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Gene Therapy for Spinal Muscular Atrophy: An Emerging Treatment Option for a Devastating Disease

Vamshi K. Rao, MBBS, MD; Daniel Kapp, PharmD, BCPS; and Mary Schroth, MD

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Learning Objectives

- Demonstrate knowledge of spinal muscular atrophy (SMA) and its contemporary treatment
- Explain genetic aspects of SMA, including its recessive nature, carriers, and recommendations for genetic screening
- Explore potential implications for gene therapy in SMA
- Summarize key clinical trial data on gene therapy for SMA

Plan approaches to formulary management to ensure timely access to newly approved therapies

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Gene Therapy for Spinal Muscular Atrophy: An Emerging Treatment Option for a Devastating Disease

Vamshi K. Rao, MBBS, MD; Daniel Kapp, PharmD, BCPS; Mary Schroth, MD

ABSTRACT

BACKGROUND: Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease that, in most cases, involves homozygous deletion of the *SMN1* gene. This causes a deficiency in survival motor neuron (SMN) protein, which plays a critical role in motor neuron development. SMA has a range of phenotype expression resulting in variable age of symptom onset, maximum motor strength achieved, and survival. Without intervention, infants with a more severe form of the disease (type 1 SMA) die before 2 years of age. Although it is rare, SMA is the most common fatal inherited disease of infancy, and until recently, treatment was primarily supportive. In 2016, a new agent, nusinersen, was approved by the FDA. Other treatments are in development, including a gene therapy, AVXS-101. These treatments are not only improving the lives of patients with SMA and their families, they are changing the disease phenotype. They have the greatest benefit when given early in the disease course.

OBJECTIVES: To discuss current knowledge about SMA, provide clinical evidence for available and emerging treatment options, and present approaches for adding new therapies to hospital/health system formularies to ensure timely access to newly approved therapies for SMA.

SUMMARY: Advances in clinical care have significantly extended the lives of individuals with SMA, and research into the genetic mechanisms leading to disease have revealed strategies for intervention that target the underlying cause of SMA. Nusinersen is now on the market, and other treatment options, such as AVXS-101, may soon be approved. This article provides an overview of SMA and the genetic mechanisms leading to SMN deficiency, then describes how new and emerging treatments work to overcome this deficiency and prevent associated nerve damage and disability. In addition, we discuss steps for incorporating AVXS-101 into hospital/health system formularies, along with barriers and concerns that may delay access, based in part on lessons learned with nusinersen.

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Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease that, in most cases, involves deletion of a gene, *SMN1*, leading to a deficiency in survival motor neuron (SMN) protein. Although rare—occurring in 1 in 11,000 births¹—it is nevertheless the most common fatal genetic disease of infancy.² Advancements in clinical care, especially technological improvements in pulmonary care and aggressive nutritional support, have significantly extended the lives of individuals with SMA.³ Furthermore, a therapy approved by the U.S. Food and Drug Administration (FDA), nusinersen (Spinraza)—a splicing modifier that increases SMN levels—has dramatically altered the natural history of the disease.⁴ Gene therapy (AVXS-101, onasemnogene abeparvovec, Zolgensma) using an adeno-associated virus 9 (AAV9) vector that carries an *SMN1* cDNA cargo is also showing great promise and has been submitted for FDA review for possible approval to treat SMA type 1 (SMA1), the most severe form of SMA,

for infants and toddlers.^{5,6} Additional treatments now in clinical trials include oral small molecules—a fast-skeletal muscle troponin activator (reldesemtiv [CK-2127107]) and 2 splicing modifiers (branaplam [LMI070] and risdiplam [RG7916]); still others are in preclinical stages of development.⁷ This article provides an overview of SMA, a review of nusinersen clinical trials and how they have improved understanding of SMA treatment, and a discussion of treatments in development, with a particular focus on gene therapy and AVXS-101 clinical trial findings. Also discussed are lessons learned from facilitating availability of nusinersen in hospitals and health care systems postapproval and ways to anticipate and prepare for availability of AVXS-101, should it be approved by the FDA.

What Is SMA?

SMA is a neurodegenerative disease affecting the motor neurons in the anterior horn of the spinal cord. It is associated with progressive motor weakness.⁸ The course of the disease is distinct from other degenerative motor neuron diseases in that the greatest rate of motor strength and function loss occurs with disease onset, followed by a slower rate of disease progression, eventually leading, in many cases, to early mortality.⁹

