Spinal muscular atrophy

A preliminary result toward new therapy

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Spinal muscular atrophy (SMA) is an anterior horn cell disease characterized by severe muscle atrophy and weakness,[1] traditionally divided into 4 subtypes.[2] Type I SMA (Werdnig-Hoffman disease) is the most severe form, associated with extreme weakness and hypotonia since birth or early infancy. These patients never sit independently. In most cases, respiratory muscle dysfunction results in early death within the first 2 years of life. Types II and III SMA have a milder course. Children with type II SMA (intermediate type) can sit but cannot walk independently. Children with type III SMA (Kugelberg Welander) are often misdiagnosed with myopathy or muscular dystrophy. They present with proximal weakness and are able to walk independently for at least a few years. The mildest variant is adult-onset type IV SMA, in which patients can ambulate in adulthood.

SMA is caused by deletions or mutations in the survival motor neuron 1 (*SMN1*) gene located on chromosome 5q13.[3] The severity is associated with the copy number of the survival motor neuron 2 (*SMN2*) gene. *SMN2* is almost identical, in genomic sequence, with *SMN1* gene, with only 11 nucleotide difference between the 2 genes. A single nucleotide difference (C to G transition) results in skipping of SMN2 exon 7 during RNA transcription, low levels of functional SMN protein expression, and only a mild compensatory effect of this gene.[4,5] As with most genetic conditions, no curative therapy is available.

In this issue of *Neurology*®, Chiriboga et al.[6] present a multicenter open-label study in 28 children with SMA II/III treated with intrathecal nusinersen (previously ISIS-SMN_{Rx}). Nusinersen (or ISIS 396443) is an antisense oligonucleotide (ASO) designed to promote inclusion of exon 7 in SMN2 and increase the production of functional protein. As ASOs do not cross the blood–brain barrier in sufficient amounts when given systemically, they were injected intrathecally.

The aims of this first human open-label phase 1 study were to examine safety, tolerability, and CSF and blood pharmacokinetics of the drug in cohorts of 6–10 children with SMA type II or III, aged 2–14 years. Each participant received a single intrathecal injection of 1, 3, 6, or 9 mg. All children completed the study and 24 of the overall 28 patients were recruited to an additional long-term extension study. No severe adverse effect (AE) was detected in this study, while headache and post–lumbar puncture syndromes were the most common reported AEs. No clinically significant changes in CSF safety laboratory testing were found and no anti-nusinersen antibody was detected after this single intrathecal nusinersen injection. The terminal half-life in the CSF was estimated at 4–6 months in the various groups; however, there was no definitive increase in CSF SMN protein level ($p = 0.06$) even in the high-dose (9 mg) group.[6]

Disease-specific outcome measures are essential tools in a drug development program to demonstrate clinical efficacy. The Expanded Hammersmith Functional Motor Scale (HFMSE) is a validated modified functional motor evaluation tool initially developed in the United Kingdom to evaluate the motor ability and monitor the functional progression of disease in children with SMA with limited ambulation and non-ambulatory children; it is an efficient outcome measure for clinical trials in children with SMA types II and III.[7,8] In the current article, the authors reported an increase in HFMSE scores after 3 and 9–14 months after 9-mg dose treatment.[6]

The results of this preliminary human study are encouraging, as no serious or notable AEs were reported after a single injection. Intrathecal treatment was associated with prolonged drug CSF half-life, and some clinical motor improvement was detected.

However, preliminary, open-label studies with a limited number of children should always be interpreted with caution. They are prone to bias, statistical errors, and placebo effects. One such example in previous SMA studies was the finding of an increase in Hammersmith functional scores following phenylbutyrate treatment in a pilot study of 10 Italian patients with SMA.[9] No efficacy was shown in a subsequent randomized, double-blind, placebo-controlled trial in a similar Italian population.[10]

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Several issues were not addressed in this phase 1 study. Should a dose higher than 9 mg be tested? What would be the adverse effects, toxicity, tolerability, and antibody response to the drug following recurrent doses?

We are in an exciting era when therapeutic options for previously untreatable disorders are evolving rapidly. In the pediatric neuromuscular field, Duchenne muscular dystrophy leads the way with various therapeutic options investigated including read-through agents for children with nonsense point mutations, exon skipping with ASO for specific deletions, gene therapy, utrophin upregulation, and anti-inflammatory and antifibrotic agents. Two ASO compounds designed for skipping of exon 51 of the dystrophin gene, drisapersen (BioMarin, San Rafael, CA) and eteplirsen (Sarepta Therapeutics, Cambridge, MA), are being evaluated in human clinical trials and new drug applications for this disorder have been submitted to the Food and Drug Administration for marketing approval in the United States. However, the immediate and long-term efficacy on the Duchenne muscular dystrophy disease course of these 2 compounds is uncertain. Combinations of several therapeutic agents will probably be needed for substantial functional improvement.

Several pharmaceutical companies are involved in the development of new therapies for SMA. Among those are compounds designed for neuroprotection (Trophos, Marseille, France; Roche, Basel, Switzerland), SMN2 promoter activation (Repligen, Waltham, MA; Pfizer, New York, NY), and SMN1 replacement (AveXis, Chicago, IL; Genzyme, Cambridge, MA).[11] In addition to nusinersen, several agents are currently developed for SMN2 splicing modulation by PTC Therapeutics (South Plainfield, NJ)/Roche, Paratek Pharmaceuticals (Roseland, NJ), and Novartis (Basel, Switzerland).[11] The results of this nusinersen phase 1 study are encouraging, providing convincing evidence for a phase II/III, double-blind, placebo-controlled study. Currently, no compound has been shown clinically effective in treating SMA. However, this article and the various therapeutic options in the pipeline led by the pharmaceutical industry support the optimism that future modification of the disease course in SMA is a possibility.

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