Fabry Disease

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Gene Therapy in Action is a digital publication casting an important spotlight on rare diseases and cancers. This series highlights the increasingly critical role of genetic engineering (also called "gene therapy" or "gene transfer") in the clinical landscape with respect to developing novel and effective therapeutics for the treatment of life-threatening conditions with an urgent unmet medical need. This blog is for educational purposes only and is not intended to replace the advice of your doctor or other health care provider.

What is Fabry Disease?

Fabry disease, also known as Anderson-Fabry disease, is a rare genetic disease that affects the metabolism of glycosphingolipids, a type of fatty substance found in cell membranes. Fabry disease belongs to a group of diseases known as lysosomal storage disorders and is caused by the absent or deficient activity of the lysosomal enzyme, α-galactosidase A (α-Gal A). The Fabry Institute estimates that Fabry disease affects approximately 1 in 40,000 males and 1 in 20,000 females, though newborn screening programs may suggest the incidence of this disease is generally underestimated.

Fabry disease is a progressive, life-threatening disorder and can manifest as a classical or late-onset phenotype, both of which can lead to renal failure, cardiac disease, stroke, and early death. Classical Fabry disease arises in early childhood, with signs and symptoms including pain, edema, hearing and eye changes, gastrointestinal issues, rash-like discolorations on parts of the skin, and reduced sweating. Late-onset Fabry disease typically manifests during the third to seventh decades of life and presents as renal and/or cardiac disease. The life expectancy of patients with Fabry disease is reduced by approximately 20 and 15 years for males and females, respectively.

What causes Fabry Disease?

Fabry disease is caused by mutations in the α-galactosidase A (GLA) gene that instructs cells to make the α-galactosidase A (α-Gal A) enzyme. The mutated α-Gal A enzyme cannot break down glycosphingolipids, leading to accumulation of fatty substances primarily in the blood and walls of the blood vessels, decreasing blood flow throughout the body. This results in the development of systemic pathologic symptoms over time, with the greatest impact seen in the kidneys, brain, and heart. The GLA gene is located on the X-chromosome, making Fabry disease an inherited X-linked disorder. Because of this, males are more likely to develop Fabry disease and are typically more severely affected by it, compared to females, who may inherit the mutated gene, but may not develop the disease due to random X-chromosomal inactivation.

Over 1,000 genetic variants have been found to cause Fabry disease, resulting in a range in severity and symptoms among individuals depending on which mutations occur in their lineage. Some mutations cause the α-Gal A to have little to no activity, resulting in the classic phenotype, whereas other mutations result in residual α-Gal A activity and the late-onset phenotype. The late-onset subtype occurs more frequently than the classical subtype, with a 3- to 10-fold higher incidence, according to the National Organization for Rare Disorders (NORD). Certain GLA mutations can also be benign and may not lead to the development of Fabry disease. The diagnosis of both types of Fabry disease is confirmed by demonstrating the enzyme deficiency and by identifying the specific GLA gene mutation.

Inheritance of Fabry disease occurs when a male passes the affected X-chromosome to their daughters, who may or may not develop symptoms of the disease. Males cannot pass the disease onto their sons. Females have a 50/50 chance of passing the mutated gene onto their children. Fabry disease occurs in all racial and ethnic populations.

Treatments for Fabry Disease

A multidisciplinary approach to treatment is recommended for Fabry disease to address both the decreased activity of α-Gal A and the resulting symptoms from complications caused by the disease. Currently, enzyme replacement therapy (ERT) is the standard treatment option for targeting α-Gal A deficiency. Two forms of recombinant enzyme are available worldwide: agalsidase alpha (Replagal®) and agalsidase beta (Fabrazyme®). Fabrazyme® was approved by the Food and Drug Administration (FDA) in 2003 in the United States and is currently the only FDA-approved ERT for Fabry disease. These ERTs serve to functionally replace the missing α-Gal A enzyme and reduce the accumulation of glycolipids in the body. ERT has demonstrated effectiveness in slowing or preventing renal function decline, particularly when delivered prior to advanced kidney damage. ERT also improves neuropathic pain and heat intolerance.

