

Commentary

Infantile spinal muscular atrophy — the potential for cure of a fatal disease

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1. Introduction

Infantile spinal muscular atrophy (SMA, type 1) is one of the most tragic progressive neurological disorders of early infancy. Affected infants rarely survive beyond two years. However, in the last several years, at least two therapies have been shown to be effective in arresting the disorder, especially when administered early after onset, and most recently, to lead to apparent cure or near cure when administered *prior to* onset of symptoms. Because symptoms of the disease may appear in utero or, more typically, in the first weeks of life, perinatologists and, especially, neonatologists must have a high index of suspicion for the disorder. Moreover, and perhaps most importantly, newborn screening for the genetic defect now is widely prevalent in the United States (approximately 34 states at present), and thus early diagnosis and prompt institution of therapy are possible. This

commentary addresses the clinical aspects of SMA type 1, the relevant molecular genetics, the available therapies, and associated ethical and economic issues.

2. Clinical aspects

SMA, type 1, is clinically apparent at birth or in the first several months of life [1]. In one large single-author series, clinical onset of type 1 SMA was at birth in 35%, in the first month in 16%, in the second month in 23% and from the end of the second month to the sixth month in 26% [2]. Importantly, among infants identified at birth or in the early neonatal period, decreased and weak fetal movements in the last trimester are reported by the infants' mothers [1]. The principal clinical features are severe, generalized weakness and hypotonia, weak cry and difficulty sucking and swallowing. Relative preservation of facial movement provides the very sad picture of a smiling but nearly motionless infant. Affected infants never attain the ability to sit. Progression of weakness results in death by two years of age. Some infants survive longer with tracheostomy, invasive

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ventilatory support, and gastrostomy. In the most severely affected infants with onset at birth or in early infancy, survival beyond one year of age is rare [3–7].

The neuropathology of SMA, type 1, involves degeneration of the anterior horn cells of the spinal cord and motor nuclei of cranial nerves [1]. The degeneration is relentlessly progressive and related to a deficiency of the protein, survival motor neuron (SMN).

3. Pathogenesis and genetics

SMA, type 1, is caused by a genetic defect that involves the q13 region of chromosome 5 [8]. This SMA region consists of a large inverted duplication containing two copies of the gene deleted in SMA. One copy is telomeric (SMN1) and the other, centromeric (SMN2). The deletions in SMA involve the telomeric copy. Homozygous deletions involving exon 7 of the SMN1 gene account for nearly all cases of SMA. The nearly identical (centromeric) SMN2 gene contains a single nucleotide change in exon 7 that markedly influences splicing and, as a consequence, produces primarily 90–95% of a truncated protein lacking exon 7, with a short half-life, and only approximately 5–10% of the normal full-length protein. Notably, because of the genomic instability of this duplicated region of chromosome 5, SMN2 copy number may increase or decrease in the presence of the deleted SMN1 gene. The importance of this phenomenon is that the copy number of SMN2 is the most critical determinant of the severity of the SMA phenotype [9–12]. Thus, in the most severely affected patients with SMA, i.e., infants with SMA, type 1, 80% carry only one or two SMN2 copies (more than 70% carry two SMN2 copies) [1], whereas later onset varieties of SMA have principally three or four copies. Notably, however, nearly approximately 15% of SMA, type 1 infants have 3 SMN2 copies, and 5% have only 1 SMN2 copy — the latter infants are likely to exhibit the rare SMA, type 0 phenotype. (The latter form of SMA is very severe, usually of prenatal onset and associated with a dire prognosis [1, 11].)

The biological functions of SMN principally involve RNA metabolism and thereby the assembly of multiple proteins [13]. Axonal growth and maintenance are key roles of these proteins. Spinal cord neurons are particularly dependent on them because of their very long axons and need for axonal mRNA transport and trafficking [1].

4. Treatment

Until relatively recently, the principal and sole treatments for SMA, type 1 were supportive measures. With progression of sucking/swallowing deficits, gastrostomy feeding is necessary, and subsequently, tracheostomy and invasive ventilation [3, 5, 6]. Infants with onset at birth or the neonatal period have the earliest needs for these interventions. The uniformly dire prognosis presented major ethical issues in decision-making concerning more and more invasive interventions. The quality of life in these paralyzed, bed-ridden infants presents parents with enormous anxiety and heartbreak (see later).

In recent years *three major types of interventions* have markedly altered the course of type 1 SMA. The three approaches include: (1) a single intravenous injection of a nonreplicating adenovirus vector that includes the normal human SMN1 genetic sequence (onasemnogene abeparvovec-OA) [14], (2) a repetitive intrathecal administration of the anti-sense oligonucleotide drug nusinersen [15], and (3) repetitive oral administration of a small molecule (risdiplam) that modulates SMN2 pre-RNA splicing. Thus, the approaches lead to an increase in functional SMN protein, either by replacement of the defective gene or by modifying SMN2 pre-RNA splicing to lead to inclusion of exon 7 in RNA transcripts and thereby to produce functional SMN protein. Each of these agents has been approved by the FDA in the past several years.