Individuals with SMA are classified into 1 of 5 types based on timing of disease onset and maximum motor function achieved, with some variation within types in level of function and clinical course. SMA type 0 is unique from the other types in that symptoms begin in utero. The disease is quite severe, and at birth, these infants typically have joint contractures, respiratory distress, and diffuse hypotonia. They do not survive the neonatal period without intervention.⁹ SMA type 1 (SMA1) is the most common form, affecting about 60% of those with the disease.¹⁰ Symptoms include hypotonia, difficulty breathing or feeding, and motor delays that start before 6 months of age. In addition to life-threatening pulmonary complications, individuals with SMA1 often have bulbar dysfunction and dysphagia because of muscle weakness. As a result, they may have nutritional compromise and failure to thrive. They may develop progressive motor weakness and fatigue, joint contractures, and scoliosis.^{3,11,12} These patients never sit and have a life expectancy of <2 years without intervention. The primary cause of death is pulmonary compromise, because of respiratory muscle weakness leading to severe restrictive lung disease and progressive respiratory failure.^{13,14} In a natural history study of 26 infants age less than 6 months with SMA1 recruited from 14 sites within the National Network for Excellence in Neuroscience Clinical Trials, median survival was 8 months.¹¹ In a second natural history study of 34 infants with SMA1 recruited from 3 clinical trial sites, median survival and/or time to ventilation dependence ≥ 16 hours was 13.5 months.¹²

FIGURE 1 Location of Genes Encoding SMN Proteins on Chromosome 5q

Note: *SMN1* and *SMN2* genes (circled in red) are found on chromosome 5q, in position 5q11.2–5q13.3.
SMN=survival motor neuron.

In children with SMA type 2 (SMA2), symptoms usually begin later but before age 18 months. These children sit but do not walk and survive into early adulthood. Children with SMA type 3 (SMA3) have comparatively mild symptoms that begin after 18 months. They stand independently and may walk, although they may lose this ability in their teens or later, and they survive well into adulthood.^{13,14} Finally, individuals with SMA type 4 (SMA4) have the mildest form of the disease. Symptoms begin in adulthood and progress very slowly. These patients stand, may walk, and usually have normal lifespans.^{13,14}

Genetics and Diagnosis of SMA

SMA is caused by abnormalities in the *SMN1* gene on chromosome 5q (Figure 1).¹⁵ The *SMN1* gene product—SMN protein—is crucial for motor neuron development. In approximately 95% of patients, SMA results from homozygous deletion or conversion of *SMN1*.¹ In about 2% of patients, de novo deletions occur in one of the *SMN1* alleles; in 3%-4%, other mutations can be found, typically with an *SMN1* deletion on the other allele.¹⁶ On the same chromosome, a nearly identical gene, *SMN2*, is often referred to as a “backup” gene for *SMN1*. It encodes the same protein, but in much lower levels, because most mRNA transcripts exclude exon 7 and are translated to an unstable protein that is rapidly degraded (Figure 2); only a small percentage of messenger RNA transcripts include all

exons and are transcribed to full-length, stable SMN protein. Individuals with SMA have at least one copy of *SMN2*, and variation in the number of *SMN2* copies is associated with severity of disease, with more copies associated with milder phenotypes (Table 1).^{7,11}

Diagnosis of SMA involves molecular genetic testing for homozygous deletion of *SMN1* in patients with symptoms typical of the disease.¹⁷ In cases where symptoms suggest SMA but 1 copy of *SMN1* is present, or genetic testing is negative, full sequencing of *SMN1* should be completed to look for other mutations. *SMN2* copy number is also obtained when testing for *SMN1*, and the number of *SMN2* copies correlates with severity of phenotype, with fewer copies associated with more severe disease.¹⁸ For example, patients with SMA1 typically have 2 copies of *SMN2* and those with SMA2 typically have 3 copies of *SMN2* (Table 1). However, there are exceptions, and in individual cases, the number of *SMN2* copies may not predict severity of disease and may not account for intrafamilial variation in siblings with SMA.^{19,20}

Current and Emerging SMA Treatments

Until recently, management of SMA has consisted primarily of supportive care to slow or prevent respiratory failure, nutritional compromise, scoliosis, and joint contractures. Respiratory care includes the use of devices that improve ventilation, especially during sleep and viral illnesses when hypoventilation is most

FIGURE 2 Expression of SMN Protein

Adapted from: Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy.⁷

^aIn normal individuals, about 90% of SMN protein is a product of the SMN1 gene. Translation of a “backup” gene, SMN2, yields a mix of mRNA—most of which lacks exon 7 and yields an unstable protein that is rapidly degraded. Only about 10% of functional SMN protein comes from the SMN2 gene.

^bIn individuals with spinal muscular atrophy, the SMN1 gene is missing or mutated. The SMN2 gene is retained, but because most mRNA transcripts lack exon 7, these individuals have very low levels of SMN protein.

SMN=survival motor neuron.

likely to occur, as well as methods to mechanically augment cough and clearance of respiratory secretions.¹¹ Nutritional support includes the use of nonoral methods to deliver enteral nutrition, typically through a surgically placed feeding tube or

temporary nasal tube, plus medical or surgical interventions to control gastroesophageal reflux.^{17,21} Management of joint contractures and scoliosis involves aggressive physical therapy assessments, daily passive range of motion exercises, and use

TABLE 1 Spinal Muscular Atrophy Classification

Type	Age at Onset	Development	Lifespan	SMN2 Copy Number
0	Prenatal	Respiratory support	<1 month	1
1	0-6 months	Never sit	<2 years	2
2	<18 months	Never stand	>2 years	3-4
3	>18 months	Stand unassisted	Adult	3-4
4	>21 years	Stand unassisted	Adult	4-8

