TRAINEE SECTION

Raphael Schneider, MD¹

¹Clinical Investigator Program and Eliot Phillipson Clinician-Scientist Training Program, University of Toronto, Toronto, Canada

CIM Journal Club: Gene therapy for spinal muscular atrophy Comment on Mendell *et al.* N Engl J Med 2017;377:1713-22.

Introduction

In their landmark paper, Mendell et al. show that infants with spinal muscular atrophy (SMA) reached important motor milestones and survived longer when treated with AVXS-101 (AveXis), a viral vector containing DNA encoding the survival of motor neuron protein (SMN). Patients not only crawled, stood and walked independently, but learned to speak. These results are very encouraging for patients with SMA and offer hope for pediatric and adult patients with other types of motor neuron diseases.

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Correspondence to:

Raphael Schneider, MD, FRCPC
Clinical Investigator Program
University of Toronto
2256 Medical Sciences Building
1 Kings College Circle
Toronto, ON M5S 1A8
Email: raphael.schneider@utoronto.ca

In their landmark paper, Mendell et al. [1] show that infants with spinal muscular atrophy (SMA) reached important motor milestones and survived longer when treated with AVXS-101 (AveXis), a viral vector containing DNA encoding the survival of motor neuron protein (SMN). Patients not only crawled, stood and walked independently, but learned to speak. These results are very encouraging for patients with SMA and offer hope for pediatric and adult patients with other types of motor neuron diseases.

Background

Motor neuron diseases are amongst the most devastating neurological disorders. Giving a diagnosis of a motor neuron disease to patients and their families is often difficult. We aim to communicate the diagnosis with honesty, but without destroying hope. Despite considerable progress in our understanding of disease mechanisms [2,3], therapeutic options remain limited with supportive care being the mainstay of treatment. With an estimated disease incidence ranging between four and 10 per 100,000 live births, SMA is one of the most common genetic diseases in infants [3].

SMA has an autosomal recessive inheritance pattern with biallelic pathogenic variants in the survival of motor neuron 1 gene (*SMN1*), resulting in decreased production of SMN protein and motor neuron dropout. Clinically, SMA is characterized by degeneration of the lower motor neurons (LMNs) in the anterior horns of the spinal cord and brainstem nuclei. The onset of SMA can range from before birth to early adulthood (SMA0-SMA4). Infants with SMA1, the most common form of the disease, typically appear healthy at birth and develop low tone, weakness, poor feeding and respiratory distress within the first six months of life.

In December 2016, the US Food and Drug Administration approved nusinersen, an antisense oligonucleotide (ASO) (Ionis Pharmaceuticals/Biogen), for the treatment of SMA. In 2017, European and Canadian regulatory authorities also approved the drug. In SMA, more copies of *SMN2* result in a milder clinical course, because *SMN2* is structurally similar to *SMN1* and can produce small amounts of SMN protein. Nusinersen modifies pre-messenger RNA splicing of *SMN2* resulting in increased production of the SMN protein. In a double-blinded, sham-controlled trial of infants (ENDEAR trial, NCT02193074) [4], a higher percentage of infants treated with intrathecally-injected nusinersen reached motor-milestones compared to the control group, resulting in early termination of the study [4] and approval of the drug for treatment of SMA. How do ASOs reach the motor neurons? Many cell types can take up ASOs

via endocytosis. Once taken up by the cell, ASOs can exhibit half-lives of several weeks and may alter the expression of targeted nucleotides for much longer. Broad tissue distribution of ASOs has been reported; however, poor penetration across the blood-brain-barrier and into the central nervous system (CNS) remains a hurdle. One way around this issue is the intrathecal injection of ASOs, such as nusinersen; a strategy used in the ENDEAR trial [4].

Contribution

Mendell et al. chose a different approach, a one-time intravenous administration of adeno-associated virus (AAV) containing DNA encoding the SMN protein (Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1, NCT02122952) [1]. AAV has emerged as a gene delivery tool that can target the entire CNS without having to inject intrathecally or directly into the CNS [5]. In their open-label, dose-escalation trial, twelve infants (with SMA1 and two copies of *SMN2*) received a high dose of AVV and three infants received a low dose of AVV. The primary endpoint was safety and the secondary endpoints were time to death or permanent ventilator assistance. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), a clinical score to evaluate motor skills in SMA, was included in an exploratory analysis [3].

The treatment resulted in longer survival, improved motor milestones, and improved motor function on the CHOP INTEND compared with historical cohorts. All fifteen patients survived longer than the previously reported median age of survival without permanent ventilation for similar patient cohorts (10.5 months). At the time of publication in November 2017, no clinical regression in motor function had been reported in follow up to two years [1]. The investigators identified two potentially grade 4 life-threatening adverse events; both were related to significantly increased alanine aminotransferase and aspartate aminotransferase (AST) and patients were treated with prednisone.

Future directions

It remains to be seen whether these impressive clinical outcomes will translate into longer-lasting benefits. Patients will be followed for up to 15 years in the follow-up study for continuous clinical and safety monitoring (START, NCT03421977). Should patients regress clinically, repeat treatment with AAV may not be an option due to the development of neutralizing antibodies against AAV. One could then imagine a combination therapy with nusinersen,

although this has not been tested in any trial to date. Notably, the most significant therapeutic benefit was observed in patients that were treated earliest. With the advent of disease-modifying treatments for SMA, establishing newborn screening programs or screening for carrier status in future parents may allow for earlier diagnosis and intervention.

Significance for patients with adult-onset motor neuron disease

Can this success be translated to adult-onset motor neuron diseases such as amyotrophic lateral sclerosis (ALS)? In about 90% of cases, ALS is a sporadic disease, and typically affects both LMNs and upper motor neurons; however, ALS and certain forms of genetic ALS can present with predominantly LMN signs, sharing clinical features with SMA [2]. Another commonality between the two motor neuron diseases appears to be perturbation of RNA homeostasis. Several recently described genetic mutations in ALS are associated with defects in RNA processing, including transcription, translation, splicing, and transport [2]. Even in sporadic ALS, RNA-binding proteins aggregate in motor neurons [2]. Currently, ASOs for ALS are in development, and clinical trials are enrolling patients (clinicaltrials.gov).

In summary, therapeutic approaches aimed at correcting genetic mutations and RNA processing hold great promise for patients with motor neuron diseases. In 2016 and 2017, several breakthroughs have been reported, giving patients, families, clinicians and researchers confidence that we are finally

entering the era of gene therapy, more than two decades after the first disease-causing mutations were described for SMA and ALS.

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Disclosure

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References

1. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med*. 2017;377(18):1713-22.
2. Therrien M, Dion PA, Rouleau GA. ALS: Recent Developments from Genetics Studies. *Curr Neurol Neurosci Rep*. 2016;16(6):59.
3. Prior TW, Nagan N. Spinal Muscular Atrophy: Overview of Molecular Diagnostic Approaches. *Curr Protoc Hum Genet*. 2016;88:Unit 9 27.
4. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med*. 2017;377(18):1723-32.
5. Dayton RD, Wang DB, Klein RL. The advent of AAV9 expands applications for brain and spinal cord gene delivery. *Expert Opinion on Biological Therapy*. 2012;12(6):757-66.