4.1. Gene replacement therapy

The adenovirus vector including normal SMN1 DNA has been shown to cross the blood-brain barrier and to produce a sustained expression of SMN protein [16]. After favorable results in a mouse model of SMA, Mendell et al. [14] administered the agent to 15 patients with SMA, type 1. Of the 12 infants who received “high dose” therapy, all were alive at 20 months, 11 sat unassisted, 9 fed orally and could speak, and 2 walked independently. None of the historical controls achieved these levels of function. However, approximately 25% exhibited elevated hepatic enzymes, abnormalities attenuated by prednisolone, which is utilized chronically after the gene infusion. (Subsequent reports also have noted signs of mild hepatotoxicity, but one described 2 cases of transient liver failure) [16, 17]. On followup of the original cohort at 20 months of age, the favorable outcome persisted, and, importantly, it became

clear that infants treated earliest had the most favorable improvements [18]. In a subsequent report of infants with SMA, type 1 ($n=19$), the functional benefits were replicated (89% experienced improvement in motor function and 11% stabilization) [19]. Most importantly, five infants identified by newborn screening and *asymptomatic* at the time of onset of therapy experienced no signs of weakness characteristic of SMA over follow-up periods of 2 to 8 months [19]. Gene replacement therapy was approved by the FDA in May, 2019 for the treatment of SMA infants less than two years of age.

The ultimate duration of benefit from the single injection of OA is unclear. Moreover, repeated treatment is challenging because of viral vector immunity. Nevertheless, the initial results are very encouraging.

4.2. Antisense oligonucleotide therapy – nusinersen

A second encouraging avenue in treatment of SMA involves use of an antisense oligonucleotide drug that modifies pre-messenger RNA splicing of the SMN2 gene such that SMN2 exon 7 transcripts are included and increased expression of SMN protein results [16]. Because antisense oligonucleotide drugs cannot cross the blood-brain barrier, the drug must be administered intrathecally. Nusinersen is administered in four loading doses over 2 months with maintenance doses every 6 months. (The drug's half-life in CSF is approximately 4–6 months). The first clear demonstration of the benefit of nusinersen in SMA, type 1 was reported by Finkel et al. [15]. In this study of 121 infants, 51% of the 73 nusinersen-treated infants had a positive motor milestone response (including achieving head control, rolling over, sitting independently) versus none of the 37 controls. Death or the need for permanent assisted ventilation was markedly lower in the nusinersen group. Most notably, beneficial results were much more common in infants treated within 13 weeks after diagnosis. Similar benefit has been described in several observational studies [16, 20–22].

The favorable initial results provoked a study of infants treated *pre-symptomatically*. This multinational study identified 25 children with genetically diagnosed SMA but prior to onset of symptoms. Of these, 15 had only 2 copies of SMN2 and thus would be expected to develop SMA, type 1 [23]. Onset of nusinersen therapy in this latter group was 28 days or less in 13 of the 15. Of these, all 15 achieved the ability to sit without support and to stand with

assistance, and in 13, to crawl, to stand alone and to walk with assistance (12 could walk alone). These extraordinary results were apparent at a median age at followup of 35 months. In a smaller sample ($n=7$), pre-symptomatically treated infants “showed no muscular weakness” at a median age of 8 months [24].

Nusinersen was approved by the Food and Drug Administration in December, 2016 and by comparable agencies in Canada, Europe and Japan.

4.3. Small molecules – risdiplam

Risdiplam is a small molecule that modulates SMN2 gene splicing at two sites (intron 7 and exon 7). This unique binding ability increases levels of full-length SMN RNA and protein without impact on splicing of other pre-mRNAs and the possibility of off-target effects [16]. Preclinical studies supported by Roche showed that after oral administration, risdiplam reaches both the central nervous system and peripheral organs *in vivo* and importantly, can lead to a 2-fold or greater increase of SMN protein in brain, blood and muscle. Increase in survival was shown in mouse models of SMA. The multisystem reach of risdiplam is important, because recent studies show that SMA involves not only anterior horn cells but also neuromuscular junction, gastro-intestinal tract, cardiovascular system, lung and liver [13].

After demonstrations of benefit for risdiplam in later onset varieties of SMA, the drug was studied in an open-label format in infants with SMA, type 1 [16]. Clear benefit was apparent. After 12 months 90% were alive with no permanent ventilation, 41% were able to sit, and 95% were able to feed orally. After 16 months of treatment improvements were maintained. Importantly, beginning in 2019, an open-label, single-arm multicenter study was commenced to investigate the efficacy and safety in *pre-symptomatic* infants. Results are pending.