Adapted from: Iannaccone ST. Modern management of spinal muscular atrophy.¹³ SMN=survival motor neuron.

of bracing to facilitate and maintain optimal positioning of extremities and maintain the spine upright against gravity. Surgical intervention with internal fixation of the spine may also be needed.^{13,17,22} Over time, these supportive interventions have prolonged life and slowed the natural history of SMA.^{3,22}

Nusinersen

In December 2016, the FDA approved nusinersen, an antisense oligonucleotide (ASO), for treatment of all SMA types. ASOs are single-stranded nucleic acid sequences designed to target specific regions of pre-mRNA and modulate gene expression. Nusinersen is designed to bind a splicing silencer region on SMN2 pre-mRNA, displacing a splicing repressor protein and boosting transcription of full-length SMN2 mRNA (Figure 3).^{23,24} This, in turn, boosts translation of full-length, stable, and functional SMN protein. Because ASOs do not efficiently cross the blood-brain barrier, nusinersen is delivered by intrathecal injection.²⁵

FDA approval of nusinersen was based on efficacy and safety findings from several clinical trials. Among them was a double-blind, randomized, phase 3 clinical trial involving 121 symptomatic infants with type 1 SMA <7 months of age.⁴ At a prespecified interim analysis, performed when 80 infants had been enrolled for ≥ 6 months, 41% of those receiving nusinersen showed motor improvements based on scores on the Hammersmith Infant Neurological Exam (HINE). By comparison, no infants who underwent the sham procedure showed improvement, and the difference between study groups was significant ($P < 0.001$; see Table 2 for a summary of neurologic function measures used in SMA clinical trials). This finding prompted early termination of the trial, and patients were enrolled in an open-label extension study wherein all would receive nusinersen.⁴ Final analysis of the data showed that nusinersen improved motor milestone achievement in 51% of treated infants compared with no infants who underwent a sham procedure. Furthermore, the likelihood of event-free survival (defined as time to death or use of permanent assisted ventilation) was also higher in the nusinersen group ($P = 0.005$).⁴ A second multicenter, double-blind, randomized, phase 3 trial involving 126 children with later-onset SMA (symptom onset

>6 months of age) revealed significant improvement on the Hammersmith Functional Motor Scale-Expanded (HFMSE) after 15 months of nusinersen treatment (least-squares mean increase of 4 points).²⁶ In contrast, patients who received the sham procedure showed loss of motor function over the same interval (least-squares mean decrease of 1.9 points). As a result, the study was terminated early, and patients were also enrolled in the open-label study.²⁶

Another ongoing open-label study is evaluating the efficacy and safety of nusinersen given before SMA symptom onset. This trial has enrolled 25 infants younger than 6 weeks with genetically diagnosed SMA and 2 to 3 copies of SMN2 (likely to develop SMA1 or SMA2, respectively, if untreated).^{14,27} At a 25-month interim analysis, all patients were alive and required neither tracheostomy nor permanent ventilation—in distinct contrast to expected outcomes based on natural history (e.g., for SMA1 without intervention, median survival and/or time to ventilation dependence ≥ 16 hours was 13.5 months). In addition, all patients achieved the motor milestone of sitting unsupported, an achievement not previously observed in SMA1, and the majority could walk.²⁷

In sham-controlled studies, a small proportion of individuals treated with nusinersen showed mild elevations in urinary protein and low platelet counts.²⁸ The overall incidence of adverse events was similar between treatment and sham groups, and severe adverse events were lower in the treatment group compared with the sham group.^{4,26} Rates of lumbar puncture-related complications in the treatment groups were similar to those reported in association with lumbar puncture and included postspinal puncture headache and local pain.^{4,26} Difficulty administering treatment for some individuals, such as those with severe scoliosis or spinal fusion, along with cost (\$125,000 per dose) and frequency of dosing (4 doses in the first 2 months, then 1 dose every 4 months thereafter) are ongoing challenges with nusinersen.^{29,30}

Although nusinersen is not a cure, the clinical trials demonstrated greater improvement in functional outcomes with earlier treatment.^{4,26} This highlights a need for early, presymptomatic diagnosis, which is possible through newborn screening for SMA. In August 2018, the U.S. Health and Human Services Secretary signed the recommendation that newborn screening for SMA be added to the Recommended Uniform Screening Panel.³¹ To date, newborn screening is available in just a few states, and access will be more widespread in the near future.

Small Molecules

Several oral small molecules are in early phase 1-3 clinical trials after showing promise in preclinical studies. These include 2 mRNA splicing correctors, branaplam (LMI070) and risdiplam (RG7916), and a fast-skeletal muscle troponin activator, relde-semtiv (CK-2127107).^{7,32,33}

FIGURE 3 Nusinersen Mechanism of Action

Adapted from: Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy.⁷

Note: Nusinersen, an antisense oligonucleotide (ASO), binds to a splicing silencer region on SMN2 pre-mRNA. This displaces a splicing repressor protein, heterogeneous ribonucleoprotein (hnRNP), and increases incorporation of exon 7 in the mRNA transcript. The result is increasing levels of both full-length SMN mRNA and fully functional SMN protein.

