Received: 21 June 2021 | Accepted: 21 June 2021

DOI: 10.1002/mus.27358

AANEM MONOGRAPH

MUSCLE&NERVE WILEY

Selecting disease-modifying medications in 5q spinal muscular atrophy

Michael S. Cartwright MD, MS | **Suraj Upadhya**

Department of Neurology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA

Correspondence
Michael S. Cartwright, Department of Neurology, Wake Forest School of Medicine, Winston-Salem, North Carolina 27157.
Email: mcartwri@wakehealth.edu

Abstract

Spinal muscular atrophy (SMA) is an inherited lower motor neuron disease. SMA occurs secondary to alterations in the survival motor neuron 1 gene (*SMN1*), which is the main driver of SMN protein production. The severity of the disease is determined by the number of copies of the *SMN2* gene, which is a homolog to *SMN1* but not as efficient in protein production. Three medications have recently been approved for the treatment of SMA. Nusinersen is an intrathecal antisense oligonucleotide that alters *SMN2* pre-mRNA, onasemnogene abeparvovec-xioi is an intravenous *SMN1* gene replacement therapy, and risdiplam is an oral small molecule splicing modifier of *SMN2*. No head-to-head studies have been conducted comparing these medications, so selection of one of these medications for an individual with SMA can be challenging. In this article we outline the efficacy, safety, and other pertinent factors to consider when selecting a therapy for an individual with SMA. The age of the individual and comorbidities, such as liver or kidney disease, help guide treatment choices. All three of these medications are efficacious, and early initiation is critical for obtaining the best outcomes.

KEYWORDS
gene therapy, nusinersen, onasemnogene abeparvovec-xioi, risdiplam, spinal muscular atrophy

1 | INTRODUCTION

Spinal muscular atrophy (SMA) is a term applied to most hereditary lower motor neuron diseases. The large majority of SMA cases are caused by deletions or point mutations in the survival motor neuron 1 gene (*SMN1*), which is on the 5q chromosome (this is sometimes termed "5q SMA").[1] Other genetic types of SMA occur, but they are rare and do not have approved genetic therapies, hence only 5q SMA is discussed in this article (and will be referred to simply as "SMA"). SMA is inherited in an autosomal recessive fashion, with approximately 1 in 50 people in the United States carrying a deletion in the *SMN1* gene such that SMA occurs in approximately 1 in 10 000 births in the United States.[2] SMA is the most common lethal autosomal recessive disease in infants.

The homozygous deletion of *SMN1* results in severely decreased production of SMN protein, which is needed for the development and maintenance of motor neurons.[3] The severity of SMA is determined mainly by the number of copies of the *SMN2* gene, a homolog of the *SMN1* gene, which can drive the production of a limited amount of functional SMN protein. It is estimated that approximately 10% of functional SMN protein is driven by the *SMN2* gene in healthy individuals.[4] *SMN2* has a cytosine-to-thymine transition in a splicing

Abbreviations: AAV9, adenoassociated virus 9; AE, adverse event; BSID-III, Bayley Scales of Infant and Toddler Development third edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CT, computed tomography; FDA, US Food and Drug Administration; HFMSE, Hammersmith Functional Motor Scale—Expanded; HINE-2, Hammersmith Infant Neurological Examination section 2; MFM-32, 32-item Motor Function Measure Scale; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.

This paper underwent peer review by the AANEM Monograph Review and Development Committee and review by the *Muscle & Nerve* editor, but did not undergo additional, external peer review. AANEM monographs are designed to be broadly educational to AANEM members and others with interests in neuromuscular, musculoskeletal, and electrodiagnostic medicine, and may at times be outside of the narrower scope of other articles published in *Muscle & Nerve*.

enhancer of exon 7, which results in most *SMN2* mRNA transcripts lacking exon 7, leading to nonfunctional SMN protein.[5] Because *SMN2* can produce some functional protein as a backup to *SMN1*, the number of *SMN2* copies determines the severity of SMA, with more copies resulting in less severe disease (Table 1). In addition, the *SMN2* gene is a target of two of the disease-modifying medications for SMA.

Prior to 2016, there were no disease-modifying medications available for SMA. The mainstay of treatment was supportive care, with noninvasive ventilation, tracheostomy and invasive ventilation, enteral feeding, bracing and surgery for scoliosis, and splinting and mobility aids (such as walkers and wheelchairs), all serving as options for individuals with SMA.[6] In December 2016, nusinersen was approved by the US Food and Drug Administration (FDA) for the treatment of SMA.[7] FDA approval for onasemnogene abeparvovec-xioi followed in May 2019 and risdiplam in August 2020.[8,9] These three medications now provide individuals with SMA several powerful options to alter their disease progression (Table 2). In this investigation we cover the key aspects of all three medications and provide guidance as clinicians assist patients in choosing the most effective treatment options.

