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Neuromuscular Disorders (C Fournier, Section Editor)

Current Treatment Options in Neurology—SMA Therapeutics

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Abstract

Purpose of review In this review, we discuss the clinical and genetic features of 5q spinal muscular atrophy and highlight approved and upcoming therapies.
Recent findings We emphasize that multidisciplinary care has been a key component of the improved quality and length of life seen in these individuals in the past decade. We discuss the evidence leading to the approval of nusinersen and the evidence leading to the anticipated approval of onasemnogene abeparvovec-xioi. Additional clinical therapies that are on the horizon are discussed and the importance of continued multidisciplinary care even after treatment is emphasized.
Summary The pursuit of therapies for spinal muscular atrophy is becoming a success story and continued development of biomarkers will allow for more informed therapeutic decision making and eventual cost-effective utilization of available therapies.

Background/introduction

Spinal muscular atrophy is the leading inherited cause of infant death. However, with recent advances in treatment, this is changing.

Spinal muscular atrophy (SMA) occurs in approximately 1 in 11,000 live births and is caused by the lack of the survival motor neuron protein due to an autosomal recessive mutation in *SMN1* [1, 2]. The survival motor neuron (SMN) protein is a key component of the SMN complex which is essential in RNA processing [3]. The absence of this protein results in the slow degeneration of the lower motor neurons in the spinal cord and somatic motor nuclei in the brainstem. In people with this condition, symmetric progressive muscle atrophy and weakness develop. The weakness begins proximally but eventually encompasses all skeletal muscles, leading to the inability to eat safely or breathe unassisted and eventual death [4•].

SMA is a monogenic condition caused by homozygous deletions in the *SMN1* gene in 95% of individuals and either a deletion and pathogenic point mutation or two pathogenic point mutations in the remaining 5% [5].

Despite the relative *SMN1* genotypic homogeneity in affected individuals, there is quite a phenotypic range, with five known types based on clinical features [6–8]. Type 0 refers to those with neonatal onset of symptoms who are so severely affected that they often die in utero or shortly after birth. Type 1 is the most common, representing approximately 50% of cases, and is characterized by disease onset prior to 6 months of age, with the children never achieving the ability to sit unassisted. Type 2 refers to children who are able to sit but never able to walk. Type 3 refers to individuals who achieve the ability to walk but then lose that skill. Finally, type 4 refers to individuals who become symptomatic in adulthood [6–8].

In general, the phenotypic severity is inversely related to the number of copies of the *SMN1* paralog, *SMN2*, present [9]. *SMN2* has a nucleotide substitution that alters splicing resulting in exclusion of exon 7 in approximately 85–90% of the *SMN2* transcripts (Fig. 1). Thus, for each copy of *SMN2* present in an individual, a small amount of full-length SMN mRNA is made and a correlation between increasing number of copies of *SMN2* and a milder phenotype can be made; interestingly, this does not always hold true [10] and the study of other modifiers is ongoing. Nevertheless, the relative genotypic homogeneity and the general dose-dependent response of *SMN2* copy number in individuals with SMA makes newborn screening an attractive option. Testing for SMA has been added to the Recommended Uniform Screening Panel for all newborns in the USA and was implemented in late 2018 in a few states, with several other states expected to follow in 2019 [11, 12][CureSMA press release, 2018]. It is estimated that with the implementation of newborn screening, up to 95% of all people with SMA could be identified at birth, allowing for early implementation of appropriate supportive care and treatments.

Historically, supportive care was the only "therapeutic" option for people with SMA. The disease was first described in 1890, and the gene was identified over 100 years later in 1995 [13]. Preventative and supportive care has dramatically improved. Regular physical therapy sessions help retain range of motion; vitamin D supplementation and bisphosphonates help reduce fractures; bracing and surgical interventions now exist for scoliosis; and early management of constipation, use of positive pressure ventilation, and consideration of gastrostomy tubes have all resulted in improved quality of life for these individuals [14, 15]. However, for most type 1 patients, despite optimal supportive care, the disease is largely fatal by age 2 [4•, 16]. For individuals with type 2, survival is shortened but not as significantly as in type 1 with a 77% chance of survival past 20 years of age [6]. In type 3, although there is no expectation of a shortened life span, the risk of complications is significant, especially after loss of ambulation, and life expectancy may shorten.

