363 - Improvement of Sandhoff Phenotype Following Intravenous Injection of Adeno-Associated Viral Vector Expressing a Hexosaminidase Isoenzyme in Adult Sandhoff Mice: Preclinical Safety and Efficacy Study

May 5, 2016, 6:00 - 8:00 PM

Keywords
Neurological Disorders,Genetic Diseases,GM2 Gangliosidosis

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Disclosures
K.J.L. Osmon: None.

Abstract
GM2 gangliosidosis disorders stem from a Hexosaminidase A (HexA) isoenzyme deficiency. In humans, HexA is the sole enzyme able to catabolize GM2 ganglioside (GM2). The inability to effectively catabolize GM2 leads to neurodegeneration of the central nervous system. HexA is comprised of 2 subunits (α, β) and works with the GM2 activator protein (GM2AP). In the recent work by Tropak et al. (Mol Ther Met Clin Dev, ***in press***), a hybrid subunit, named μ-subunit, was created (patent pending) by combining the stabilization and GM2AP binding sites of the β-subunit while conserving the catalytic properties of the α-subunit. The 'μ'-subunit, coded by ***HEXM***, can homodimerize and form a stable, functional enzyme, named HexM, which can interact with GM2AP to hydrolyse GM2. Previous work for successful correction of Sandhoff mice using AAV was only shown in neonatal mice (with immature blood-brain barrier (BBB)) and may not directly help in designing a human clinical trial. In the current study, we examined the efficacy/safety of IV injections of the scAAV9/***HEXM*** vector at two doses in adult SD mice (with mature BBB). In addition, we also tested if an adjunct IV injection of mannitol provides any enhancement in efficacy. At 6 weeks old, the vector was injected via tail vein in cohorts of n=17 and n=15 SD mice at 2.5E+12 or 1.0E+13 vg/mouse, respectively. Another cohort of 16 mice received IV mannitol (3g/kg) prior to an IV injection of 2.5E+12 vg scAAV9/***HEXM***. Some mice from low dose group were euthanized at 16 weeks for direct analysis with untreated SD control mice, while the remainder were left until for terminal survival. Analysis of survival benefit, locomotor behaviour, biochemical and molecular parameters were performed. While untreated SD mice had a 16 week humane endpoint, 4 of 7 mice in higher dose group are now surviving past 56 weeks, 1 of 12 mice in the low dose cohort, and 4 of 9 mice in the mannitol cohort are surviving past 52 weeks. These increases in survival are all highly significant compared to the ~16 week humane endpoint of untreated SD mice. Behaviourally, there are no major significant differences in locomotion between the groups until after 15 weeks, when the adjunct mannitol group significantly outperforms the PBS group. Survival and behaviour monitoring, and the

biochemical analyses for this study are ongoing. The preliminary results from this study show delayed onset of the SD phenotype with a single AAV9/***HEXM*** injection and a significant benefit of a pre-injection of IV mannitol. This study is the first to show that an IV gene transfer using a scAAV/***HEXM*** vector can provide survival and behavioural benefit in adult SD mice especially with adjunct use of mannitol. We propose that these results can advise the design of a human gene therapy trial for SD and the related Tay-Sachs disease.