New study expands evaluation of gene therapy for spinal muscular atrophy

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The rarity of spinal muscular atrophy (SMA) means that promising new treatments may be tested in only a limited spectrum of patients before approval. Investigators evaluated a newly approved drug, onasemnogene abeparvovec, in a broader spectrum of patients in order to obtain expanded data on its side effects profile. They report in the *Journal of Neuromuscular Diseases* that the drug is associated with an immune response against the adeno-associated viral vector and needs careful monitoring, but showed no long-term adverse effects.

In recent years, the availability of a growing number of drug treatments has significantly changed the course of the SMA. One of these is onasemnogene abeparvovec (Zolgensma), an adeno-associated viral (AAV9) vector-based gene therapy that introduces a functional copy of the *SMN1* gene into motor neurons by means of a single intravenous injection.

SMA is designated as an orphan disease as it affects just one in 6,000-10,000 newborns worldwide. SMA type 1 accounts for about 60% of all cases. In the main clinical study on which approval of onasemnogene abeparvovec was based, just 22 babies were given this therapy. Twenty of these were alive and breathing without a permanent ventilator after 14 months, when normally only a quarter of untreated patients would survive without needing a ventilator. Based on these results, the US Food and Drug Administration (FDA) approved the therapy for all types of SMA up to the age of two years, and the European Medicine Agency (EMA) extended the label to all patients either showing a phenotype of SMA type 1 or having up to three SMN2 copies.

"SMA is a rare disease and pivotal studies only included SMA type 1 patients up to the age of eight months," explained lead investigator Prof. Dr. Janbernd Kirschner, MD, Department of Neuropediatrics, University Hospital Bonn, Bonn, Germany. "However, FDA and EMA approved the treatment for a broader spectrum of patients, which has resulted in discussions about how safe and effective the treatment is in older and heavier patients and in those with SMA type 2."

Investigators report their experience with eight consecutive patients with SMA who were treated with the standard dose of onasemnogene abeparvovec (1.1×1014 vg/kg) at the University Hospital Bonn, Germany. All patients received prophylactic immunosuppression with prednisolone for four weeks starting on the day before gene therapy. The patients (four male, four female, age range 10-37 months) weighed between seven and 12 kilograms. All patients had two or three copies of the SMN2 gene and had been previously treated with nusinersen, also approved for treatment of SMA.

Following treatment, all of the patients showed a temporary increase of body temperature and an increase of transaminase levels (transaminases are enzymes that are important in the synthesis of amino acids, which form proteins). In all but one patient, it was necessary to increase or prolong the standard steroid dose to control the immune response. In one severe case, liver damage was associated with impaired liver function. This patient received a steroid pulse therapy for five days after which liver function fully recovered. Following the therapy, six patients had asymptomatic thrombocytopenia (abnormally low blood platelets). Liver values and blood counts returned to normal or almost normal levels during the post-treatment observation period. Four patients had an increase in troponin I levels, which can be a sign of cardiac injury, but cardiac evaluation showed no abnormalities.

"Our experience with eight patients older than eight months adds important findings to the increasing body of evidence that treatment of SMA with onasemnogene abeparvovec is often associated with an immune response against the AAV vector," noted Prof. Dr. Kirschner. "This immune response mainly affects the liver and the hematopoietic system and can be severe in some cases. However, it was possible to control the immune response in all patients by proactive monitoring and adapting the steroid dose, and we did not detect any long-term side effects due to the immune response.

"It is premature to judge whether severe organ damage with long-term consequences can always be avoided. Further research is needed to better understand the immune response following gene therapy and ideally to identify patients at risk for a more severe reaction," he concluded.

Spinal muscular atrophy (SMA) is a rare genetic neurodegenerative disease. It primarily affects spinal motor neurons and leads to progressive muscle weakness. The spectrum of severity ranges from severe cases with onset during the first six months of life (SMA type 1) to later onset during childhood or adolescence (SMA types 2-4). SMA is caused by mutations of the survival motor neuron gene. Without treatment, SMA type 1 is associated with death or the need for permanent ventilation within the first two years of life.

More information: Johannes Friese et al, Safety Monitoring of Gene Therapy for Spinal Muscular Atrophy with Onasemnogene Abeparvovec–A Single Centre Experience, *Journal of Neuromuscular Diseases* (2021). DOI: 10.3233/JND-200593

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