Because of its favorable efficacy and safety profiles, risdiplam was approved by the Food and Drug Administration in May, 2020 for use in SMA, type 1 patients.

5. Importance of newborn screening

As noted earlier, available evidence indicates that the earlier diagnosis of SMA, type 1, is made and therapy initiated, the better the outcome. The denervation process is rapid in the first six months of life in this disorder. Unfortunately, however, large-scale studies have shown a considerable delay

in diagnosis of SMA, type 1, such that although the *mean* age of symptom onset is generally 2.5 months, the mean age at confirmed diagnosis is 6.3 months [25]. Other studies indicate that age at diagnosis is 4.7 months [16]. Thus, it is critical to have a high index of suspicion for the disease in early infancy or the neonatal period. Most strikingly, treatment of the *pre-symptomatic* infant is markedly more effective in preventing deterioration and allowing near-normal motor development. This observation has led to newborn screening for the genetic defect in many European countries and in 34 states in the USA.

The results of newborn screening suggest that the incidence of SMA, type 1 is approximately 1.2/10,000 [24, 26]. Thus in the USA, with universal screening, it could be predicted that more than 400 cases of SMA, type 1 would be identified and be candidates for intervention(s) that appear to be lifesaving and markedly ameliorative or curative. The carrier frequency of the genetic defect is approximately 1/54, and, thus, value for prenatal screening is apparent.

6. Economic/ethical issue

The remarkable advances in genetic diagnosis and targeted therapies for SMA, type 1 and the onset of newborn screening have provided hope that this uniformly fatal disorder of infancy can be markedly ameliorated or even cured. However, enormous economic and ethical issues are raised by the high costs of the interventions and the relatively brief period of detailed followup of the treated patients. Concerning the latter, the most promising group likely to achieve maximal benefit from treatment, i.e., pre-symptomatic infants, have been the subjects of study for only a relatively brief period and in relatively small numbers (see earlier). Nevertheless, thus far, normal or near normal development appears feasible.

The economic cost of the new treatments is considerable [27–30]. For example, nusinersen costs approximately \$125,000 per dose, and thus total cost in the first year is \$750,000 (four loading doses and two maintenance doses) and in subsequent years, \$375,000 (maintenance doses every 4 months). Gene therapy cost is not yet clear but is expected to be approximately \$2,150,000 for the single injection. The cost of oral risdiplam is not yet established but is expected to be in excess of \$300,000 per year.

The economic cost of genetic therapies, albeit high, should be weighed against the economic and health-

related quality of life burden of spinal muscular atrophy. Although data are limited, one careful study indicated that the average total annual costs, direct and indirect, of SMA, type 1 per household (prior to nusinersen treatment) was approximately \$230,000, with substantial deficits in health-related quality of life for both affected infants and their caregivers [31].

Defraying the economic cost of genetic therapies in SMA, as in other genetic disorders, is challenging and beyond the scope of this commentary. Federal and State payment systems (e.g., Medicaid), pharmaceutical company research costs and revenue issues, and insurance company premium adjustments are among the difficult parameters to be balanced [29, 30]. It is perhaps too simplistic to conclude, as I feel we must, that as an advanced and humane society, we must work together to find a way to treat every eligible infant.

7. Conclusions

SMA, type 1, a rapidly progressive, fatal neuromuscular disorder presents in early infancy, including the neonatal period. A high index of suspicion for the disorder by neonatologists is important. Degeneration of anterior horn cells results because of a deficiency of the SMN protein. The genetic defect is a homozygous deletion affecting the gene SMN1, that normally is the principal source of this protein. However, a second gene, SMN2, which normally produces minimal SMN protein, can be induced to undergo alternative splicing of pre-mRNA to produce larger amounts of SMN protein. Newborn screening can detect the genetic defect involving the SMN1 gene as well as the number of copies of the modifiable SMN2 gene.

Recent therapeutic approaches to this disorder include (1) single-dose replacement of the SMN1 gene, (2) intrathecal administration several times yearly of an antisense oligonucleotide drug, nusinersen, that leads to increased SMN protein by provoking alternative splicing of pre-mRNA, and, most recently, (3) oral administration of a small molecule, risdiplam, that also causes alternative splicing and increase in SMN protein. The longest studied approaches, gene replacement and nusinersen, have been shown to lead to arrest of progression and improved motor function. Risdiplam also appears to be beneficial and oral administration is a major advantage. Benefit with all therapies is greatest in infants treated earliest. Initial data with infants detected by

newborn screening and treated pre-symptomatically (with nusinersen or gene replacement) suggest that the therapies are near-curative or curative. Longer followup will be critical. The high cost of these life-saving interventions raises enormous economic and ethical issues. Nonetheless, a remarkable new era has begun in management of this once uniformly fatal disease.

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