2 | MEDICATION OVERVIEW

Nusinersen is an antisense oligonucleotide. Nusinersen is sometimes referred to as an exon-skipping therapy or as a phosphorodiamidate morpholino oligomer, as these are subsets of antisense oligonucleotides. This class of medication generates its effect by binding to DNA or RNA and subsequently altering transcription and translation.[10] Nusinersen, specifically, binds to *SMN2* pre-mRNA and alters transcription so exon 7 is included in the mRNA transcript. This, in essence, alters *SMN2* transcripts so they are the same as *SMN1* transcripts, and are therefore much more effective in producing functional SMN protein.[11] As nusinersen is a large molecule, it must be injected intrathecally to reach the central nervous system. Four loading doses are given initially over 2 months, which is then followed by injections every 4 months, indefinitely. Nusinersen is approved for all individuals with SMA.[12]

Onasemnogene abeparvovec-xioi is a gene replacement therapy in which *SMN1* is delivered intravenously via an adenoassociated virus 9 (AAV9) vector. This is given as a single 60-minute infusion and is dosed based on the patient's weight. Onasemnogene abeparvovec-xioi is approved for individuals less than 24 months of age.[13]

Risdiplam is a small molecule splicing modifier. Similar to nusinersen, risdiplam exerts its effect on *SMN2* pre-mRNA to alter splicing and increase the number of mRNA transcripts that include exon 7, which leads to increased amounts of functional SMN protein.[14] Because risdiplam is a small molecule, it can be delivered orally, absorbed, and cross the blood-brain barrier.[15,16] Risdiplam dosing is weight-based, and it is administered daily in liquid form, either by mouth or through a feeding tube. Risdiplam is approved for individuals with SMA who are 2 months of age or older.

3 | SCALES USED TO ASSESS MEDICATION EFFICACY

Perhaps the most critical feature of the disease-modifying medications for SMA is the efficacy of each medication. Because SMA is a condition that causes progressive weakness, measures of strength, function, and mobility are key. Several different scales have been developed to assess disease progression, or conversely, disease improvement, in SMA. Each scale is different; therefore, it is important to understand the scales to understand the improvement they can potentially detect in those undergoing treatment. The scales are tailored toward different age groups, so they are only used in the

TABLE 1 Different SMA types

SMA type	SMN2 copy number	Onset	Motor milestone	Prognosis	Eponym
0	0-1	Birth	Non-sitter	Death in utero	—
1	1-2	0-6 months	Non-sitter	Death before age 2 years	Werdnig-Hoffmann
2	2-3	7-18 months	Sitter	Live at least 20 years	Dubowitz
3	2-4	>18 months	Stander	Normal lifespan	Kugelberg- Welander
4	4^{+}	Adult	Stander	Normal lifespan	—

TABLE 2 Disease-modifying therapies

Medication	Mechanism of action	Delivery route and dosing	Indications
Nusinersen	Antisense oligonucleotide, improves *SMN2* efficacy	12 mg intrathecally, four loading doses followed by dosing every 4 months	All ages
Onasemnogene abeparvovec-xioi	*SMN1* gene replacement	Single 60-minute intravenous infusion of 1.1×10^{14} viral genomes/kg	Age <24 months, <16 h/day of mechanical ventilation, not completely paralyzed
Risdiplam	RNA splicing modifier, improves *SMN2* efficacy	Oral liquid daily dosing, variable based on weight	Age ≥2 months

Abbreviation: *SMA2*, spinal muscular atrophy gene.

TABLE 3 Overall medication efficacy

Age at treatment initation	Scale	Nusinersen	Onasemnogene abeparvovec-xioi	Risdiplam
<2 months	CHOP-INTEND (max = 64)	After mean 33.9 months: *SMN2* two copies, 62.1; *SMN2* three copies, 63.4	By 6 months of age: *SMN2* two copies, 100% (14 of 14) reached 50 points, 86% (12 of 14) reached 60 points	NA
	HINE-2 (max = 26)	Scores increased from baseline: *SMN2* two copies, 2.7-23.9; *SMN2* three copies, 3.2-26	NA	NA
	Survival without permanent assisted ventilation	After mean 33.9 months: 100%	After 6 months: 100%	NA
2-24 months	CHOP-INTEND (max = 64)	≥4 point increase at end of trial[a]: 71%	Mean points increase after: 1 month, 6.9; 3 months, 11.7; 5 months, 14.3; mean points increase at end of trial[b]: high dose, 24.8 points; low dose: 7.7 points	≥4 point increase after 12 months: 90%
	HINE-2 (max = 26)	Response[c] at end of trial[a]: 51%	NA	Response[c] after 12 months: 78%
	Survival without permanent assisted ventilation	At end of trial[a]: 61%	After mean 8.2 months, in STR1VE: 89.5%; at end of trial for START[b]: 100%	After 12 months: 90%
	Ability to sit (BSID-III)	NA	For ≥30 seconds after mean 8.2 months: 50%	For ≥5 seconds after 12 months: 29%
>24 months	HFMSE (max = 66)	Changes from baseline after 15 months: 3.9; change from baseline after 38 months: SMA II, 10.8; SMA III, 1.8	NA	Difference in HFMSE favoring risdiplam after 12 months: 0.58 (not significant)
	RULM/ULM (max = 37)	Change from baseline after 38 months: 4.0	NA	Score difference between risdiplam and control, favoring risdiplam; after 12 months: 1.59