SMN = survival motor neuron.

Both branaplam and risdiplam work by promoting inclusion of exon 7 in SMN2 mRNA, thereby increasing levels of SMN protein. Recruiting for a first-in-human trial for branaplam began several years ago, and preliminary findings hinted at efficacy and safety,³³ but the trial was suspended temporarily because of nerve injury observed in a parallel, preclinical toxicology study.³² The problem has since been resolved, recruiting has resumed, and the study continues.³²

Risdiplam is under study in several trials, including FIREFISH (a phase 2/3 open-label study involving patients with SMA1 ages 1-7 months) and SUNFISH (a phase 2/3, placebo-controlled study involving patients ages 2-25 years with SMA2 or SMA3).^{34,35} Results to date show that risdiplam is well tolerated and increases blood levels of SMN protein. In addition, after 8 months of treatment, many infants in the FIREFISH study achieved improvements on motor milestones, as assessed using the HINE section 2 and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND); further, none of the infants required tracheostomy, had to be placed on permanent ventilation, or lost the ability to swallow.³⁵ Patients in the SUNFISH trial showed stabilization

or improvement in motor function, as assessed using the Motor Function Measure-32; a greater percentage of younger patients (ages 2-11 years, 77%) than older patients (ages 12-24 years, 46%) showed motor function improvements.³⁴

Reldesemtiv works by increasing the sensitivity of the sarcomere to calcium, essentially reducing fatigue.⁷ A phase 2, randomized, double-blind, placebo-controlled trial has tested this agent in adolescents and adults (≥ 12 years) with SMA2, SMA3, or SMA4.³⁶ After 8 weeks of treatment, reldesemtiv was associated with increases from baseline on 6-minute walk distance (a test of aerobic capacity and endurance) and maximal expiratory pressure (a test of respiratory muscle strength). No differences were seen, however, on a number of other tests, including the HFMSE and a test of mobility (timed up-and-go). Adverse events were similar in treatment and placebo groups. Additional studies are in planning stages and may include patients already taking another disease-modifying therapy.³⁶

AVXS-101 Clinical Trial

Years of progress in gene therapy (see the sidebar) set the stage for its development and application in SMA. Investigators designed a vector—called scAAV9.CB.SMN in early studies,

TABLE 2 Select Neurological Function Assessments Used in SMA Clinical Trials

Measure	Description
Hammersmith Infant Neurologic Exam (HINE Section 2) ^{83,84}	<ul style="list-style-type: none"> • Used for assessing various aspects of neurologic function in infants ages 2 months to 2 years • 3 sections, 26 items <ul style="list-style-type: none"> ◦ Section 1: Neurologic assessment ◦ Section 2: Developmental milestone assessment ◦ Section 3: Behavioral assessment • Section 2 may be used alone <ul style="list-style-type: none"> ◦ 8 items, scores of 0 to 2, 3, or 4 ◦ Children with SMA1 may score 0 on all 8 items
Hammersmith Functional Motor Scale, Expanded (HFMSE) ^{85,86}	<ul style="list-style-type: none"> • Used to evaluate motor function in individuals with later-onset SMA (SMA2 and SMA3) • 33 items • Total score ranges from 0 to 66; lower scores indicate poorer function • Scores in patients with SMA2 or SMA3 may decline over 12 months
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) ^{87,88}	<ul style="list-style-type: none"> • Used to evaluate motor skills of children with SMA ages ~4 months to 4 years • Includes 16 items to assess motor skills, each graded on a scale of 0 (no response) to 4 (complete response) • Total score ranges from 0 to 64; lower scores indicate poorer function • Infants with SMA may score much lower than unaffected infants • A score exceeding 40 is rarely seen in infants with SMA1
Motor Function Measure—32 Item (MFM-32) ⁸⁹	<ul style="list-style-type: none"> • Used to evaluate motor function in children and adults with neuromuscular diseases • Assesses 32 items in 3 dimensions (standing and transfers, axial and proximal motor function, distal motor function) • Total score ranges from 0 to 96; lower scores indicate poorer function

SMA=spinal muscular atrophy.

now known as AVXS-101—that carries DNA-encoding, fully functional human SMN under control of a continuous promoter. The vector is designed to boost levels of SMN protein (Figure 4). Preclinical studies demonstrated efficacy and safety in mice and nonhuman primate models of SMA, paving the way for the first clinical trial in humans.^{60,61}

This was a single center, open-label trial designed primarily to study safety of a single intravenous dose of AVXS-101, and secondarily to assess efficacy of the treatment in children with SMA1 and 2 copies of SMN2.⁵ Sixteen children were screened; 1 was excluded because of persistent elevation of anti-AAV9 antibody titers. There were 2 treatment cohorts: patients in

Gene Therapy

In the nearly 50 years since the concept of gene therapy was first put forth,³⁷ its use in humans has been met with overt enthusiasm as well as guarded concern. Gene therapy can target specific mutations to ameliorate or potentially cure disease. Approaches include replacing a mutated gene with a healthy gene, inactivating or “knocking out” a malfunctioning gene, or providing a missing gene. Pioneering studies conducted in the late 1990s were marred by serious adverse effects, including inflammatory responses to vectors and malignancies related to proto-oncogene activation.³⁸ Despite these setbacks, the field moved forward with research to better understand mechanisms of vector delivery, mitigate host responses to vectors, and enhance clinical trial safety protocols. Improvements in tools, technologies, and safety ushered in gene therapy trials for congenital blindness, hemophilia, immunodeficiencies, cancer, and neuromuscular diseases.³⁹ Several gene therapies have since been approved, including

voretigene neparvovec (Luxturna) for treatment of Leber congenital amaurosis, and tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) for treatment of certain B-cell cancers.⁴⁰⁻⁴²

Vectors such as lentiviruses and adeno-associated viruses (AAV) carrying the gene of interest have shown great promise. Lentiviral vectors can carry relatively large (up to ~8 kb), complex genes (such as beta-globin genes).^{39,43,44} They also integrate preferentially into coding regions of the host gene, unlike the gamma retroviral vectors of the 1980s and early 1990s, which integrated into noncoding promoter and enhancer regions, increasing the risk of oncogenic mutagenesis.⁴⁵ Lentiviral vectors have proven useful, for example, in the treatment of certain hemoglobinopathies as well as the metabolic disorder adrenoleukodystrophy and the lysosomal storage disease metachromatic leukodystrophy.⁴⁶⁻⁴⁸

(continued on next page)

FIGURE 4 AVXS-101 Mechanism of Action

Adapted from: Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy.⁷

Note: AVXS-101 is a self-complementary AAVP (scAAV9) vector that carries full-length SMN1 cDNA under control of a continuous promoter. Inside the cell, it is rapidly transcribed to SMN1 mRNA, which is then translated to full-length, fully functional SMN protein.

SMN=survival motor neuron.

cohort 1 (n=3, mean age 6.3 months) received a low dose of AVXS-101 (6.7×10^{13} vg per kg); those in cohort 2 (n=12, mean age 3.4 months) received a higher dose (2.0×10^{14} vg per kg). Treatment was infused intravenously over 60 minutes.

At the time of initial publication, all patients had reached at least 20 months of age without needing permanent ventilation.⁵ All patients demonstrated increases from baseline in scores on the CHOP INTEND. The mean increase was 7.7 points in

Gene Therapy (continued)

AAV vectors have been engineered from a nonpathogenic, naturally nonreplicating parvovirus. A “cassette” containing the gene of interest replaces all viral DNA sequences—the lack thereof ensures that the vector does not integrate into host DNA.⁴⁹ Following entry into the host cell and transport to the nucleus, the transferred DNA remains there in a stable episomal form.

The mid-1990s saw successful gene transfer using these vectors in mice.^{50,51} Subsequent studies demonstrated that AAV vectors can transduce a wide variety of target cells in various animals, with specific tropism for tissues such as liver, retina, and even the central nervous system.⁵² Safety in humans was first demonstrated in hemophilia B trials conducted in the late 1990s.^{53,54}

AAV vectors have limitations, such as not being able to package more than ~5 kb of DNA.⁵⁵ In addition, because they do not integrate into host DNA, long-term expression is limited to nondividing cells, which may be less than optimal for some diseases. However, in one study, transgene expression in the human brain was found to persist as long as 10 years after initial administration.⁵⁶ Emergence of large-scale manufacturing and purification techniques have allowed for large-animal studies and multicenter clinical trials.⁵⁷ Research into immune responses to the viral capsid (and strategies to overcome them) has been central to understanding their full potential.⁵⁸ Finally, redesigning AAV vector genomes to be self-complementary (scAAVs) has reduced dependence on host cell transcription and improved speed and efficiency of therapeutic protein synthesis.⁵⁹

TABLE 3 10 Lessons Learned from Commercialization of Nusinersen

1. Anticipate delays because of unknowns of the therapy (e.g., REMS requirements, care setting for administration) before product launch, to avoid inefficiencies during the formulary review process; the time to address unforeseen obstacles is amplified by each step of formulary review. This is especially important for therapies where age or weight cut-offs are likely to be imposed on the approved labeling.
2. Provide education to address concerns or misconceptions about gene therapy (such as doubts about efficacy and safety that linger from early trials), to ensure safe and efficient delivery of care.
3. Engage in collaboration and knowledge-sharing with local and regional providers early to assist in developing care-delivery mechanisms.
4. Ensure that stakeholders thoroughly understand the processes involved in adding complex, high-cost therapies to their health system formularies to maintain trust and support shared decision-making among colleagues.
5. Continue and improve upon a patient-focused system of advanced care.
6. Promote engagement between senior leadership and clinical specialists requesting formulary additions, to ensure that provision of these therapies aligns with the system's overall mission. This interaction should facilitate better connection with patient care and, consequently, with patients themselves.
7. Ensure that decision-making bodies communicate the scope of their authority before any formulary evaluation. Providing clear expectations of what it means to add or deny an item to the formulary system can help avoid miscommunication throughout the process and assist in the resolution of conflicts.
8. Recognize that conditions requiring the therapy are frequently devastating to patients and their families. Providers involved with patient care should act as their champions while understanding the consequences of limited health care resources when a system provides high-cost therapies. The primary provider should appreciate the methodical approach that is required to responsibly add therapies to the formulary.
9. Establish a multidisciplinary committee that includes patient representatives, ethicists, finance experts, senior leadership, and chairs/leaders from multiple clinical disciplines to accept accountability for advising the system on major formulary decisions. This committee works together with the P&T committee to ensure shared decision-making and stakeholder engagement throughout the evaluation process.
10. Strive to avoid or reduce the time between potential FDA approval and payer coverage determinations (i.e., when reimbursement is possible). Unfortunately, delays are inevitable and often outside of the provider's control. To assist both providers and patients during this period, senior leadership should consistently engage staff and the community to provide updates and direction.

