Gene Therapy for GM1 Gangliosidosis

How can gene therapy help GM1 gangliosidosis?
GM1 gangliosidosis (GM1) is an inherited disease caused by mutations in the GLB1 gene that encodes instructions to make an enzyme called β-galactosidase (β-gal). β-gal normally breaks down waste products in some cells, especially in the brain. Because GM1 patients don't make normal amounts of β-gal, the waste products that β-gal would normally break down build up in the brain, causing progressive neurological symptoms.

The goal of gene therapy is to deliver a normal copy of the gene encoding β-gal to cells in the brain so that they can make enough β-gal to prevent buildup of waste products and stop the progression of neurological symptoms.

How does this gene therapy work?
Gene therapy uses a harmless virus, otherwise known as a vector, to deliver the desired gene into the patient's cells[1-4]. First, all of the virus's own genes are removed, leaving only its outer shell (capsid) behind. In place of the viral genes, a normal copy of the desired gene, in this case β-gal, is inserted into the virus. By engineering the virus in this way, it is possible to safely deliver the β-gal gene into human cells.

Once the gene has been packaged inside a viral vector, the vector can be given to a patient using several different methods. For the GM1 program described here, the vector will be injected into the cerebrospinal fluid (CSF) which surrounds the brain and spinal cord. This approach, called intrathecal delivery, allows the vector to reach cells throughout the brain and spinal cord following a single injection. Although the β-gal gene only gets into a small fraction of those cells, the cells that receive the gene can secrete large amounts of the β-gal enzyme that neighboring cells can use.

Is gene therapy safe and effective?
For this program, the vector is built out of an adeno-associated virus (AAV). AAV vectors have been evaluated in clinical trials since the mid-1990s with some success. One drug based on an AAV vector has been approved in the European Union, and another is approved in the United States. In clinical trials, AAV vectors have been safely delivered to the brain in both adults and children[1, 2]. Preclinical studies using AAV vectors have been successful in raising β-gal levels in animal models of GM1 gangliosidosis and alleviating symptoms of the disease. More studies are now being conducted in animal models to evaluate the safety and potential efficacy of gene therapy for GM1 gangliosidosis. If the findings from animal studies are favorable, the safety and efficacy of this gene therapy will be evaluated in clinical trials.

How long will this treatment last?
Clinical trials using AAV in patients with hemophilia have shown that the effects of a single administration of gene therapy can last for over a decade, as observed with one patient thus far.[4] As such, gene therapy is intended to be a one-time treatment option, but more clinical trials are needed to understand how long gene therapy will last.

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References:

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