DEFINING THE THERAPEUTIC WINDOW IN SPINAL MUSCULAR ATROPHY: 
TIME POINTS STUDY

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ABSTRACT

Spinal muscular atrophy (SMA) is caused by the loss of a single gene, *survival motor neuron-1* (*SMN1*), which results in the rapid deterioration of motor neuron integrity and function, most often leading to infantile death. Administration of self complementary adeno-associated virus expressing full-length SMN cDNA (scAAV-SMN) has proven an effective means to rescue the SMA phenotype in SMA mice, either by intravenous (IV) or intracerebroventricular (ICV) administration at very early time points. We have recently shown that ICV delivery of scAAV9-SMN is more effective than a similar dose of vector administered via an IV injection, thereby providing an important mechanism to examine a timeline for ameliorating the disease and determining the optimal therapeutic window. SMNΔ7 mice were injected with scAAV9-SMN vector via ICV injection on a single day, from P2 through P8. 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 SMNΔ7 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.