Phase 1 study shows encouraging data for gene replacement therapy for SMA type I

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Jerry Mendell, M.D. Credit: Nationwide Children's Hospital

A one-time intravenous infusion of the high dose of gene therapy extended the survival of patients with spinal muscular atrophy type 1 (SMA1) in a Phase 1 clinical trial, according to a study published today

in the *New England Journal of Medicine*. The study was conducted by Researchers from Nationwide Children's Hospital in collaboration with AveXis, Inc. and The Ohio State University College of Medicine.

"My team at Nationwide Children's has worked with commitment and dedication to develop a therapy that may subsequently be shown through future clinical trials to potentially alter the course of this unforgiving condition and provide a therapeutic option for the families and infants with SMA1," says Jerry Mendell, MD, principal investigator in the Center for Gene Therapy at Nationwide Children's.

SMA1 is a progressive, childhood, neuromuscular disease caused by a mutation in a single gene. Children with SMA1 fail to meet motor milestones and typically die or require permanent mechanical ventilation by 2 years of age. The phase 1 clinical trial is the first to test the functional replacement of the mutated gene responsible for SMA1.

A one-time intravenous injection of modified adeno-associated virus serotype 9 (AAV9) delivered the SMN gene to 15 patients. Three patients received a low dose, while 12 patients received a high dose. In the Phase 1 trial, patients in the high dose group demonstrated improvement in motor function and they had a decreased need for supportive care compared to the natural history of the disease.

Specifically, at the end of the study period, all 15 patients appeared to have a favorable safety profile and to be generally well tolerated. Of the 12 patients treated with the high dose, 92 percent of patients have achieved head control, 75 percent of patients can roll over and 92 percent of patients can sit with assistance. Seventy-five percent of these patients are now sitting for 30 seconds or longer. Two patients can crawl, pull to stand and stand and walk independently.

According to natural history of the disease, patients require nutritional

and respiratory support by 12 months of age, and are not able to swallow or speak effectively. Of the patients who received the high dose in study, 11 patients are able to speak, 11 patients are fed orally and seven do not require bi-level positive airway pressure as of the data cut-off (August 7, 2017).

"In this first phase of clinical trials, we have observed preliminary results that appear to be promising compared to the natural history of SMA Type 1," says Dr. Mendell, also a faculty member at The Ohio State University College of Medicine.

This study builds on nearly three decades of foundational research led by teams at Nationwide Children's and Ohio State's Wexner Medical Center and exemplifies the strong basic science and clinical bonds between the two institutions. Arthur Burghes, PhD, of Ohio State created a ground-breaking SMA mouse model that remains the standard by which all therapies, including AVXS-101, are initially tested. Senior author of the study, Brian Kaspar, PhD, during his appointment at Nationwide Children's discovered that the AAV9 vector was capable of crossing the blood brain barrier when injected into the vascular system to deliver genes directly to motor neurons. The two laboratories then collaborated to show that scAAV9-SMN, when delivered to SMA mice shortly after birth, completely prevented their neuromuscular disorder. The laboratories also collaborated to successfully prove that reversing a protein deficiency through gene therapy is effective in improving and stabilizing SMA in a large animal model. "In neurological disease, it is rare to go from gene defect to therapy so directly, and the fact that this has happened here in one place is perhaps even rarer," said John Kissel, MD, chair of Neurology at Ohio State and director of the SMA Clinic at Nationwide Children's.

AveXis, Inc., a clinical-stage gene therapy company developing treatments for patients suffering from rare and life-threatening

neurological genetic diseases, announced in July 2016 that the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy Designation for the treatment based on preliminary clinical results from the trial of AVXS-101.

"At AveXis, we are enormously pleased to see that all children who received AVXS-101 are alive and free of permanent ventilatory support at 20 months of age and older - an age where, sadly, only eight percent of untreated children with SMA Type 1 are expected to survive without permanent breathing support," said Dr. Kaspar, now serving as Chief Scientific Officer at AveXis. "The *New England Journal of Medicine* publication marks an exciting milestone in the development of AVXS-101."

Provided by Nationwide Children's Hospital