Today, although supportive care remains imperative, the treatment landscape for SMA is changing rapidly (Table 1). One therapy is currently FDA approved with a rather dramatic impact on phenotype, and several other promising therapies are in the pipeline. In this review, we will describe current and future SMA therapies and provide some predictions about the future therapeutic landscape for individuals with SMA.

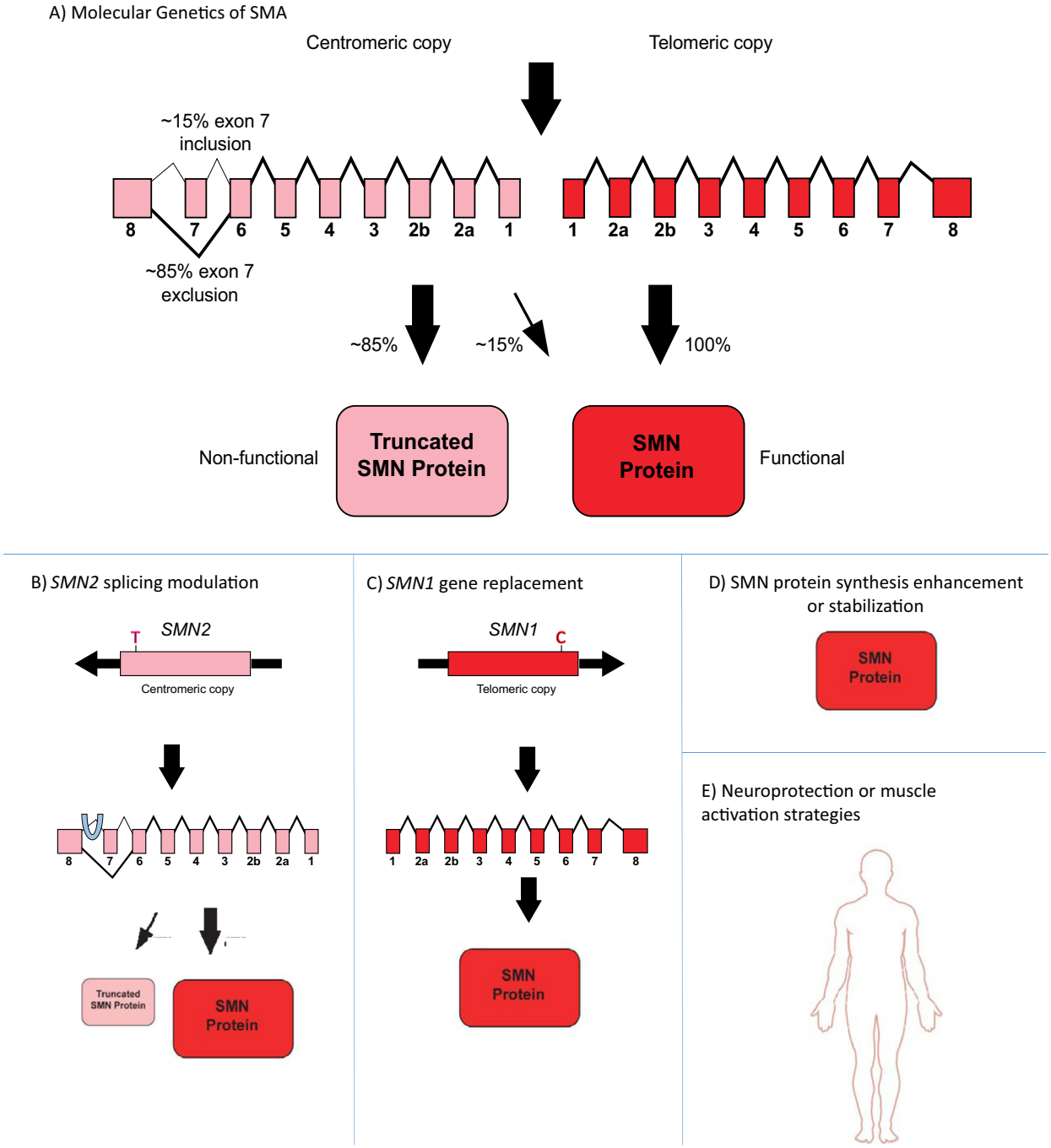

Fig. 1. a Molecular genetics of spinal muscular atrophy and genetic therapies. The *SMN1* and *SMN2* genes are located on chromosome 5q. The centromeric copy refers to the *SMN2* gene and the telomeric copy refers to the *SMN1* gene. In patients with SMA, no protein is produced from the telomeric copy and the only functional protein made is from the *SMN2* gene the small percentage of the time (~ 15%) that exon 7 is not spliced out. **b** Splicing modulation therapies target the *SMN2* mRNA to increase the percentage of the time that exon 7 is included and increase the amount of full-length functional protein made. **c** Gene replacement therapies aim to replace the human *SMN1* cDNA to allow the patient to make their own full-length functional protein. **d** Other therapies are in development that seek to enhance the synthesis of SMN protein or stabilize the SMN protein present. **e** Other therapeutic strategies are more broad, seeking to provide overall neuroprotection or muscle activation.

