

Karumuthil-Melethil S, Marshall MS, Heindel C, Jakubauskas B, Bongarzone E, Gray SJ. *Intrathecal Administration of AAV/GALC Vectors in 10-11 Day old Twitcher Mice Improves Survival and is Enhanced by Bone Marrow Transplant*. Journal of neuroscience research. 2016;94(11):1138-1151. doi:10.1002/jnr.23882.

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Background

Hematopoietic stem cell transplant (HSCT) is the standard of care for patients with presymptomatic infantile-onset Krabbe disease and mildly affected late-onset patients; however, HSCT provides modest benefit in presymptomatic patients and falls well short of a cure. Recent studies have provided compelling evidence that a combination approach with gene therapy plus HSCT is capable of treating different aspects of GLD and produce a significantly better therapeutic outcome than any single treatment.

Gene transfer utilizing viral vectors to deliver the correct copy of the defective gene is becoming an attractive approach for treating several lysosomal storage diseases including Krabbe disease. Animal models, especially the twitcher mice, have helped researchers to better understand the pathology of the disease, as well as to test different therapeutic interventions.

Summary

This study, comparing three AAV vectors effectively demonstrates that gene therapy directly into the spinal fluid (lumbar intrathecal (IT) delivery) can significantly enhance the life-span of twitcher mice treated 10-11 days after birth and in combination with bone marrow transplant (BMT) further improves survival.

Results

- The present study compares three single-stranded (ss) AAV serotypes.
- The rAAV gene transfer facilitated *GALC* gene biodistribution and detectable enzymatic activity throughout the CNS, as well as in sciatic nerve and liver.
- Analysis of brain, spinal cord, and sciatic nerve tissue showed significant improvement in preservation of myelin, with ssAAV9 providing the greatest benefit.
- The median life span for the control mice was 40 days.
- The combined AAV+BMT treatments had further extensions in median lifespan to 79 and 57, for AAV9 and AAVrh10 respectively.
- It isn't clear if the addition of BMT to the AAVrh10 treatment conferred a greater benefit, but the addition of BMT to the AAV9 treatment provided the best survival outcomes of all the treatments tested.

Key Points

- Two major conclusions from this study were observed:
 - 1) Using the intrathecal route of administration, AAV9 is the best of the 3 vectors tested.
 - 2) BMT clearly synergized with the intrathecal AAV9 treatment, providing a substantial benefit over AAV9 alone.
- Taken together, studies identified that both AAV9 and AAVrh10 could provide a benefit, but only AAVrh10 was tested in Rafi *et al.* One can not infer from these results whether AAV9 might be better by an intravenous route of administration, and this remains to be tested.
- It is important to note that this study was conducted in twitcher mice and not humans.
- It is the hope that this combination therapy can lead to a clinical trial in human patients with Krabbe disease in the near future.