FDA=U.S. Food and Drug Administration; P&T=pharmacy and therapeutics; REMS=Risk Evaluation and Mitigation Strategy.

cohort 1 (from a mean baseline of 16.3 points) and 24.6 points in cohort 2 (from a mean baseline of 28.2). These gains were maintained throughout study duration. Eleven children in cohort 2 were able to sit without support for at least 5 seconds; 11 achieved head control; 9 could roll over. Two could crawl, pull to stand, stand, and walk independently; 11 achieved the ability to speak. No children in prior natural history studies had gained these motor milestones.^{11,12} Data updates after 24 months showed continued survival and improvement in motor function.⁶² In addition, as observed in nusinersen trials, the earlier the treatment, the better the outcomes; generally, those treated at the youngest ages made the greatest gains, while the patients treated the latest showed the least improvement.⁵

Adverse events observed with AVXS-101 were mostly unrelated to treatment. However, 1 patient in cohort 1 had treatment-related elevations in liver transaminases (31 times the upper limit of normal for alanine aminotransferase and 14 times the upper limit of normal for aspartate aminotransferase); these elevations responded to prednisolone, which was subsequently given to all other patients as part of the treatment protocol. One patient in cohort 2 had similar elevations in liver enzymes and required additional prednisolone. Transaminase elevations were not associated with other liver function abnormalities or clinical changes, and treatment with AVXS-101 appears safe overall.⁵

Several additional multicenter trials of AVXS-101 are underway. One ongoing trial is a phase 3, open-label, single-arm, single-dose trial of intravenous AVXS-101 in symptomatic

children aged <6 months with type 1 SMA and 1 to 2 copies of SMN2 (NCT03306277).⁶³ Another trial involves infants aged <6 weeks, before onset of SMA symptoms, with a biallelic deletion of SMN1 and 2, 3, or 4 copies of SMN2 (NCT03505099); they, too, will receive a single intravenous dose of the study drug.⁶⁴ A third trial is studying single-dose intrathecal administration of AVXS-101 in 2 cohorts of children with 3 copies of SMN2 who are sitting but not standing. Cohort 1 includes children aged <2 years, and cohort 2 includes children aged ≥2 and <5 years (NCT03381729).⁶⁵ A fourth trial, still in planning, will be an “all-comers” study enrolling patients with SMA who are aged between approximately 6 months and 18 years and do not qualify for other clinical trials.⁶⁶ The FDA has granted AVXS-101 orphan drug designation for all types of SMA, and breakthrough therapy and fast track designations for the treatment of SMA1.⁶⁷ Further, the first request for FDA approval—a biologics license application (BLA) for use of AVXS-101 in infants with SMA1 up to 9 months of age—was submitted in October 2018, and requests for older patients and other SMA types are anticipated.⁶ If the FDA accepts the BLA (a decision is expected within 60 days), review is expected to take 6 months. Thus, approval may be fairly imminent.

Anticipating Availability of Gene Therapy for SMA: How Do Hospitals and Health Care Systems Need to Prepare?

Approval of novel therapies for rare and untreated conditions have been trending upward in recent years, and in 2017, 39%

(18 of 46) of the drugs and biologics approved by the FDA's Center for Drug Evaluation and Research had orphan drug status.^{68,69} These therapies for rare and ultrarare conditions continue to challenge the traditional paradigm of maintaining a health system formulary consisting only of medications appropriate for routine use, as recommended by the 2008 American Society of Health-System Pharmacists' Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System.⁷⁰ Consideration of an institution's formulary system is important, as it is the pivotal drug management tool to maintain high-quality care while minimizing health system costs. In principle, formulary systems are designed to assist in clinical decision-making by ensuring access to efficacious, safe, and cost-effective medications; although certain practical components may differ, these founding principles should guide the evaluation process for all novel therapies.⁷¹

Potential Effects of Cost on Adoption of New Therapies

In the United States, health care practitioners must function within a system that promotes a difficult duality. The FDA supports 2 seemingly disparate goals: fostering market-based incentives for drug manufacturers (e.g., unregulated market-entry drug pricing) while ensuring public access to affordable medications.⁷² Many health care systems, especially those also acting as the payer, experience only the costs of innovative therapies and must further operationalize provision of these typically complex therapies.