Abbreviations: BSID-III, Bayley Scales of Infant and Toddler Development third edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE, Hammersmith Functional Motor Scale—Expanded; HINE-2, Hammersmith Infant Neurological Examination section 2; max, maximum; NA, not applicable; RULM, Revised Upper Limb Module.

[a]ENDEAR trial had first infant treated on August 21, 2014 and last infant treated on November 21, 2016 (28 months).

[b]START trial ran from May 2014 (low dose)/December 2014 (high dose) to August 2017 (40 months/31 months).

[c]HINE-2 response defined as having more motor milestones improve than worsen.

appropriate age groups in clinical trials, which can make direct comparisons of medication efficacy in SMA challenging.

In SMA type I, infantile onset, the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Infant Neurological Examination section 2 (HINE-2), and Bayley Scales of Infant and Toddler Development third edition (BSID-III) measures can be used to assess efficacy. Another indicator of efficacy is the chance of surviving without permanent assisted ventilation. The CHOP-INTEND is a 16-part scale that totals 64 points (maximum of 4 points per item). Each item tests a different motor function, such as upper extremity movement, lower extremity movement, and head control.[17] The HINE-2 is designed for those 2 to 24 months of age and is a pure motor milestone test. There are eight items and a maximum score of 26.[18] The BSID-III has sections that focus on fine motor (66 items) and gross motor (72 items) skills of children between 1 and 42 months of age.[19]

SMA types II and III typically are assessed with different scales than SMA I, as increased age usually is associated with more motor function. The Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM), and 32-item Motor Function Measure Scale (MFM-32) are used to evaluate the efficacy of different medications in SMA II and III. The HFMSE has 33 motor

ability items with a total of 66 points and is designed for individuals with SMA.[20] The RULM has 19 items totaling 37 points, and it focuses on upper body function only.[21] The MFM-32 has 32 items with 128 total points and is validated in those 6 years of age and older with neuromuscular disease.[22]

4 | EFFICACY DATA

Once the efficacy scales are understood, then attempts can be made to compare the efficacy of the different medications in their respective clinical trials (Table 3). When making these comparisons, it is critical to note that all three medications clearly have greater efficacy when started early in life, and the earlier they are started the more efficacious the medication.[23] In addition, the number of *SMN2* copies is also crucial in determining the disease severity in SMA. Therefore, when comparing these three medications it is critical to try to compare studies involving cohorts of similar age at treatment and *SMN2* copy number.

4.1 | Presymptomatic (under 2 months of age at treatment initiation)

Two trials were undertaken in presymptomatic infants to assess the benefit of early treatment. The open-label NURTURE trial (n = 25) assessed nusinersen in infants with two and three copies of *SMN2*. After a mean of 33.9 months, the average CHOP-INTEND score was 62.1 and 63.4 points for infants with two and three copies of *SMN2*, respectively, all surviving without permanent assisted ventilation.[24] With onasemnogene abeparvovec-xioi, the interim analysis of the ongoing open-label SPR1NT trial (n = 29) saw all infants with two *SMN2* copies reach a CHOP-INTEND score of 50 by 6 months of age, with 86% reaching 60 points. In addition, all infants survived without requiring permanent assisted ventilation.[25]

4.2 | Infantile onset (2-24 months of age at treatment initiation)

Several trials were conducted to test efficacy among symptomatic infants. For nusinersen, two trials were conducted, CS3A and ENDEAR. CS3A, an open-label, dose-escalating trial, had a duration of 14 months. The two dosage groups were an initial dose of 6 mg, then later 12 mg (n = 4) and 12 mg (n = 16) throughout. Of the four subjects in the first dose group, one reached a HINE-2 milestone, whereas all 15 in the higher dose group reached HINE-2 milestones.[26] ENDEAR, a double-blind, placebo-controlled trial (n = 122) began in August 2014 and ended early in November 2016. The study showed that nusinersen-treated subjects had a higher chance than the placebo group of having a HINE-2 response (51% vs 0%) and surviving without permanent assisted ventilation (61% vs 32%; hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.32-0.89; P = .005). Furthermore, 71% in the nusinersen group had an increase of at least 4 points in their CHOP-INTEND score vs only 3% in the placebo group.[11]