Table 1. SMA drug pipeline. List of current drugs under development for the treatment of spinal muscular atrophy. A select subset is discussed in the text. Abbreviations: ASO, antisense oligonucletide; GT, gene therapy; CNS, central nervous system; IV, intravenous; IT, intrathecal; SM, small molecule. This information was provided by and used with permission from CureSMA

Developing Organization & Drug Name	Preclinical/Discovery			Clinical Development			FDA Review	FDA Approved
	Identification	Optimization	Safety	Phase 1	Phase 2	Phase 3		
SMN2 splicing modulation								
Biogen-Ionis Spinraza								
Roche-Genetech/PTC/SMAF-RG7916								
Novartis-LM1070								
MU/Shift - E1 ASO								
Biogen 2nd gen ASO								
Gene Replacement								
AveXis/Novartis Zolgensma (IV)								
AveXis/Novartis Zolgensma (IT)								
Biogen GT								
Genzyme/Voyager - CNS GT								
Muscle targets								
Cytokinetics/Astellas-CK-2127107								
Scholar Rock-SRK-015								
Biogen BIIB110								
Other								
AurimMed Pharma/Nemours SM								
Calibr SM								
Spotlight Innovation U -STL-182								
Indiana U/Brigham & Women's SM								
Columbia/NU-p38aMAPK inhibitor								
Praxis Biotech protein synthesis enhancer								
Harvard SM								
Long non-coding RNA project								
Patten Zebrafish screen								
Monani Modifier Program								
Meriney/Wipf Ca^{2+} channel modifier								

FDA-approved therapy

Nusinersen, an antisense oligonucleotide designed to modify pre-messenger RNA splicing of the *SMN2* gene product, results in an increase in the inclusion of exon 7 and, thus, production of full-length survival motor neuron protein [17]. It was approved December 23, 2016, in the USA for all types of SMA in both pediatric and adult populations with four intrathecal loading doses followed by maintenance dosing every 4 months. This widespread approval was based on efficacy clinical trials in participants with the most severe form of SMA [18••, 20]. A multicenter, randomized, double-blind, sham-controlled phase 3 trial was conducted on infants with SMA type 1 age 1 month to 262 days old who had symptom onset before 6 months of age. Participants were given 12 mg of nusinersen intrathecally or underwent a sham procedure. The primary endpoints were the Hammersmith Infant Neurological Examination and event-free survival. Interim analysis showed that 41% of treated participants, versus 0% of control participants, had a motor milestone response and the study was terminated early due to success. At the time of final analysis, only 39% of the treated infants versus 68% of the control infants had died or required permanent ventilation [18••]. A multicenter, double-blind, sham-controlled phase 3 trial was also conducted on children with type 2 SMA between the ages of 2 and 9 years. Subjects were given 12 mg of nusinersen intrathecally or underwent a sham procedure. The primary endpoint was the mean change from baseline in the Hammersmith Functional Motor Scale-Expanded score at 15 months, and in the treatment group, 57%, versus 26% in the control group, had an increase of at least three points ($p < 0.001$) [19].

Overall, nusinersen has been shown to be safe, increases SMN levels in the cerebrospinal fluid in a dose-dependent manner, and improves motor function in treated children with type 1 or 2 SMA [18••, 19, 20]. Prospective evidence of improved motor function in older children and adults or individuals with milder disease (types 3 and 4) is currently being collected, and it is hoped that milder individuals will also see benefit. Nusinersen is administered intrathecally and is a life-long treatment, requiring three lumbar punctures per year in the maintenance phase. Side effects from repeated lumbar punctures have been minimal [17, 19–23].

