

Public Abstract

First Name:Kate

Middle Name:Lynn

Last Name:Robbins

Adviser's First Name:Christian

Adviser's Last Name:Lorson

Co-Adviser's First Name:

Co-Adviser's Last Name:

Graduation Term:FS 2013

Department:Veterinary Pathobiology

Degree:MS

Title:Defining the Therapeutic Window in Spinal Muscular Atrophy: Time Points Study

Spinal muscular atrophy (SMA) is a devastating hereditary disease affecting 1 in 6,000 – 10,000 babies born, and is the second leading genetic cause of infantile death. SMA results from low levels of SMN protein caused by the deletion or mutation of a single gene, survival motor neuron-1 (SMN1), which leads to the loss of motor neurons in the spinal cord. Humans are the only species that possess a nearly identical copy gene, called SMN2, which functions as an important disease modifier because it produces low levels of fully functional SMN protein. The majority of therapeutic strategies aim to replace the missing gene (SMN1) or alter SMN2 messenger RNA leading to an increase in SMN protein levels.

Gene replacement using a non-replicating virus to carry the code for SMN protein into cells of SMA mouse models has proven an effective means to rescue these mice from the disease phenotype when delivered during the neonatal period before symptoms arise. Recently, we have shown that delivery of this virus (scAAV9-SMN) directly into the central nervous system via the ventricular system (intracerebroventricular injection, ICV) is more effective than a similar dose of viral vector administered via an intravenous (IV) injection; thereby providing an important mechanism to examine a timeline for ameliorating the disease and determining the optimal therapeutic window.

In this study, we used a specific SMA mouse model (termed SMN Delta7) that lives on average, 13 – 15 days. We injected each mouse with a single dose of scAAV9-SMN vector (equal to 100 billion viral genomes) via ICV injection, on a single day, from postnatal day 2 (P2) through P8. Our aim was to delay delivery of the therapeutic (in 24 hour increments) to determine at which point the therapy is no longer effective.

At each delivery point from P2 through P7, scAAV9-SMN decreased disease severity, ranging from a near complete rescue (P2) to a significant, albeit lesser degree (P7) in which animals lived ~130% longer. Our study demonstrates that a maximal benefit is obtained when treatment is delivered during a specified therapeutic window of the pre-symptomatic stages of SMA in the SMN Delta7 mouse model. Although disease severity can be significantly decreased when SMN levels are increased at later stages of the disease, there is a time (after postnatal day 8) at which therapy is no longer effective.

This systematic investigation into the effect of delaying therapeutic intervention using scAAV9-SMN in the SMN Delta7 mouse model, has laid the foundation for others to elucidate the correlation between our observations of the overt phenotype of these mice with the molecular attributes involved in SMA pathogenesis. The results from this study support the idea that early intervention provides the maximal benefit for ameliorating SMA disease pathogenesis and this is clinically relevant as the field moves forward with designing therapeutics suitable for SMA patients in the near future.