For onasemnogene abeparvovec-xioi, STR1VE and START tested efficacy in infants. STR1VE (n = 22) is an open-label study. Of the 19 of 22 subjects who remained in the study, 17 (89.5%) survived without permanent assisted ventilation. The CHOP-INTEND scores increased by an average of 6.9, 11.7, and 14.3 points after 1, 3, and 5 months, respectively, with a mean baseline score of 32.[27] START, a two-drug dosage cohort study, ran from May 2014 to August 2017. All participants survived without permanent assisted ventilation. Those in the high-dose group (n = 12) had a mean increase in CHOP-INTEND of 24.8 points; in the low-dose group (n = 3), patients saw a mean increase of 7.7 points.[13]

For risdiplam, the FIREFISH trial studied the efficacy in infants. FIREFISH had two parts, with the first part assessing safety and the second part efficacy. Part I (n = 21) was a two-dosage cohort study, where 90% survived without permanent assisted ventilation.[28] In part II (n = 41), after 12 months of treatment, 29% were able to sit independently for at least 5 seconds, as evaluated using the BSID-III. In addition, 90% showed an increase in CHOP-INTEND score of at least 4 points.[29]

4.3 | Late onset (over 24 months of age at treatment initiation)

The CHERISH trial and the CS2/CS12 extension study assessed the efficacy of nusinersen in treating SMA II and III. CHERISH (n = 126), a double-blind, placebo-controlled study, lasted 15 months. At the end, the nusinersen group had a mean increase in HFMSE score of 3.9 points, whereas the placebo group had a mean decrease of 1 point.[30] The other clinical trials in evaluating late-onset SMA efficacy began with CS1, an open-label dose escalation of 1, 3, 6, or 9 mg. Those who took 3 mg, could enroll in CS10, whereas those who took 1 mg could enroll in CS2. CS12 is an extension study of CS10 and CS2.[31] In the CS12 (n = 24) extension study, patients with SMA II had an increase of 10.8 points in HFMSE score and patients with SMA III had an increase of 1.8 points after 38 months of treatment.[32]

For onasemnogene abeparvovec-xioi, the STRONG (n = 31) clinical trial evaluated efficacy in older patients, and the medication was delivered intrathecally. STRONG is a phase 1 study of SMA patients who could sit but not walk. After a mean of 9.3 months, patients saw a HFMSE score change of 5.9 points. This trial was put on hold because animal data showed inflammation of dorsal root ganglia.[33]

The SUNFISH trial assessed the efficacy of risdiplam in late-onset SMA patients. The study had two parts, with the first part evaluating safety and dose and the second testing efficacy. In part I (n = 51), after 24 months, 81% had an increase in MFM-32 score and 54% had at least a 3-point increase.[34] In part II (n = 180), risdiplam was compared with a placebo. There was a statistically significant difference of 1.55 points in MFM-32 score, favoring risdiplam after 1 year (P = .016). A difference in HFMSE, favoring risdiplam, was noted, but significance was not met (P = .302).[35]

5 | SAFETY DATA

After efficacy, perhaps the second most important quality of SMA medications for patients and their families is safety (Table 4). For these medications, safety is determined both by the medicine itself as well as the mechanism of medication delivery.

5.1 | Nusinersen

In the clinical trials, moderate and severe adverse events (AEs) were common in both the treatment and placebo groups (mainly respiratory illness), but no clear association with nusinersen was found. Post–lumbar puncture symptoms were prevalent in the nusinersen group. At 24, 72, 120, and 168 hours after treatment, the incidence of lumbar puncture–associated adverse effects were 9%, 14%, 15%, and 15%, respectively, in the nusinersen group and 3% at all time-points in the placebo group.[30]

Two more serious AEs potentially associated with nusinersen include thrombocytopenia and renal toxicity. One clinical study showed six (11%) nusinersen-treated patients with normal or above normal baseline platelet levels had platelet levels below accepted levels after treatment, whereas the control group had no patients with thrombocytopenia. With regard to kidney function, 17 (33%) infantile-onset patients treated with nusinersen had increased urine protein, whereas only 5 (20%) placebo-treated patients showed an increase. In late-onset cases, 36 (69%) had higher urine protein.[7]

Based on these findings, it is recommended that platelet count and urine protein are measured and coagulation studies are obtained before each dose of nusinersen. In general, the most common and notable side effects of nusinersen are related to the intrathecal method of delivery (such as post–lumbar puncture headache).

