Gene Therapy for HoFH

What is homozygous familial hypercholesterolemia?
Individuals with familial hypercholesterolemia (FH) have very high blood levels of LDL-cholesterol, or LDL-C, commonly known as “bad” cholesterol. The high levels of LDL-C lead to deposition and buildup of cholesterol and plaque in the arteries, known as atherosclerosis, which may lead to heart disease or stroke.1–6

Some individuals with FH have inherited a single copy of an FH disease-causing mutation from one of their parents, leading to “heterozygous” FH (HeFH). For others, both parents have passed on the FH mutation, which causes a more serious form of the disease, known as “homozygous” FH (HoFH).3–6 Patients with HoFH have severely elevated LDL-C levels and develop early cardiovascular disease, often in childhood. In the absence of aggressive treatment, many HoFH patients suffer serious cardiac events before the age of 30.3–6

What causes “bad” cholesterol to accumulate in patients with HoFH disease?
In healthy individuals, LDL molecules are captured and broken down by the liver, preventing a buildup of LDL-C in the blood. In patients with HoFH, however, this process is severely compromised, allowing “bad” cholesterol to accumulate in the individual’s bloodstream. For many individuals with HoFH, this is caused by an underlying genetic mutation that prevents the LDL receptor (LDLR) on the surface of the liver from properly capturing and removing LDL from the blood.3–6 In patients with HoFH, the LDLR can be either markedly defective or completely absent, which may result in a range of residual LDLR activity and disease severity.

What are the current treatment options for HoFH and why do they fall short?
Some of the pharmacologic treatment options for reducing LDL-C, such as statins and the newly approved PCSK9 inhibitors, work through increasing the levels of LDLR and therefore do not work all that effectively in patients with HoFH in whom LDLRs are markedly impaired or absent. Two other medications approved for HoFH reduce LDL-C by a mechanism separate from the LDLR, but can increase fat in the liver.7 LDL apheresis has been used in patients with HoFH, but requires prolonged weekly or biweekly visits. In severe cases of HoFH, particularly in children, liver transplant has been used. At this time, none of the therapies available are able to restore LDLR function as an approach to treat the disease.

What is gene therapy and how could it help patients with HoFH?
Gene therapy for HoFH attempts to treat the disease by delivering a normal, functional copy of the LDLR gene into the patient’s own liver. With this healthy copy in place, the patient’s liver cells could begin to make functional LDLR, allowing the liver to capture and break down LDL to prevent the buildup of “bad” cholesterol.8

How does gene therapy work?
In order to deliver a healthy LDLR gene into a patient’s cells, gene therapy utilizes an engineered virus as a delivery vehicle, or “vector.” The viral genes that cause infection are removed from the vector and replaced by genes that enable the liver to make healthy LDLR without causing toxicity. The outer shell of the vector acts like a vessel to transport the healthy LDLR gene into the liver cells. Engineering the virus particle in this way ensures that the necessary gene is delivered safely and efficiently to patient cells.

Might gene therapy for HoFH be effective?
Studies in animal models of HoFH have shown that a specific adeno-associated virus (AAV8) vector carrying the LDLR gene can be delivered to the liver by injecting it into a vein.9–11 Delivering the LDLR gene in this way resulted in an increase in LDL receptor levels in the animals, which then markedly lowered the levels of LDL-C in the blood for a sustained period of time. These results suggest that the approach to gene therapy for HoFH might be effective.
Is gene therapy safe?
Clinical trials of AAV vectors in patients with other diseases such as hemophilia have demonstrated that gene therapy can be used safely in humans. For instance, vectors based on the same delivery vehicle that will be used in the HoFH gene therapy clinical trials have been well tolerated, and have shown evidence of effectiveness, in clinical studies of patients with another genetic disease, hemophilia B. In addition, Glybera®, a gene therapy product using a similar AAV vector, is currently approved for use in Europe for the treatment of another rare disease, known as lipoprotein lipase deficiency. Upcoming clinical trials will assess possible advantages and disadvantages of this approach in people with HoFH.

What is the future of gene therapy for HoFH?
Early experiments have shown that AAV8-based gene therapy for hemophilia can be effective and last for several years. Upcoming clinical trials in patients with HoFH will evaluate both the safety and effectiveness of this approach for treating this disease. The goal of gene therapy is to offer a lasting, one-time treatment option to patients with HoFH. Future clinical studies will be essential for determining the duration and extent of clinical benefit.

References: