



National Tay-Sachs & Allied Diseases Association

Gene Therapy – GM1 Gangliosidosis

Introduction

GM1 gangliosidosis (GM1) is a neurodegenerative condition caused by pathogenic variants in the *GLB1* gene which causes deficiencies in the enzyme β -galactosidase. This enzyme is responsible for breaking down GM1 gangliosides, a fatty substance important in the nervous system. Pathogenic variants in *GLB1* impair the enzyme's function and lead to toxic accumulation of GM1 gangliosides in the central nervous system (CNS) and subsequent damage to the brain and spinal cord.

Currently, there are no curative therapies for GM1 gangliosidosis. Gene therapy offers potential as it aims to stop or slow the progression of these diseases by introducing working copies of the *GLB1* gene into brain and nerve cells. The goal is to restore enzyme function and improve neurological outcomes.

Delivery & Administration

Different delivery and administration routes have been explored. The preferred delivery method for GM1 gene therapy is adeno-associated viral (AAV) vectors due to their capability of reaching the brain and spinal cord to effectively target specific CNS cell types. Several ongoing preclinical and clinical trials are using AAV vectors (AAV9), specifically chosen because of their ability to cross the blood brain barrier and target nerve cells (PMID: 33859490). In preclinical trials, AAV gene therapy via intravenous administration was given to affected mice and resulted in reductions of GM1 accumulation, decreased neuronal damage, and regression of disease features (PMID: 38018878). Additional trials in animal models yielded similar results and focused on optimizing various administration and dosing methods.

Intravenous systemic administration is commonly utilized but faces the challenges of penetrating the BBB. The BBB protects the CNS by strictly regulating the transport of substances and drugs, prompting exploration of methods to bypass the BBB to deliver gene therapy to the brain and nerve cells. Some AAV types, however, have the ability to cross the BBB intravenously.

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. Current clinical trials are exploring both intravenous and intracisternal administration methods.

Because symptoms begin *in utero* and worsen over time, gene therapy may achieve best clinical outcomes best when given at younger ages. Additionally, some gene therapies may only be available for patients with specific forms of the disease (e.g., Type 1, Type 2a) (PMID: 38018878).

Although AAV vectors exhibit lower immunogenicity compared to other methods, 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 of gene therapy for GM1 gangliosidosis, please check out this educational resource created by ASGCT: <https://patienteducation.asgct.org/disease-treatments/gm1-gangliosidosis>

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.