5.2 | Onasemnogene abeparvovec-xioi

Of all patients treated with onasemnogene abeparvovec-xioi in clinical studies, the most common AEs were hepatic transaminase increase (12.4%) and vomiting (8.2%). In addition, thrombocytopenia occurred in 4.1% of subjects, but resolved within 2 weeks. Troponin I levels were also observed to increase in 3.1% of subjects.[8] Postmarketing surveillance has identified cases of thrombotic microangiopathy within weeks of receiving onasemnogene abeparvovec-xioi. Given these findings, there is a black-box warning for "acute serious liver injury," and this medication may not be appropriate in those with known hepatic disease. In addition, prednisolone 1 mg/kg/day should be administered starting 1 day prior to the onasemnogene abeparvovec-xioi infusion and continued for at least 1 month (and until transaminases normalize). Prior to the first infusion, an AAV9 antibody titer needs to be assessed and, if elevated, onasemnogene abeparvovec-xioi cannot be administered (although it can be repeatedly checked and, if it normalizes, then treatment can proceed). It is also recommended to check cell counts, transaminases, bilirubin, coagulation studies, hemoglobin, creatinine, and troponin I prior to the first infusion, weekly for the next month, and every 2 weeks afterward for months 2 and 3 and until values normalize.[8]

5.3 | Risdiplam

In the risdiplam clinical trials AEs were common, with pneumonia being the most common severe AE.[28,29,34,35] Upper tract respiratory infections, fever, constipation, diarrhea, and vomiting also occurred more commonly in the risdiplam group.[9] Based on these results, no specific monitoring is required with risdiplam. In our experience, nausea and vomiting are relatively common and often resolve over weeks.

TABLE 4 Medication safety

Medication	Black-box warning	Common side effects	Major side effects	Medication monitoring
Nusinersen	NA	Lower respiratory infection, upper respiratory infection, and constipation	Thrombocytopenia and renal toxicity; intrathecal access also includes risk of infection, bleeding, and post–lumbar puncture syndrome	Platelet count, prothrombin and partial thromboplastin time, and urine protein prior to each dose
Onasemnogene abeparvovec-xioi	Acute liver injury and increased aminotransferases can occur	Vomiting, fever, increased aminotransferases, thrombocytopenia, and increased troponin I levels	Liver injury, thrombocytopenia, and thrombotic microangiopathy	Platelet count, aminotransferases, bilirubin, prothrombin time, hemoglobin, creatinine, and troponin I weekly for the first months and then every 2 weeks for months 2 and 3 and until values normalize
Risdiplam	NA	Fever, diarrhea, and rash; among infantile-onset: upper respiratory tract infection, pneumonia, constipation, and vomiting	Nausea, vomiting, and diarrhea: adverse effects on male fertility in animal models	No standard laboratory monitoring; consider sperm banking

Abbreviation: NA, not applicable.

Preclinical animal studies suggested that risdiplam could affect male fertility, so this warning is included in the risdiplam package insert.[9]

6 | CONTRAINDICATIONS AND FDA LABELING

Nusinersen is approved for all individuals with SMA. No absolute contraindications exist for nusinersen, but caution should be used in those with poor kidney function or thrombocytopenia. In addition, severe scoliosis and/or surgically implanted rods for scoliosis may limit access to the thecal sac, which in rare circumstances results in an inability to administer this medication. Fluoroscopic guidance, computed tomography (CT) guidance, implanted catheters, and high cervical access points have all been used to administer nusinersen in those with complicated spines.[36]

Onasemnogene abeparvovec-xioi is approved for those with SMA and between 0 and 24 months of age. Some providers may not recommend this medication for those with complete paralysis and/or more than 16 hours/day of mechanical ventilation, as it was not studied in these populations. Liver dysfunction and persistently elevated AAV9 antibody titers are absolute contraindications to onasemnogene abeparvovec-xioi.

Risdiplam is approved for those with SMA who are at least 2 months of age. There are no absolute contraindications to risdiplam, although the drug not be appropriate if an individual is unable to take a daily liquid medication. Animal studies raised the concern that risdiplam may affect male fertility, although this has not been demonstrated in humans. For this reason, some physicians advocate for sperm banking prior to initiation of risdiplam.

