Spinal Muscular Atrophy: Huge Steps

By Kelly Howell, Ph.D., Rebecca M. Gibbs, and Lee L. Rubin, Ph.D.

Editor’s Note: Spinal muscular atrophy is the number one genetic cause of infant death. Until recently, half the babies born with it would die before their second birthdays, their hearts and lungs becoming too weak to continue. Medical care improved the odds somewhat, but new discoveries and therapeutic developments have improved survival rates significantly—and more good news may be on the horizon.
In 2016, Bloomberg published an article that described Lauren Gibbs, who was born with spinal muscular atrophy (SMA) and enrolled in a clinical trial for a drug called nusinersen. The story reported that Gibbs enjoyed wheelchair basketball but was known primarily for her defense because she didn’t have enough strength to heave the ball high enough to reach the rim. “After the second time I got the drug, I hit probably 50 baskets in a row,” said Gibbs, who later attended Baylor University.

Later that year, nusinersen became the first SMA treatment to be approved by the Federal Drug Administration (FDA). It is one of many promising developments in the past decade in understanding and treating SMA, a genetic neuromuscular disorder first described in the 1890s by Austrian physicians Guido Werdnig and Johann Hoffman.

The pair observed infants with flaccid limb and trunk muscles, accompanied by the degeneration of motor neurons in the spinal cord. They learned that the loss of these neurons—specialized nerve cells responsible for stimulating skeletal muscle contraction—results in muscle atrophy and weakness, the hallmarks of SMA. Over the next century, further studies revealed highly variable disease severity and age of onset, making it unclear if SMA was one disease with a broad array of symptoms in different patients, or a number of distinct diseases.

In 1995, scientists discovered that SMA is, in fact, one disease caused primarily by a mutation or deletion in the survival motor neuron 1 (SMN1) gene. SMN1 makes SMN, a ubiquitous protein that plays a role in several important cellular processes in tissues throughout the body. Without sufficient SMN, motor neurons die, leading to the widespread muscle atrophy characteristic of SMA. Humans have a second “backup” SMN gene, SMN2, that is nearly identical to SMN1 and also produces SMN protein. However, a single genetic variation in SMN2 causes it to mainly produce a truncated protein that is unstable and nonfunctional. SMN2 does produce a small amount of functional, full-length SMN protein, although not enough to completely compensate for the loss of SMN1. The number of SMN2 gene copies varies among individuals; patients carrying more copies tend to have more SMN protein and less severe forms of the disease.
Today, the incidence of SMA in the US is 1 in 11,000 births, making it the leading genetic cause of infant mortality. It is classified into types based on age of onset and motor function. Patients with SMA Type I, the most severe form, develop symptoms before six months of age and never achieve the ability to sit without support. They have trouble swallowing and breathing due to muscle weakness, and many die or require permanent ventilatory support by age two. Patients with less severe forms of SMA, such as Type II and III, develop symptoms later in childhood and achieve motor milestones such as independent sitting and walking—although they may lose these abilities over time.

**Progress Toward SMA Therapy**

The past decade has seen much progress in the development of therapies for SMA protein. The majority of these aim to increase SMN levels, either by targeting SMN2 to produce more full-length SMN or by delivering a fully functional SMN gene into patients’ motor neurons to supplement their own production of the protein. Additional therapies are being developed to treat affected tissue types outside the central nervous system (CNS) directly and in an SMN-independent fashion.

Nusinersen (Spinraza), the drug given to Lauren Gibbs, was developed by Ionis Pharmaceuticals and Biogen. It targets SMN2 to increase its production of full-length SMN protein. In a Phase 3 clinical trial for patients with infantile-onset SMA (typically consistent with the severe Type I form of the disease), a significantly higher percentage of infants treated with nusinersen achieved motor milestones and survived without permanent ventilatory support, compared to those not receiving the drug.

Nusinersen also demonstrated efficacy in a trial for children with later-onset SMA (consistent with the intermediate Type II form of the disease); here too, a greater percentage of treated patients showed increased motor function compared to patients in the control group. Both trials were terminated early due to the positive results observed and, in late 2016, nusinersen was approved by the FDA.
The approval of nusinersen was a milestone welcomed enthusiastically by the SMA community, but in addition to a $750,000 price tag for the first year of treatment, the therapy has drawbacks. Nusinersen cannot cross the blood-brain barrier, a network of specialized blood vessels that prevents substances from entering the brain or spinal cord. Therefore, in order to reach motor neurons, the drug must be delivered through repeated intrathecal injection (i.e., into the spinal fluid via lumbar puncture, a procedure also known as a spinal tap).\textsuperscript{13}

These recurring injections may require sedation, which carries the risk of respiratory compromise in some patients.\textsuperscript{14} Moreover, lumbar puncture is associated with headache, backache, and leakage of spinal fluid, and can be complicated by scoliosis and spinal rods (which many SMA patients have). In addition to the burdens of the procedure, delivering nusinersen directly into the spine limits SMN upregulation (meaning an increase in SMN protein levels) to the CNS—a potentially significant drawback, as increasing evidence suggests that the protein plays an important role in other tissues as well.\textsuperscript{15,16,17}

Two other therapies that target \textit{SMN2} are currently in clinical development. Brapaln (Novartis) and risdiplam (Roche, PTC Therapeutics, SMA Foundation) are small molecules that, like nusinersen, aim to increase the production of full-length SMN protein by targeting \textit{SMN2}.\textsuperscript{18,19} These drugs are orally-administered, which lessens the burden on patients, compared to nusinersen’s mode of delivery, and allows for SMN upregulation in peripheral tissues as well as the CNS. A Phase 1/2 clinical study of brapaln is currently underway in patients with SMA Type I. Risdiplam is being tested in three different clinical trials: FIREFISH for Type I patients, SUNFISH for Type II/III patients, and JEWELFISH for patients who had previously received another \textit{SMN2} targeting therapy or the investigative neuroprotective drug, olesoxime.

Preliminary results from the FIREFISH clinical trial look promising: babies that received daily risdiplam were able to meet developmental milestones such as head control and unassisted sitting, achievements not typical of SMA Type I patients.\textsuperscript{20} Preliminary data from the SUNFISH clinical trial have also shown improvements in motor function.
In contrast to therapeutic strategies that target SMN2 to increase SMN protein levels, the gene therapy AVXS-101 (AveXis, Novartis) works to replace the faulty SMN1 gene in SMA patients. The drug uses the nonpathogenic virus AAV9 to deliver a functional SMN gene directly to cells for sustained expression. The virus can cross the blood-brain barrier, at least when given to very young children, allowing for a less onerous route of delivery than nusinersen, and for upregulation of SMN in tissues outside the CNS.\textsuperscript{21,22,23,24}

AVXS-101 demonstrated promising results in a Phase 1 open-label clinical trial for SMA Type 1.\textsuperscript{25} All 15 infants who received a single intravenous dose of the drug were still alive without the need for permanent ventilation at 20 months of age, in contrast to the eight percent event-free survival rate predicted from natural history studies. A total of 11 of the 12 patients who received a higher dose of AVXS-101 also achieved milestones such as head control, unassisted sitting, oral feeding, and speaking; and two of the three patients who were treated before two months of age were even able to walk independently. Serious adverse events related to treatment were limited to elevated levels of liver enzymes, which could reflect an immune response to the virus; however, these events were resolved with steroid treatment. A larger Phase 3 study is now underway to confirm the safety and efficacy of AVXS-101. A Phase 1 trial for SMA Type II is also ongoing, but in this study, AVXS-101 is delivered by intrathecal administration, with the accompanying drawbacks noted in the discussion of nusinersen.\textsuperscript{26,27}

Despite the encouraging results of the AVXS-101 clinical trial, there are potential limitations to gene therapy. Due to concerns about a possible immune response to the virus, patients who develop antibodies after the first dose of AAV9 might be ineligible for additional treatments.\textsuperscript{28} While improvement in patients’ motor function was sustained for two years after a single dose of AVXS-101, in the Phase 1 clinical trial, efficacy for longer periods is not yet certain. In addition, because the virus does not integrate into a cell’s genome, it can be lost when a cell divides. While this is not an issue with motor neurons, which do not divide, tissues that do may lose SMN expression from the virus over time. Future studies with longer follow up should clarify the impact of these limitations, especially on patients who are treated systemically.
SMN-Independent Therapies:
While SMN upregulation is undoubtedly critical in treating SMA, other approaches should also be considered for a number of reasons. Firstly, numerous studies of SMN-upregulating therapies have underscored the importance of timing—if levels of the protein are restored too late, substantial therapeutic benefit may not be achieved. For example, in both the nusinersen and AVXS-101 trials, patients treated earlier in their disease course showed the greatest improvements. Others showed a stabilization or a decline in progress. This poses a particular challenge for those with milder forms of SMA, who are often diagnosed after substantial numbers of motor neurons have been lost. Furthermore, because SMA is partly a disorder of tissue development, raising SMN levels after the process is complete may not sufficiently restore tissue function.

