrate and modulate, it also comes with a broader side effect profile than the previously more targeted intrathecal administration. Some of the most notable include constipation, diarrhea, rash, fever, pneumonia, and vomiting. Others that are less common may include UTIs, arthralgias, and ulcers. The research on the effect of Risdiplam on reproductive organs and pregnancies has shown potential adverse effects, and thus its use in the pregnant population is currently advised against.

As research on Risdiplam for SMA proceeds, more information should be gathered on these adverse effects to gain further insight on how and if the benefits of the drug outweigh the side effects. Additional testing should also determine more definitively the safety profile of pregnancy with the administration of this drug, along with a further comparison of Risdiplam against other available therapies for SMA.

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Table 1. Clinical Safety and Efficacy

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
Study 1	The patient population studied: Healthy adults vs. patients with Types 1-3 SMA. Intervention: Patients with SMA were given Risdiplam for 4 weeks before and after which their SMN protein levels in the blood were measure and compared with healthy adults.	Results: Risdiplam treatment for 4 weeks did increase the blood SMN protein level in the patients with SMA to equal or higher levels of the controls. This increase was more dramatic in the Type 1 SMA patients and was sustained throughout the duration of the treatment past four weeks.	Risdiplam treatment in SMA patients did increase SMN protein expression in the blood.
Studies 2-4:	Patient population:25 healthy male adults Intervention: Single ascending dose study of Risdiplam to measure pharmacokinetics and tolerability.	Risdiplam was well tolerated up to 18 g. An 18 g dose led to a 41% increase in SMN2 full-length mRNA expression. Itraconazole, a potent CYP3A inhibitor, only had a mild effect on the metabolism of Risdiplam. Treatment did evoke an expression of full-length SMN2 mRNA.	Oral Risdiplam was well tolerated in the fasted and fed state in healthy male adults. A minimal amount of Risdiplam is metabolized by CYP34. This drug does induce SMN2 full-length mRNA expression.
Studies 5-8	Patient population: Type 1 SMA patients 1-7 months old receiving placebo vs. Type 1 SMA patients 1-7 months old receiving Risdiplam Intervention: These patients received Risdoplam to determine safety, tolerability, pharmacodynamics, pharmacokinetics, and an effective dose to be used in part 2.	93% of patients receiving Risdiplam showed an increase in the CHOP-INTEND score of ≥ 4 -points and 14 patients achieved an increase in HINE-2 scores, which are used to measure motor function and developmental milestones, respectively. 90.5% of the infants in the study experience event-free survival (survived and didn't need permanent ventilation). Of those that survived, none needed tracheostomies, permanent ventilation, and they were all able to swallow. There were also no adverse events that led to withdrawal from the study.	Risdiplam was well tolerated in patients with Type 1 SMA aged 1- 7 months. Patients experienced increased motor function and developmental milestones were reached.
Studies 9-11	Patient population: Type 1 SMA patients 1-7 months old receiving Risdiplam Intervention: The dose of Risdiplam from part 1 was administered to the patients for 12 months, with the primary endpoint being the ability of the patients to sit up unsupported for five seconds.	29% of patients who received Risdiplam could reach the primary endpoint of sitting up unsupported for five seconds. 78% of patients had a positive response to Risdiplam according to the HINE-2 measurements, with patients achieving milestones such as head control and sitting. 90% had a ≥ 4-point increase of their CHOP-INTEND score. There was an overall survival rate of 93%, with 3 infants perishing from complications of Type 1 SMA unrelated to Risdiplam. There was an 85% event-free survival rate. There were no adverse ophthalmologic events related to Risdiplam.	Risdiplam was well tolerated in Type 1 SMA patients of the ages 1-7 months. With 12 months of treatment, a large portion of patients had an increase in their motor function and met multiple developmental milestones.
Studies 12-13	Patient population and Intervention: Type 2-3 SMA patients age 2-25 years old receiving placebo vs. Type 2-3 SMA patients receiving Risdiplam for 12 months. These patients received Risdoplam to determine safety, tolerability, pharmacodynamics, pharmacokinetics and an effective dose to be used in part 2	Out of those who received the dose selected for part 2, there was a persistent elevation of SMN protein levels, which were average > 2 times their baseline. 70% of patients receiving Risdiplam had an increase in Motor Function Measure 32 (MFM32) score of ^{3} 1 point, while 63.3% had an increase of ^{3} 3 points. There were no adverse events that led to withdrawal from the study. No	Risdiplam was well tolerated amongst patients with Type 2-2 SMA ages 2-25 years old. Overall, those who received the dose used in part 2 of the trial exhibited an increase in SMN protein levels.

		adverse ophthalmologic events linked to Risdiplam were reported.	
Study 14	Patient Population and Intervention: Type 2-3 SMA patients receiving the dose of Risdiplam selected in part 1 for 12 months to assess for safety and efficacy using the MFM32 and RULM as primary endpoints.	Overall, there was a significant increase of the MFM32 score from the baseline of those receiving Risdiplam versus placebo. Similarly, there was an increase from the baseline of the RULM score after 12 months of treatment. Finally, many caregivers and patients ≥ 12 years old reported higher levels of independence, using the SMAIS score, after treatment. There were no major adverse events that led to the withdrawal of any patients from the study.	Risdiplam treatment for 12 months led to an increase in motor function and greater levels of independence in Type 2-3 SMA patients compared to placebo. Risdiplam was also well tolerated.
Studies 15-16	Patient population: Patients with ambulatory and non-ambulatory Type 2-3 SMA from the ages of 6 months- 60 years old who had previously received some pharmacologic treatment for SMA, Intervention: Patients were treated with Risdiplam for 12 months to assess safety, efficacy, pharmacokinetics, and dynamics.	On average, there was a > 2 times increase in SMN2 protein level from baseline with Risdiplam treatment. This elevation was also persistent and comparable with numbers seen in the SUNFISH part 1 trial, even after cessation of treatment. There were no adverse ophthalmologic events related to Risdiplam or adverse events, leading to withdrawal from the study.	Risdiplam was well tolerated in non-naïve Type 2-3 SMA patients ages 6 months- 60 years. Treatment led to a persistent increase in SMN2 protein levels.
Studies 17	Patient Population and Intervention: 10 pre-symptomatic patients ages birth-42 months with genetically confirmed SMA will who have a compound muscle action potential of ≥ 1.5 mV and at least 2 SMN2 copies will be treated for 12 months to determine multiple endpoints such as motor function using the CHOP-INTEND score, development of symptoms, need for permanent ventilation, SMN protein level, etc. This is an ongoing study.	-	-

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