Emerging therapies/therapies on the horizon (Table 1)

Gene therapy

Gene replacement is a viable option in spinal muscular atrophy as it is a disease of haploinsufficiency. If a functional copy of the defective gene could be introduced into the individual, the disease could theoretically be reversed. The *SMN1* gene is relatively small and can be successfully packaged into a viral vector to be delivered to cells and is self-replicating. AAV9 is one serotype of the adeno-associated virus that can transfect the CNS and cross the blood-brain barrier making it an ideal vehicle for *SMN1* delivery [24]. Preliminary studies completed in mouse and large animal models of SMA showed a marked improvement in function, neurophysiology, and an essential rescue of phenotype [25–27]. These studies informed an open-label, single center, phase I/II clinical trial of onasemnogene abeparvovec-xioi [28••]. The *SMN1* gene was

packaged in AAV9 with a hybrid CMV enhancer/chicken-ß-actin promoter and delivered intravenously to 15 children with SMA who had two copies of *SMN2* and were 0.9 to 7.9 months of age at the time of treatment. Participants were divided into low dose (6.7×10^{13} vg/kg) and high dose cohorts (2.0×10^{14} vg/kg) and the primary outcome was safety with secondary outcomes of time between birth and death or time to requirement of assisted ventilation for > 16 h per day. There were no safety concerns, aside from four participants with an increase in AST and ALT levels which was controlled with the administration of prednisone 1 mg/kg for 30 days. The study began May 5, 2014, and as of August 7, 2017, no participants had died or required permanent ventilation. Furthermore, all participants in the high-dose cohort experienced significant improvements in motor function with 11 out of 12 sitting independently and two walking.

Interim long-term follow-up has shown sustained improvements and no safety concerns [29]. Current studies are ongoing looking at intrathecal administration and pre-symptomatic treatment (NCT03381729, NCT03505099).

Although concerns have been raised about the safety of high-dose vector administration [30], the first participant in the gene therapy trial was dosed almost 5 years ago now and no concerns for toxicity in that participant, or any of the participants, have been raised. Nevertheless, the question of how much virus is too much remains and highlights the importance of considering more targeted delivery (intrathecal) and pre-symptomatic treatment (at a younger age and lower weight) to try to reduce risk. Long-term monitoring of all treated individuals is also critical to understand the persistence of therapeutic effect in this form of gene therapy.

SMN2 splicing modulation via orally administered small molecules

While much attention has been deservedly placed on the transformational biologic therapies described above, small molecule therapies will have a large role to play in the future. Preclinical studies in mice identified a few highly specific orally delivered small molecules that stabilize the U1-snRNP complex and SMN2 pre-messenger RNA (RG7800, RG7916-risdiplam, LM1070-branaplam) that resulted in increased levels of SMN protein, improved motor function, and survival [31–33]. A phase I study (RG7800) and a phase I/II study (branaplam) were halted when toxicity was noted during the long-term follow-up phases of preclinical subjects [34, 35]. However, branaplam has recently resumed recruitment after an approximate 2-year hiatus, presumably as none of the safety concerns found in animals have been found in any treated subjects [Novartis press release, 2017]. Risdiplam has had more success and is now in phase II trials in Europe (NCT02913482 and NCT03032172) and has received PRIME designation by the EMA [Roche press release, 2018]. The advantages of the orally bioavailable small molecule that can specifically target *SMN2* is an exciting alternative to nusinersen due primarily to ease of administration. It may also have the advantage of increasing SMN levels in all tissues, including those outside the central nervous system.

Neuroprotection via small molecules

The main pathophysiologic feature of SMA is degeneration of the lower motor neurons, so a reasonable treatment strategy would be to secondarily protect

motor neuron function and survival. Olesoxime is a cholesterol-like compound that preserves mitochondrial function by altering membrane permeability and has been shown to be neuroprotective in vitro and in vivo [36]. A randomized, double-blind, placebo-controlled phase II trial was conducted in Europe on individuals with SMA type 2 or 3 ages 3–25 years. There were no safety concerns but the primary endpoint of change in baseline on the MFM D1 + D2 was not met. However, results were deemed promising because secondary endpoint analysis showed a slowing in the natural decline in function seen in SMA [37]. Further analysis at 18 months showed a decline in motor function and pursuit of this therapy was halted [Roche press release, 2018]. Although this agent was not successful, other small molecules are in development (Table 1) and one may consider this approach in combination with therapies designed to increase SMN levels, or it may be a viable option for people who are not eligible for other therapies.

Muscle activation

Another technique to combat the effect of loss of motor neurons that occurs in SMA is to enhance the contractility and mass of the muscles remaining. CK-2127107 is a skeletal muscle troponin activator that has done just that in healthy human volunteers [38]. A double-blind, randomized, placebo-controlled phase II study was just completed in subjects with SMA types 2–4 (NCT02644668). Results have not been reported.