Secondly, there remains the question of which tissue types require SMN restoration for maximum therapeutic benefit. Although SMA has long been considered a motor neuron disorder, it is now widely viewed as a multi-system disorder with pathology beyond the CNS. Multiple organs, including skeletal muscle, heart, bone, and gastrointestinal systems, show deficits in preclinical SMA models, although the incidence of systemic defects in patients is not yet fully understood.29 These results suggest that SMN-upregulating treatments (such as nusinersen) that only affect the CNS will not cure many patients. In fact, interim results from the ongoing NURTURE trial of nusinersen in genetically diagnosed, pre-symptomatic SMA patients showed that even with early intervention, not all achieve age-appropriate milestones.30 Therefore, treatments that also target cells other than motor neurons will likely be crucial.

For these reasons, considerable effort has gone into developing therapies that do not depend on raising SMN levels. Most of these therapies have focused on muscle, since muscle weakness is so prominent in SMA. However, as Type I patients treated with nusinersen begin to live longer, it is likely that additional peripheral phenotypes may emerge, suggesting the need for drugs acting on other tissue types. SMN-independent therapies have the potential to be used in combination with the SMN-upregulating drugs described above to achieve maximum benefit.

Potential Developments
To improve muscle size and function directly, the pharmaceutical company Scholar Rock is currently developing SRK-015, an intravenously-administered antibody against myostatin, a protein that inhibits muscle growth.\textsuperscript{31} It has been shown in animals (including SMA mouse models) that, by blocking the activation of myostatin, SRK-015 increases muscle size and strength.\textsuperscript{32,33} The antibody is currently being evaluated in a Phase I clinical trial assessing the effects of single and multiple doses in healthy adults.\textsuperscript{34} If approved, it might be used to treat muscle weakness in patients with milder, adult-onset SMA, either alone or in combination with SMN-upregulating therapy.

Other myostatin inhibitors are already in use for other indications and might be repurposed to treat the muscle component of SMA. An entirely different approach is being investigated through a collaboration between the biopharmaceutical companies Cytokinetics and Astellas Pharma, which are developing reldesemtiv, a small molecule shown in clinical studies to increase skeletal muscle force. The drug works by sensitizing muscle to calcium, amplifying contractions even with submaximal nerve stimulation.\textsuperscript{35} This approach could increase strength in SMA patients despite motor neuron and nerve degeneration. Cytokinetics recently completed a Phase II clinical trial assessing two doses of reldesemtiv in patients 12 years or older with SMA Types II, III, or IV. The results showed clinically meaningful improvements in ambulation and muscle fatigue, suggesting increased muscle strength.\textsuperscript{36}

Given the approval of nusinersen and the host of ongoing clinical trials for other drugs, there is realistic hope for substantial progress in SMA treatment. Evidence of recent achievement and future potential can be found on the press page of the SMA Foundation, where more than 50 articles and press releases dating back to 2002 trace drug development, clinical trials, fund raising, and accounts of lives transformed. As we move forward, researchers will continue to assess combinatorial therapies leveraging both SMN-dependent and SMN-independent mechanisms of action to provide maximum benefit to all patients.

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Bios

Lee L. Rubin, Ph.D., is a professor of stem cell and regenerative biology at Harvard University and director of therapeutic medicine at the Harvard Stem Cell Institute. Rubin received his Ph.D. in neuroscience from the Rockefeller University and completed postdoctoral fellowships in pharmacology from Harvard Medical School and in neurobiology from Stanford University School of Medicine. Since then, his work has been mostly in translational neuroscience, both in academic and industrial settings. Work from his lab has led to the discovery of approved treatments for multiple sclerosis and for cancer. Rubin’s group currently focuses on studying neurodegenerative and neuropsychiatric diseases, including various aspects of spinal muscular atrophy.

Kelly Howell, Ph.D., is an associate director at the SMA Foundation and supports project teams and coordination of research activities between pharmaceutical companies and research institutions. Howell has 15 years of research experience related to neurodevelopment and genetics. Prior to joining the SMA Foundation, she was an associate research scientist in the laboratory of Oliver Hobert at Columbia University. Howell’s postdoctoral studies focused on understanding how connections between neurons and muscles are regulated. She received her BS in biochemistry and molecular biology from Ursinus College and her Ph.D. in cell and molecular biology from the University of Pennsylvania.

Rebecca Gibbs is a Ph.D. candidate in the stem cell and regenerative biology department at Harvard University. Her thesis work is focused on understanding the role of muscle defects in spinal muscular atrophy and developing novel therapeutics that stimulate skeletal muscle stem cells to regenerate atrophic muscle. Gibbs earned her M.S. in biotechnology from Georgetown University, completing her thesis work with Kenneth Fischbeck at the National Institutes of Health, and her B.A. in neuroscience and biological sciences from the University of Southern California.

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References


