Intrathecal Gene Therapy for MPS I

Mucopolysaccharidosis type I, or MPS I, is a rare, genetic disease that impairs a person’s ability to metabolize complex carbohydrates (also known as mucopolysaccharides or glycosaminoglycans). In healthy individuals, these long chains of sugar molecules are broken down by an enzyme called lysosomal alpha-L-iduronidase, or IDUA. In patients with MPS I, however, genetic mutations prevent normal levels of functional IDUA from being made. Without enough IDUA activity in the body, complex sugar molecules begin to accumulate in the patient’s tissues. This buildup causes damage to many of the patient’s organs, including the brain, spinal cord, and heart.1,2

MPS I can be caused by a number of different inherited mutations in the IDUA gene. Each of these genetic mutations can impact mucopolysaccharide metabolism to varying degrees. As a result, some patients with MPS I are still able to produce a small amount of functional IDUA, resulting in a less severe form of the disease referred to as attenuated MPS I. Alternatively, other genetic mutations may completely eliminate functional IDUA from the body, resulting in severe MPS I. Historically, milder forms of the disease were also known as Scheie or Hurler-Scheie syndrome, while severe MPS I was referred to as Hurler syndrome.1,2

As disease severity depends upon the amount of residual IDUA activity, life expectancy among patients with MPS I also varies accordingly. Most patients with attenuated MPS I do suffer from significant disabilities; however, they may live a relatively normal lifespan. In contrast, individuals with the most severe form of the disease rarely live beyond 10 years of age unless they are treated with a life-saving procedure called hematopoietic stem cell transplantation (HSCT, see below for an explanation of this treatment).3 The serious, potentially life-threatening nature of MPS I symptoms emphasizes the need for effective treatment options for patients suffering from this disease.

What are the current treatment options and why do they fall short?

The standard treatment option for patients with attenuated MPS I is referred to as enzyme replacement therapy, or ERT. With ERT, a synthetic version of IDUA is delivered to the patient’s vein (intravenously) every week in order to maintain a constant level of functional IDUA in the body. A drug called laronidase (Aldurazyme®, manufactured by BioMarin Pharmaceutical, Inc. and the Genzyme Corporation) was FDA approved for this purpose in 2003.1,2,4

Unfortunately, when ERT is delivered through the patient’s veins, it is unable to pass from the blood into the brain. As a result, ERT is unable to treat the cognitive symptoms of MPS I that affect the brain and spinal cord (collectively called the central nervous system, or CNS).4 Some research studies have attempted to deliver ERT directly to the brain through what is known as an intrathecal injection that targets the cerebrospinal fluid (CSF) flowing through the CNS.5 Unfortunately, because the enzyme does not last long and needs to be repeatedly injected, intrathecal ERT is not an ideal treatment option for CNS symptoms.

HSCT is another treatment approach that has been used primarily for patients with severe MPS I. Unlike ERT, HSCT is able to benefit CNS symptoms. Unfortunately, this technique is only partially effective in preventing these CNS symptoms, and as many as 10% of patients undergoing HSCT may die as a direct result of this high-risk procedure.6

Overall, despite available treatments, cognitive decline affects 100% of patients with severe MPS I and 30% of those with attenuated forms of the disease. As a result, the inability of ERT...
and HSCT to safely and reliably repair cognitive function represents a major limitation of current treatment approaches.

**How can gene therapy help MPS I?**

Due to the limitations of current treatment options, there is a significant need for a therapy that can deliver functional IDUA to the CNS in a safe and long-lasting manner. This concept is the basis for gene therapy in MPS I. There are several approaches to gene therapy currently being developed for this disease, which utilize different strategies for delivering functional IDUA to the brain. One such strategy strives to deliver a healthy copy of the IDUA gene directly into the patient’s CNS cells by a single intrathecal injection. With a normal copy of the IDUA gene in place, the patient’s own cells can then begin to synthesize functional IDUA in the CNS. Even if the gene is only delivered to a few cells within the CNS, the IDUA those cells produce is continually released into the CSF, providing an ample amount of the enzyme throughout the brain and spinal cord. This approach has the potential to eliminate the need for HSCT, as well as weekly or monthly intrathecal ERT injections.

**How does gene therapy work?**

Gene therapy uses a harmless virus as a vehicle, or vector, for delivering the desired gene into the patient’s cells. First, all of the viruses’ 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 IDUA for MPS I, is inserted into this outer shell. By engineering the virus in this way, it is possible to safely deliver the IDUA gene into human cells.

**Is gene therapy safe and effective?**

In the case of MPS I intrathecal gene therapy, the vector is built out of an adeno-associated virus (AAV), known as AAV9. AAV vectors have been evaluated in clinical trials since the mid-1990s with some success. In fact, one gene therapy product (Glybera®, manufactured by UniQure) is already approved for use in Europe for the treatment of another rare disease, lipoprotein lipase deficiency. AAV has also been safely delivered into the brain in clinical trials of children with various other diseases, including another type of mucopolysaccharidosis, called MPS IIIa.

In MPS I, preclinical studies using the AAV9 vector have been successful in raising IDUA levels in animal models and alleviating symptoms of the disease throughout the CNS. The levels of IDUA being made can be increased by optimizing the exact location of the intrathecal injection. As demonstrated previously with other MPS therapeutics, it is optimal to administer the therapeutic agent early in life to prevent the onset of disease. We anticipate that this will be even more important with gene therapy, in order to possibly prevent the decline in brain function that begins at an early age, prior to the onset of neurocognitive symptoms.

Despite promising studies, it is important to keep in mind that gene therapy is still in preclinical development. Therefore, upcoming clinical trials will be essential for determining the safety and potential benefits of this approach.

**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. As such, gene therapy is intended to be a one-time treatment option for patients with MPS I; future clinical trials will be essential for determining the duration of potential benefits that this exciting, single-dose approach may offer.
References