The revolutionary potential of gene therapy—to bring cure to what is otherwise incurable—likely plays a large role in determination of market-entry pricing.⁷³ Indeed, the substantial costs associated with nusinersen and those expected with AVXS-101 have raised concerns from providers and payers alike (see Table 3 for useful lessons learned from commercialization of nusinersen).^{73,74} Further confounding the determination of drug value are the small populations studied, alternative trial designs employed, and short follow-up durations reported; these are all factors that decrease the certainty of safety and efficacy. Since health care practitioners are accustomed to the FDA's gold standard of large randomized controlled trials supporting drug approval, this uncertainty, along with comparatively high market-entry prices (e.g., ranging from \$373,000 to \$850,000 for one-time treatment with currently approved gene therapies⁷⁵⁻⁷⁷), inevitably turn the focus of conversation to drug cost. Yet too great an emphasis on cost of therapy without fair consideration of its benefits may block or delay access to care.^{74,78}

Ultimately, providers must implement a strategic and methodical approach to formulary management to ensure accessible care while avoiding unrecoverable financial consequences. Guiding this approach should be consideration of patient benefit from therapy, including improved quality of life and function and decreased health care utilization and hospitalizations, while giving due credence to the balancing act

a payer needs to engage with in respect to financial resource allocation. Whatever the financial climate, health system leaders should navigate the formulary evaluation process with diligence to maximize the likelihood of making beneficial therapies available. Participation of various stakeholders across the health care spectrum in the formulary decision-making process would increase the chances of a balanced viewpoint.

Steps in Getting Gene Therapy on Formulary

Formulary evaluation and addition of AVXS-101 (or other gene therapies) should be as methodical as that for routinely used medications, despite the potential for infrequent use.

A proactive pipeline-monitoring approach to ensure adequate lead time for evaluating innovative treatments can help systems anticipate future product availability. For most institutions, this task is delegated to the pharmacy department or (if established) a drug information center, and close collaboration with clinical specialists helps to guide selection of potential formulary additions. Table 3 lists lessons learned from implementation of nusinersen, the first treatment approved for SMA. Table 4 provides a checklist and illustrates a possible pathway from anticipation of availability to implementation of clinical use for AVXS-101.

Once a therapy is identified for formulary addition, a team should be established to oversee development of information and clinical support tools (e.g., clinical practice guidelines, therapy administration policies, standard operating procedures) that are readily accessible and ensure a uniform and efficient medication-use process within the system. Early involvement of health informatics specialists is advised to ensure safe and timely integration of the therapy into the electronic health record.

In most settings, oversight for formulary evaluation is provided by a pharmacy and therapeutics (P&T) committee; however, delegation to a specialized subcommittee may be required.⁷⁰ Such subcommittees are often needed to assist with formulary management. They provide focused representation to address complexities in specific areas (e.g., oncology, neurology, infectious diseases); without them, evaluation of medication use would be limited in scale and scope. Similarly, stewardship programs may be developed to facilitate the safe and appropriate use of medications within health systems, the archetype being the antimicrobial stewardship program frequently implemented across institutions and supported by evidence of beneficial clinical and economic outcomes.⁷⁹ In addition, institutions may establish multidisciplinary subcommittees that specifically evaluate products granted accelerated approval or designated as orphan or breakthrough therapies. Members should include patient representatives, physician leaders from various specialties, finance representatives, ethics representatives, and senior leadership representatives (e.g., chief medical officer, chief executive officer, or chief of staff) to ensure shared decision-making and stakeholder engagement throughout the evaluation process.

TABLE 4 Checklist for Organizations: Transitioning from Protocol to Practice for AVXS-101^a

- ☐ Organize a team of clinical and operational experts, led by a champion who anticipates use of the therapy within the system, to act as a primary resource to support formulary management and clinical implementation.
- ☐ Inform the appropriate decision-making bodies (e.g., P&T, medical board) about the anticipated therapy to start a transparent flow of information. Petitioning leadership to allocate resources to the formulary review process before possible FDA approval may be needed to ensure minimal time between approval and a formulary addition decision.
- ☐ Determine the effects of providing therapy on patients, providers, and the health system, with consideration of potential effects on standards of care (e.g., frequency of patient visits), implications of SMA inclusion in the Recommended Uniform Screening Panel, any significant unknowns of efficacy or safety (e.g., durability of effect, benefit for children and adults with type 2, 3, or 4 SMA), and other factors. Addressing these issues early may expedite the formulary review process.
- ☐ Address any misconceptions about gene therapies and safety of their use. For example, a high biosafety-level setting for administration of AVXS-101 is unnecessary and would add excessive burden.
- ☐ Identify efficiencies in administration. Addressing misconceptions can greatly reduce barriers to efficient delivery. Additionally, early establishment of a gene therapy delivery team and communication with leadership will help identify the ideal medication-use system. Performing a gap analysis can then allow staff to address additional potential barriers.
- ☐ Commit organizational leadership to a formulary decision as soon as feasible. In most cases, this will require prior FDA approval. Ensure decision-making bodies are well informed of any FDA review updates or decisions.
- ☐ Consider additional unknowns requiring a flexible formulary review process. These include regulatory approval, specifics of label, cost, and product availability timeline. By engaging in the review process early and developing novel ways to address these unique issues, a system will be better prepared for AVXS-101 and future gene therapies.

^aOrganizations can follow the same general steps when preparing for AVXS-101 availability irrespective of clinical trial site status.

FDA=U.S. Food and Drug Administration; P&T=pharmacy and therapeutics; SMA=spinal muscular atrophy.

Regardless of variations in the committees and subcommittees involved, several universal strategies direct medication use within health systems. These include establishment of specific-use criteria (e.g., predefined patient clinical criteria that must be met); restrictions criteria (e.g., highly trained individuals for prescribing or a specialized service for administering) for discontinuation of therapy; development of clinical practice guidelines; and requirement of approval by a medical director, division chair, or other clinical leader. Traditional strategies will be deployed, as well, to ensure appropriate use of gene therapies.

Strict external regulations governing use of these therapies are expected given their specialized nature. Designees to oversee implementation of and adherence to regulations, such as requirements of the Risk Evaluation and Mitigation Strategy (REMS) program, should be appointed well in advance of the formulary addition, as audits are likely to occur within the first 6-12 months of therapy provision.

Working with Payers

The focus on cost, despite the potential and perceived benefits of novel therapies, is inevitable when considering a health system's revenue cycle. For most providers, the margin of error is essentially zero for the inappropriate use of a costly therapy (e.g., one 12 mg dose of nusinersen is \$125,000 based on wholesale acquisition cost).⁸⁰ Unlike routinely used treatments, for which occasional misadministration and subsequent loss of reimbursement is tolerable, a single misstep could have grave financial implications. Establishment of comprehensive processes for medication use is required to prevent systemic issues

that risk multiple misadministrations. In addition, errors in use could represent missed opportunities to provide potentially beneficial therapies.

Early collaboration between health systems and payers is critical to the health system's process for evaluating novel therapies. Despite increasing numbers of approved orphan drugs, in 2016, these treatments accounted for 7.9% of overall drug spending, and 1.6% were priced at >\$500,000 per year.⁶⁹ At the same time, growth in orphan drug spending is decreasing relative to nonorphan drug spending.⁶⁹ Payers are frequently implementing strict reimbursement practices in an effort to contain costs and maintain member benefits. Investigation into the reimbursement landscape should occur in tandem with review of clinical safety and efficacy; this may include consultation with local private payers and state Medicaid programs, review of national coverage determinations from the Centers for Medicare & Medicaid Services, and consideration of potential drug administration sites such as those eligible for the 340B Drug Pricing Program.⁸¹ Once reimbursement potential is determined, collaboration with internal finance teams to model the expected patient and payer mix could provide insight into the revenue cycle effects of adding a high-cost formulary item. Involvement of finance teams is also critical for identifying all potential avenues for reimbursement, such as new technology add-on payments.⁸²

Summary

SMA is an autosomal recessive disease caused by deficiency in SMN protein that can lead to disability and death. Thus, it

is a devastating diagnosis for families, particularly in its most severe form. However, a new treatment, nusinersen, is available, and others are emerging, including a promising new gene therapy, AVXS-101. In patients with SMA, both treatments are most effective if given early, before the onset of extensive nerve damage and associated symptoms. Still, there is evidence to support their use in improving or stabilizing disease after symptoms appear. Clinical trials are ongoing, but at this time, AVXS-101 may have an advantage of a single intravenous administration. If it receives FDA approval, both payers and providers will need to be prepared for its implementation. The future seems bright, but many steps remain; careful planning with attention to principles of sound formulary practice may help limit gaps between approval and access.

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Posttest Questions

1. What was the median time of death in the NeuroNEXT natural history study of patients with type 1 spinal muscular atrophy (SMA) ages <6 months?
 - a. 18 months
 - b. 12 months
 - c. 8 months
 - d. 4 months
2. Which of the following is NOT a characteristic of the adeno-associated viral (AAV) vectors currently used in gene therapy protocols?
 - a. They can carry up to 5 kb of DNA.
 - b. They typically integrate into the host genome.
 - c. They form stable episomes in host cells.
 - d. They were engineered from a nonpathogenic parvovirus.
3. Which is the underlying genetic defect in ~95% of cases of SMA?
 - a. Point mutations in the *SMN2* gene
 - b. Point mutations in the *SMN1* gene
 - c. Mutations in the promoter that regulates *SMN2* gene expression
 - d. Homozygous deletion in *SMN1*
4. At the time of publication of the AVXS-101 phase 1 clinical trial, how many of the 12 children who received the higher dose of gene therapy had rolled over (compared to no children achieving this motor milestone in natural history studies)?
 - a. 12
 - b. 9
 - c. 6
 - d. 3
5. Which of the following is NOT a universal strategy directing use of a medication identified for formulary inclusion within a health system?
 - a. Adherence to specific-use criteria
 - b. Development of clinical practice guidelines
 - c. Requirement for approval by a medical director, division chair, or other clinical leader
 - d. Placing cost of treatment as most important in the hierarchy of considerations

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Supplement