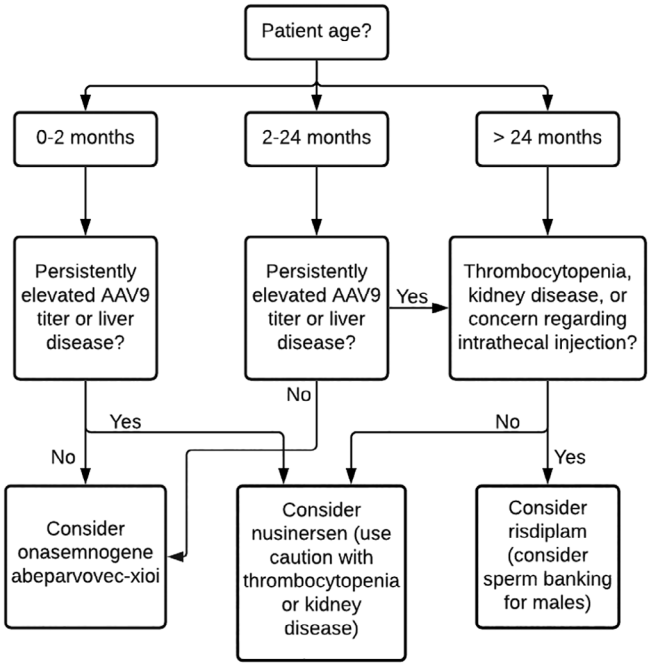

FIGURE 1 Decision tree for choosing best available medication for spinal muscular atrophy. AAV9, adenoassociated virus 9

7 | TREATMENT ALGORITHM

Choosing one of three medications can be a daunting task, especially given the lack of head-to-head comparisons. For some individuals with SMA, one or more of the medications may be contraindicated. Perhaps the most common contraindication is patient age, with onasemnogene abeparvovec-xioi only approved for patients up to 24 months of age and risdiplam only approved for those 2 months of age and older. Other considerations when choosing which of these medications to use include the presence of a complicated spine, liver disease, persistently elevated AAV9 antibody titers, thrombocytopenia, and kidney disease. As previously stated, comparing the efficacy of these medications is challenging because each study used different SMA types, ages at treatment initiation, *SMN2* copy numbers, lengths of treatment, and outcome measures. Figure 1 presents our treatment strategy while considering contraindications, safety, and efficacy.

8 | BRIEF EXAMPLE CASES

The following cases are based on presentations we have seen in our practice, and they were chosen because they help illustrate the process used to select a medication.

Case 1. A 9-month-old girl presented with hypotonia. Genetic testing confirmed SMA with two copies of *SMN2*. She had no other underlying medical conditions; her AAV9 antibody titer was normal; and laboratory studies were normal, including complete blood count, comprehensive metabolic panel, prothrombin time/partial thromboplastin time, and troponin I. In consultation with her mother, we selected treatment with onasemnogene abeparvovec-xioi, as it could be delivered with a single infusion. The patient was in the treatable age range, and there were no contraindications.

Case 2. A 28-year-old woman presented with SMA III and three *SMN2* copies. She had scoliosis rods that had been placed at 12 years of age, but a pretreatment CT scan showed areas where the thecal sac could be accessed with fluoroscopic guidance. This patient traveled frequently for work and she thought intermittent dosing every 4 months would work better than daily medication dosing for her schedule. In consultation with her we selected nusinersen as an appropriate treatment.

Case 3. A 15-year-old boy presented with SMA III and three *SMN2* copies. He had minimal scoliosis, no history of back surgery, and no other medical conditions. He did not want to undergo repeat lumbar punctures for treatment, so we selected risdiplam as an appropriate treatment option. He and his parents opted against sperm banking prior to the initiation of treatment.

9 | SUMMARY AND THE FUTURE OF SMA TREATMENT

Three medications are currently approved for the treatment of SMA. Two of these work by increasing the efficacy of *SMN2* production of

SMN protein and the other works by replacing the *SMN1* gene. For each of these medications, it is clear that the sooner they are started the more efficacy they provide. Selecting the appropriate medication requires consideration of the patient's age, comorbidities, and preferred medication delivery route.

