



National Tay-Sachs & Allied Diseases Association

Gene Therapy – Canavan Disease

Introduction

Canavan disease is caused by pathogenic variants in the *ASPA* gene. The *ASPA* gene is expressed in oligodendrocytes, a type of glial (non-neuronal) cell, and encodes for aspartoacylase, an enzyme responsible for effectively breaking down N-acetylaspartic acid (NAA). NAA, an abundant amino acid, is essential for proper myelin formation. Myelin is a fatty substance that protects nerves in the brain. Pathogenic variants impair the enzyme's function and lead to toxic accumulation of NAA in the central nervous system (CNS). When myelin formation is disrupted, cells cannot properly send and receive messages, which leads to a type of progressive neurodegeneration of the brain's white matter called leukodystrophy (PMID: 17194761).

Currently, there are no curative therapies for Canavan disease. Gene therapy is promising as it aims to stop or slow the progression of these diseases by introducing working copies of the *ASPA* gene into brain and nerve cells. The goal is to restore enzyme function and improve neurological outcomes.

Delivery & Administration

Currently, the preferred gene delivery method for Canavan disease gene therapy is adeno-associated viral (AAV) vectors. Initial gene transfer clinical trials using nonviral vectors were deemed safe but showed minimal and variable clinical improvements (PMID: 37601414). Additional studies using lentiviral vectors were limited in their capacity to target specific cell types. Later advancements focused on using AAV-mediated delivery systems (i.e., AAV9) that can cross the blood-brain barrier (BBB) and effectively target specific CNS cell types. Other AAV-mediated delivery systems rely on direct injections to reach the brain and nerve cells without having to cross the BBB.

In 2019, a phase 1 clinical trial for Canavan disease using an AAV2 delivery system via intracranial infusions was shown to be well tolerated with minimal immune response and resulted in some biochemical and clinical improvements (PMID: 33967698).

Several administration routes are being explored. Intravenous systemic administration is commonly utilized but may face challenges from the BBB depending on the type of vector used. The BBB protects the CNS by strictly regulating the transport of substances and drugs, prompting exploration of methods and/or vectors to bypass the BBB to deliver gene therapy to the brain and nerve cells. Some AAV types can cross the BBB. Additionally, intracranial administration can directly deliver treatment to the CNS, but it is a more medically invasive procedure and does not always achieve broad treatment distribution. Currently, there are two gene therapy clinical trials for Canavan Disease in progress: one uses intravenous and the other intracranial administration.

A recent 2023 patient study explored gene therapy using a AAV9 delivery system administered both intravenously and intracerebroventricularly coupled with immune modulation (PMID: 37601414). The study demonstrated clinical safety and observed improvements in myelination, motor function, and epileptic symptoms two years post treatment. More so, NAA levels were reduced and stabilized up to four years following treatments. Importantly, this study also provided insight into the use of immunomodulation and dual-route administration with AAV gene therapy for Canavan disease.

Because symptoms begin *in utero* and worsen over time, gene therapy may achieve best clinical outcomes best when given at younger ages. One study suggests interventions be given within the first two years of life, with interventions given within the first year of life having the largest effect and clinical response (PMID: 34011350). However, current gene therapies have faced challenges in targeting oligodendrocyte populations during the period of neonatal development, so research is needed to improve therapeutic applicability.

Animal models targeting astrocytes, a type of glial cell and the most abundant cell type in the CNS, have shown promising potential in restoring biochemical and clinical function in Canavan disease (PMID: 33967698). Astrocytes play significant roles in myelin maintenance and CNS metabolism and may allow for widespread CNS distribution. While the exact mechanism behind the effectiveness of astrocyte-targeted gene therapy is not well understood, there are important implications for the reversal of demyelination and disease treatment.

Although AAV vectors exhibit lower immunogenicity compared to other vectors, AAV gene therapy has been seen to elicit innate and adaptive immune responses and immune-mediated adverse responses have been observed in clinical trials with AAV gene therapy (PMID: 35994385). To minimize this risk, administration may be limited to one dose and immunosuppressive therapy is needed in the treatment process. Additionally, vector design continues to be optimized to limit the potential for toxicity.

For more information about gene therapy, vectors, and the clinical trial process, please check out the following educational resources created by the American Society of Gene and Cell Therapy (ASGCT):

Gene therapy basics: <https://patienteducation.asgct.org/gene-therapy-101/gene-therapy-basics>

Gene Therapy Approaches: <https://patienteducation.asgct.org/gene-therapy-101/gene-therapy-approaches>

Clinical Trial Process: <https://patienteducation.asgct.org/gene-therapy-101/clinical-trials-process>

Vectors 101: <https://patienteducation.asgct.org/gene-therapy-101/vectors-101>

To access the literature reference, enter the PMID number into the PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) search box or Google “PMID XXXXXXXX”, replacing the “X’s” with the appropriate number.

Data is current as of August 2024.