Non-medicinal therapies

With the rather remarkable improvements in the treatment landscape for SMA, it is clear that the natural history will change; however, the underlying pathophysiology remains. We know that the timing of treatment is extremely important and for individuals who begin treatment when symptomatic, it is expected that motor neurons have already been lost. Thus, a majority of treated individuals will likely remain symptomatic to some degree and still need long-term multidisciplinary SMA care with regular assessments of swallowing and nighttime ventilation, and preventative management of constipation, bone health, scoliosis, and joint contractures. Additionally, we do not know the persistence of these therapies or if any significant adverse effects may develop after prolonged exposure to the drug. Thus, the mainstays of SMA supportive care must be continued for all people with SMA and the recently published care recommendations from the SMA care group should be followed, even in treated individuals [14, 15].

Near future treatment landscape

Newborn screening will be implemented in at least a few more states in 2019 and hopefully all states shortly thereafter. Once newborn screening is widely available, the majority of children born with SMA will be identified early and will be able to start treatment early. Early treatment will allow for the "rescue" of injured motor neurons which we know have an impressive reinnervation capacity based on preclinical and clinical experience with nerve repair [39] and poliomyelitis [40]. It is likely that single-dose gene therapy will be approved for people with SMA soon, and it may be a popular choice due to its one-time intravenous administration. Oral agents that act upon the *SMN2* gene

to increase full-length mRNA production will likely also be an option soon. And so the therapeutic landscape will broaden and will require the decision making of which therapy to use and when. Issues of route of administration, frequency of dosing and cost are all likely to become important factors in making these decisions for individuals with SMA and their providers. In addition, non-SMN-directed therapies will certainly be developed to be used in combination with SMN-directed therapies. The era of combinatorial therapies will play an ever larger role in this population as individuals with SMA and families seek to fully optimize the function and reinnervation capacity of remaining motor neurons.

Finally, we anticipate an influx of people with SMA into the SMA and neuromuscular clinics due to improved diagnosis with the implementation of newborn screening and the increased awareness of significant therapeutics options in the community. The phenotypic spectrum of the disease will broaden with individuals at varied functional levels based on timing of treatment. A new "natural" history will be defined as treated individuals age. And a comprehensive SMA care clinic will become even more important to clearly document functional responses to treatment and the implications for long-term monitoring and care.

Key to the longitudinal management of people with SMA will be the development of validated biomarkers to predict responsiveness to therapy and signal disease activity. Both physiologic and molecular biomarkers to monitor disease progression and response to treatment will become an important component guiding care and treatment decisions in people with SMA. Biomarkers such as compound muscle action potentials and SMN mRNA and protein levels have been well documented in both untreated and treated SMA populations [41, 4•, 17–19, 42].

Continued characterization of these will be important to help distinguish and further define SMA subpopulations, in addition to work aimed at defining more molecular biomarkers. Many serum analytes have been obtained from a large prospective natural history study in infants with SMA and a few have been identified that correlate with motor function and may serve as prognostic biomarkers [41]. Other promising potential biomarkers to explore are neurofilaments (heavy and light chains) which were recently shown to be valuable biomarkers in ALS [43].

Continued development of biomarkers will allow for more informed therapeutic decision-making and eventual cost-effective utilization and implementation of a treatment plan as more and more therapies become available. This is an active area of research and there is great potential for meaningful biomarkers to emerge for clinical use soon.

Conclusions

Transformative, life-saving therapies for SMA are now entering clinics that will alter the approach to and management of individuals with SMA. Combinatorial therapies involving treatments to increase SMN levels and treatments to support muscle function and motor neuron repair will be tailored to each individual. Molecular and physiological biomarkers will aid in the decision-making process of when and how to treat. Overall, the story of the development of SMA therapies is becoming a success story in the treatment of what was once thought

to be an incurable motor neuron disease. As this story continues to be written, lessons and hope for similar success stories in other incurable diseases affecting motor neurons such as amyotrophic lateral sclerosis and hereditary spastic paraparesis will follow.

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Compliance with Ethical Standards

Conflict of Interest

Stephen J. Kolb reports consulting fees from AveXis, Biogen Idec, and Genentech outside the submitted work. Megan A. Waldrop reports personal fees from The France Foundation outside the submitted work.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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