Over the past 4 years, the treatment of SMA has been revolutionized, and it is anticipated that more advances will occur over the next 5 years. Potential advances include expanded age indications, different delivery mechanisms, combination treatment with the medications currently available, development and approval of new SMA-specific medications, and development and approval of medications to increase strength in a wide variety of neuromuscular conditions. Some health-care providers have already begun prescribing combinations of the currently available medications, which typically includes administration of onasemnogene abeparvovec-xioi followed in combination with either nusinersen or risdiplam.[37] These combinations are chosen based on differing mechanisms of action, but clinical trials assessing these combinations have not been conducted. Clinical trials have begun with new splicing medications and non–disease-specific medications, such as myostatin inhibitors. The results of these trials, as well as clinical experience with the currently available medications, will guide the promising future of SMA treatment.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Lefebvre S, Bürglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*. 1995;80:155-165.
2. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet*. 2012;20:27-32.
3. Gabanella F, Carissimi C, Usiello A, Pellizzoni L. The activity of the spinal muscular atrophy protein is regulated during development and cellular differentiation. *Hum Mol Genet*. 2005;14:3629-3642.
4. Feldkötter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time LightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. *Am J Hum Genet*. 2002;70:358-368.
5. Lorson CL, Hahnen E, Androphy EJ, Wirth B. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. *Proc Natl Acad Sci USA*. 1999;96:6307-6311.
6. Wijngaarde CA, Brink RC, de Kort F, et al. Natural course of scoliosis and lifetime risk of scoliosis surgery in spinal muscular atrophy. *Neurology*. 2019;93:e149-e158.
7. Spinraza (nusinersen) injection, for intrathecal use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf. Accessed December 8, 2020.
8. Zolgensma, INN-Onasemnogene abeparvovec. https://www.avexis.com/us/content/pdf/prescribing_information.pdf. Accessed December 8, 2020.
9. Evrysdi (risdiplam) for oral solution. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213535s000lbl.pdf. Accessed December 8, 2020.
10. Muth CC. ASO therapy: hope for genetic neurological diseases. *JAMA*. 2018;319:644-646.
11. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med*. 2017;377:1723-1732.
12. Michelson D, Ciafaloni E, Ashwal S, et al. Evidence in focus: nusinersen use in spinal muscular atrophy. *Neurology*. 2018;91:923-933.
13. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med*. 2017;377:1713-1722.
14. Sturm S, Günther A, Jaber B, et al. A phase 1 healthy male volunteer single escalating dose study of the pharmacokinetics and pharmacodynamics of risdiplam (RG7916, RO7034067), a *SMN2* splicing modifier. *Br J Clin Pharmacol*. 2019;85:181-193.
15. Ratni H, Ebeling M, Baird J, et al. Discovery of risdiplam, a selective survival of motor neuron-2 (SMN2) gene splicing modifier for the treatment of spinal muscular atrophy (SMA). *J Med Chem*. 2018;61:6501-6517.
16. Poirier A, Weetall M, Heinig K, et al. Risdiplam distributes and increases SMN protein in both the central nervous system and peripheral organs. *Pharmacol Res Perspect*. 2018;6:e00447.
17. Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord*. 2010;20:155-161.
18. Dubowitz L, Dubowitz V, Mercuri E, et al. Hammersmith neurological examinations. https://hammersmith-neuro-exam.com. Accessed December 8, 2020.
19. Lennon EM, Gardner JM, Karmel BZ, Flory MJ. Bayley Scales of Infant Development. *Encyclopedia of Infant and Early Childhood Development*. Toronto: NCS Pearson; 2008:145-156.
20. Hammersmith Functional Motor Scale Expanded for SMA (HFMSA). http://columbiasma.org/docs/hfmse_2019_manual.pdf. Accessed December 8, 2020.
21. Mazzone ES, Mayhew A, Ramsey D, et al. Revised upper limb module for SMA (RULM for SMA). http://columbiasma.org/docs/cme-2010/rulm-generic-manual-16-dec-2014.pdf. Accessed December 8, 2020.
22. Vuillerot C, Payan C, Iwaz J, et al. Responsiveness of the motor function measure in patients with spinal muscular atrophy. *Arch Phys Med Rehabil*. 2013;94:1555-1561.
23. Govoni A, Gagliardi D, Comi GP, Corti S. Time is motor neuron: therapeutic window and its correlation with pathogenetic mechanisms in spinal muscular atrophy. *Mol Neurobiol*. 2018;55:6307-6318.
24. De Vivo DC, Bertini E, Swoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscul Disord*. 2019;29:842-856.
25. Results from the ongoing presymptomatic SMA study of zolgensma. https://www.zolgensma.com/clinical-studies/presymptomatic-study-results. Accessed December 8, 2020.
26. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet*. 2016;388:3017-3026.
27. Shell R, Day JW, Chiriboga C, et al. Onasemnogene abeparvovec-xioi gene-replacement therapy for spinal muscular atrophy type 1 (SMA1): Phase 3 US Study (STR1VE) Update (1828). *Neurology*. 2020;94:1828.
28. Baranello G, Servais L, Day JW, et al. FIREFISH Part 1: 1-year results on motor function in babies with type 1 SMA (S25.003). *Neurology*. 2019;92(Suppl.):S25.003.
29. Servais L, Baranello G, Masson R, et al. FIREFISH Part 2: efficacy and safety of risdiplam (RG7916) in infants with type 1 spinal muscular atrophy (SMA) (1302). *Neurology*. 2020;94:1302.
30. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med*. 2018;378:625-635.