Another treatment option for Fabry disease is chaperone therapy, which maintains α-Gal A activity by assisting in correctly folding the enzyme. Galafold® (migalastat) is the only FDA-approved (2018) pharmacologic chaperone in the US and functions by binding to, stabilizing, and enhancing the residual activity of α-Gal A with specific missense mutations. Symptomatic treatment to address stroke prevention, lower blood pressure, and manage kidney and heart disease and pain is also recommended.

Gene Therapy Highlights for Fabry Disease

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Highlight #1:

Trial Title: An Open-label, Phase 1/2 Trial of Gene Therapy 4D-310 in Adult Males with Fabry Disease.

ClinicalTrials.gov Identifier: NCT05306457 **Status:** Currently recruiting participants.

Intervention/treatment: Biological - 4D-310

Trial Summary: This Phase I/II study is an experimental gene therapy study designed to assess the safety, maximum-tolerated dose, and efficacy of a recombinant, replication-defective adeno-associated virus (AAV) vector designed to produce ("express") cDNA encoding the human gene for α -galactosidase A (GLA) in adult males with Fabry Disease due to loss-of-function mutations in the GLA gene. This virus, modified in the laboratory so that it cannot reproduce once introduced into the body, acts as an efficient delivery system ("vector") to introduce cDNA for the body to use in production of the α-Gal A enzyme. The study agent, 4D-310, is administered as a one-time intravenous infusion and results in gene transfer into cells of the heart, liver, and kidneys as well as secretion of the encoding α-Gal A enzyme into the circulatory system, with the goal of producing functional α-Gal A throughout the body to enable reduction and clearance of glycolipids. Use of an AAV vector for gene transfer allows for the beneficial long-term production of α-Gal A enzyme.

Highlight #2:

Trial Title: A Phase 1/2, Baseline-controlled, Non-randomized, Open-label, Single-ascending Dose Study of a Novel Adeno-associated Viral Vector (FLT190) in Patients with Fabry Disease.

ClinicalTrials.gov Identifier: NCT04632225 **Status:** Ongoing but no longer recruiting/enrolling new participants.
Intervention/treatment: Biological – Engensis (VM202)
Trial Summary: This Phase IIa study is a gene therapy study designed to assess the safety and preliminary efficacy of Engensis (VM202) for the treatment of ALS compared to placebo. Engensis consists of a small circular DNA molecule (called a plasmid) that is engineered to produce two forms of human growth factor (HGF), a protein that stimulates the formation of new blood vessels (angiogenesis), promotes nerve survival and regeneration (neurotrophic factor), and may contribute to muscle tissue regeneration. Engensis is injected directly into selected muscles and the subsequent production of HGF is anticipated to protect nerves and promote the regeneration of motor neurons while also ameliorating atrophic conditions associated with ALS thereby slowing or preventing ALS progression.

Highlight #3:

Trial Title: *Pending* – A Phase I/II multi-center, three-part trial is planned for 2022.

ClinicalTrials.gov Identifier: *Pending* **Status:** Not yet recruiting.
Intervention/treatment: Biological – APB-102 **Summary:** This planned Phase I/II study is a gene therapy study intended to assess the safety and
efficacy of APB-102 in patients with mutations in the SOD1 gene that are associated with ALS disease. APB-102 is derived from adeno-associated virus serotype rh10 (AAVrh10), a virus that is not known to cause disease in humans. This virus, modified in the laboratory so that it cannot reproduce once introduced into the body, acts as an efficient delivery system ("vector") to introduce a small RNA molecule (known as a microRNA) into the body that can inhibit, or silence, production of the mutated SOD1 protein. Reduction in the levels of the mutated SOD1 protein is expected to provide therapeutic benefit by improving the survival and function of motor neurons in patients with ALS.

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For Patients, Family Members and Caregivers

Looking for resources on Fabry Disease?

- ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?cond=fabry&term=&cntry=&state=&city=&dist=
- Fabry Connect (https://www.fabryconnect.com/)
- Fabry Institute (https://fabry-institute.com/)
- Fabry International Network (FIN) (https://www.fabrynetwork.org/)
- Fabry Support & Information Group (FSIG) (https://fabry.org/)
- National Fabry Disease Foundation (NFDF) (http://www.fabrydisease.org/)
- National Institutes of Health (NIH) (https://www.ninds.nih.gov/health-information/disorders/fabry-disease)
- National Organization for Rare Diseases (NORD) (https://rarediseases.org/rare-diseases/fabry-disease/)

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