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MOTOR NEURON DISEASE

Positive trial results published for ground-breaking SMA therapies

The results from two clinical trials of novel therapies for spinal muscular atrophy (SMA) have been published in the *New England Journal of Medicine*. The antisense oligonucleotide (ASO) nusinersen and the gene replacement therapy AVXS-101 improved survival and achievement of motor milestones in patients with the disease.

SMA is an autosomal recessive, progressive motor neuron disease that typically manifests in children with a prevalence of ~1 in 11,000 live births. Mutations or deletions in *SMN1* cause a reduction in survival motor neuron protein (SMN) expression, which results in degeneration of lower motor neurons.

SMA type 1 is the most common subtype of the disease, comprising 60% of all cases, and also has the most severe symptoms, with onset at ≤6 months of age. Patients with SMA type 1 do not achieve motor milestones, such as unassisted sitting, and eventually experience a decline in swallowing and respiratory functions, with a median survival <2 years without respiratory support.

In the past year, the first disease-modifying treatment for SMA, nusinersen, was approved for clinical use after interim analysis of the phase III ENDEAR trial demonstrated the safety and efficacy of the agent. Now, the final analysis of this randomized, double-blind, sham-controlled trial has been published.

Nusinersen functions by modifying splicing of *SMN2* (a paralogue of *SMN1*) to increase the production of full-length SMN protein. The trial included a total of 121 patients, of whom 80 were assigned to receive repeated intrathecal injections of nusinersen and 41 were assigned to undergo a sham procedure as controls. Primary end points were the achievement of motor milestones and event-free survival.

At the final analysis, 51% of patients who received nusinersen achieved motor milestones (including independent sitting by eight patients and standing by one patient) compared with 0% of sham-treated controls. Furthermore, event-free survival was higher in the nusinersen-treated group than in sham-treated controls, with a hazard ratio for death or permanent ventilation of 0.53. A similar frequency and severity of adverse events were observed in both groups. Interestingly, a shorter disease duration at screening was associated with a greater benefit from the intervention, highlighting the importance of early treatment.

The results from the trial of a novel gene-replacement therapy for SMA were published back-to-back with the ENDEAR trial results. The open-label phase I–II trial tested the safety and efficacy of AVXS-101, an adeno-associated virus serotype 9 (AAV9) vector containing a human *SMN* gene. A single intravenous dose of virus was administered to 15 children with SMA type 1. At 20 months of age, all participants were alive and free from ventilator support compared with an 8% rate of survival at the same age in historical controls. Patients who received AVXS-101 also showed better achievement of motor milestones and better motor function than historical controls, including 11 patients who could sit unassisted and two patients who could stand and walk.

These new therapeutic approaches enable modification of the SMA disease course for the first time, which will undoubtedly transform management of this condition. However, there remains much room for improvement. "Neither therapy currently provides a cure," comments Ans van der Ploeg in an editorial accompanying the papers, noting that only a small percentage of treated individuals go on to achieve motor milestones such as standing. "One option may be to start treatment earlier … another option is to combine the two treatments," suggests van der Ploeg.

The effects of early treatment are currently being investigated in the NURTURE trial, in which presymptomatic patients with SMA will receive nusinersen. In addition, AveXis are expected to move forward with a multicentre confirmatory phase III trial of the AVXS-101 gene therapy.

Charlotte Ridler

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ORIGINAL ARTICLES Finkel, R. S. *et al.* Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N. Engl. J. Med.* **377**, 1723–1732 (2017) | Mendell, J. R. *et al.* Single-dose gene-replacement therapy for spinal muscular atrophy. *N. Engl. J. Med.* **377**, 1713–1722 (2017)