31. Darras BT, Farrar MA, Mercuri E, et al. An integrated safety analysis of infants and children with symptomatic spinal muscular atrophy (SMA) treated with nusinersen in seven clinical trials. *CNS Drugs*. 2019;33:919-932.
32. Darras BT, Chiriboga CA, Iannaccone ST, et al. Nusinersen in later-onset spinal muscular atrophy. *Neurology*. 2019;92:e2492-e2506.
33. Finkel RS, Day JW, Darras BT, et al. One-time intrathecal (IT) administration of AVXS-101 IT gene therapy for spinal muscular atrophy: phase 1 study (STRONG). Abstract of the annual meeting of the Muscular Dystrophy Association, August 2020.
34. Mercuri E, Baranello G, Kirschner J, et al. Update from SUNFISH part 1: safety, tolerability and PK/PD from the dose-finding study, including exploratory efficacy data in patients with type 2 or 3 spinal muscular atrophy (SMA) treated with risdiplam (RG7916) (S25.007). *Neurology*. 2019;92(suppl):S25.007.
35. Mercuri E, Barisic N, Boespflug-Tanguy O, et al. SUNFISH Part 2: efficacy and safety of risdiplam (RG7916) in patients with type 2 or non-ambulant type 3 spinal muscular atrophy (SMA) (1260). *Neurology*. 2020;94:1260.
36. Cartwright MS, Ward ZT, White EP, West TG. Intrathecal delivery of nusinersen in individuals with complicated spines. *Muscle Nerve*. 2020;62:114-118.
37. Lee BH, Collins E, Lewis L, et al. Combination therapy with nusinersen and AVXS-101 in SMA type 1. *Neurology*. 2019;93:640-641.

CME Content

Intended audience and objectives: This monograph is intended for physicians who treat individuals with spinal muscular atrophy (SMA). Upon completion of this monograph and associated questions, the reader will be able to describe the three treatments available for SMA, discuss the mechanism of action of each treatment, and describe the considerations that are involved in choosing a specific treatment.

Summary description: Spinal muscular atrophy (SMA) is an inherited lower motor neuron disease. Three medications have been approved for the treatment of SMA over the past several years. This monograph describes these treatments and the important aspects of each treatment that need to be considered prior to selecting a treatment for an individual with SMA.

Questions:

What is the mode of inheritance for SMA?

A. Autosomal dominant
B. Autosomal recessive
C. X-linked dominant
D. X-linked recessive
E. Mitochondrial

Answer: B

What gene is altered in individuals with SMA?

A. *SMN1*
B. *SMN2*
C. *SMN3*
D. SMA gene
E. *GJBP*

Answer: A

An increased copy number of which gene is associated with less severe SMA?

A. *SMN1*
B. *SMN2*
C. *SMN3*
D. SMA gene
E. *GJBP*

Answer: B

What is the mechanism of action of nusinersen?

A. *SMN1* gene replacement
B. Small molecule splicing modifier of *SMN2* pre-mRNA
C. Direct replacement of survival motor neuron protein
D. Antisense oligonucleotide binding to *SMN2* pre-mRNA
E. Myostatin inhibition

Answer: D

What is the mechanism of action of onasemnogene abeparvovec-xioi?

A. *SMN1* gene replacement
B. Small molecule splicing modifier of *SMN2* pre-mRNA
C. Direct replacement of survival motor neuron protein
D. Antisense oligonucleotide binding to *SMN2* pre-mRNA
E. Myostatin inhibition

Answer: A

What is the mechanism of action of risdiplam?

A. *SMN1* gene replacement
B. Small molecule splicing modifier of *SMN2* pre-mRNA
C. Direct replacement of survival motor neuron protein
D. Antisense oligonucleotide binding to *SMN2* pre-mRNA
E. Myostatin inhibition

Answer: B

Which of the following medications may cause severe hepatotoxicity?

A. Nusinersen
B. Oral albuterol
C. Oral prednisolone
D. Risdiplam
E. Onasemnogene abeparvovec-xioi

Answer: E

Which of the following medications may cause nephrotoxicity?

A. Nusinersen
B. Oral albuterol
C. Oral prednisolone
D. Risdiplam
E. Onasemnogene abeparvovec-xioi

Answer: A

Which of the following medications may adversely affect male fertility?

A. Nusinersen
B. Oral albuterol
C. Oral prednisolone
D. Risdiplam
E. Onasemnogene abeparvovec-xioi

Answer: D

A 3-year-old boy has recently been diagnosed with SMA. Which of the following medications is not approved for treatment of this child?

A. Nusinersen
B. Oral albuterol
C. Risdiplam
D. Onasemnogene abeparvovec-xioi

Answer: D

How to cite this article: Cartwright MS, Upadhya S. Selecting disease-modifying medications in 5q spinal muscular atrophy. *Muscle & Nerve*. 2021;1-9. https://doi.org/10.1002/mus.27358