MPS I Webinar

Clinical trials and treatment update

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Our first webinar on developing treatments for Mucopolysaccharidosis type I (MPS I) on 17th June 2021, brought together clinical experts to answer your questions about clinical trials and the latest research into new treatment approaches.

MPS I

MPS I is a rare genetic condition caused by a mutation of the IDUA gene. The mutation means that the body cannot make an enzyme called alpha-L-iduronidase properly. This enzyme is essential for breaking down the long chains of sugar molecules dermatan sulphate and heparan sulphate in almost every cell in the body. When these molecules are not completely broken down, they remain stored, and their build-up over time can lead to damage throughout the body including the skeleton, internal organs and brain.

MPS I is divided into three subtypes, depending on the severity of symptoms.

- Hurler is the most common and severe form, with symptoms appearing at a young age and both the body and brain being affected.
- Those with the milder Scheie type develop symptoms later; their disease progresses slower and may only affect the body.
- Those with symptoms between these two extremes are classified as Hurler-Scheie.

To watch this webinar, click here:

Disclaimer

This document summarises the information presented at the MPS I Webinar held on 17th June 2021 by the MPS Society. **This summary does not provide medical advice, always seek the advice of your consultant with any questions you may have regarding your medical condition or treatment.**

Current treatments

Enzyme Replacement Therapy

For people with Hurler-Scheie and Scheie, enzyme replacement therapy is a long-term treatment that replaces the missing or deficient enzyme via a weekly intravenous infusion.

This treatment, known as laronidase (Aldurazyme®), addresses many of the symptoms of MPS I, but is not able to cross the blood-brain-barrier and treat the brain.

For this reason, a different type of therapy is preferred for those with Hurler.

Hematopoietic Stem Cell Transplant

A hematopoietic stem cell transplant (HSCT) is the treatment of choice for Hurler.

Here a bone marrow transplant is given that provides cells from a donor that can make the missing enzyme. Following treatment, these individuals are able to produce their own enzyme which reaches both the body and brain.

Better results are achieved when the transplant is given at a younger age and where higher enzyme levels are achieved.

Supportive Therapies

Supportive therapies are also an important part of the strategy for treating MPS I. For example, joint and spinal problems, may benefit from physiotherapy and orthopaedic or spinal surgery.

Unmet Needs

A number of new ways of treating MPS I are currently being investigated in the hope that future treatments can address some of these unmet needs.

Unmet Needs

While these current treatments address many of the symptoms of MPS I, the outcomes can vary and those affected may have issues with:

- Brain function – the outcome is varied with HSCT
- Issues with heart valves, hearing, corneal clouding or hormones
- Orthopaedic problems that may require surgery

New Treatment Approaches

Gene Therapy

In gene therapy, patients are treated with a working copy of the IDUA gene that enables them to make alpha-L-iduronidase enzyme themselves. There are currently two types of gene therapy in clinical trials. In both, a harmless virus (known as the vector) is used to deliver the healthy IDUA gene to the patient's cells. In ex vivo gene therapy this happens outside the body and the patient's treated cells are then returned to them. In in vivo gene therapy, the virus containing the healthy IDUA gene is administered to the patient and their cells are treated in the body.

Ex Vivo Gene Therapy

An ex vivo gene therapy is currently undergoing its first clinical trial in MPS I at the San Raffaele Telethon Institute for Gene Therapy in Italy. This approach is being tested in several diseases and has already been approved in another rare metabolic disease (metachromatic leukodystrophy).

1. The patient's **hematopoietic stem cells** are collected from the bone marrow or blood
2. These cells are treated with the virus to provide a working copy of the IDUA gene
3. The patient has a cycle of chemotherapy to prepare them for receiving the treated stem cells
4. The treated cells are infused back into the body where they are able to produce enzyme

Eight children with MPS I under 3 years of age have been treated. Following treatment, they had above normal levels of enzyme in the blood, and enzyme could also be detected in the brain. Two years after receiving gene therapy their motor and cognitive skills were stable and they continued to grow normally. Improvements in facial features, joint stiffness and corneal clouding were observed.

These early results need to be confirmed and a further study is planned for 2021/2022.

Hematopoietic stem cells are immature cells that can develop into all types of blood cells.

In Vivo Gene Therapy

RGX-111 is an in vivo gene therapy, designed to deliver a working IDUA gene to the brain; preventing further neurodegeneration. The virus vector used in this treatment is AAV9, chosen because it is particularly good at accessing cells in the brain.

1. AAV9 virus is engineered to deliver the working gene
2. AAV9 is administered through a single injection into the fluid that surrounds the brain
3. Brain cells that now have a working copy of the IDUA gene can produce enzyme
4. AAV9 may also migrate outside the brain to deliver the gene to other tissues of the body

A first clinical trial is underway and will treat five patients in total. So far three have been treated, the first in October 2020.

IV Therapy

Standard enzyme replacement therapy is unable to get through the blood-brain barrier (BBB) and enter the brain. To counter this, fusion proteins can be used. A fusion protein has an antibody, that is able to attach to a receptor on the BBB, at one end and the required enzyme at the other. The presence of the antibody allows the fusion protein to pass through the BBB and therefore deliver the enzyme to the brain. With this type of therapy, a standard weekly infusion given via the arm or a port on the body is able to supply enzyme to both the body and brain.

Two fusion proteins have been trialled for MPS I. AGT-181 has an insulin receptor as part of the fusion protein and JR-171 has a transferrin receptor. In a clinical trial of AGT-181 in Brazil, 16 children with Hurler or Hurler-Scheie were treated. After 1 year of treatment, there was evidence of stabilization of the effects of MPS I on both the body and brain. An early clinical trial of JR-171 is ongoing in Japan, Brazil and other countries.

Another fusion protein that includes the transferrin receptor has already been approved for treatment of MPS II (Hunter disease) in Japan.

Non-Viral Engineered Cell-Based Therapy

For this therapy, human cells are modified outside the body, to produce the enzyme lacking in MPS I. These cells are then wrapped inside a protective sphere about 1.5mm in diameter. Each sphere will contain 20,000—40,000 modified cells. The spheres are then placed inside the patient's body in the space between the abdominal wall and the intestines. When inside the body, the modified cells produce enzyme, and the sphere protects these cells from attack by the patient's immune system.

2022

A potential treatment of this type for MPS I, SIG-005, is due to start clinical trials in 2022. This technology is currently in clinical trials for hemophilia.

Activating RNA Therapy

In individuals with MPS I that have received a HSCT, those that produce the most enzyme have the best outcomes. It may be possible to increase the amount of enzyme made following HSCT using a technology known as activating **RNA** therapy.

- Small pieces of RNA are able to alter how much enzyme a gene produces without changing the gene itself.

- These cannot be given directly by mouth or injected but need to be wrapped in tiny particles of cholesterol and given as regular infusions into the bloodstream.

While there are currently over 80 ongoing studies of this kind of treatment in various diseases, clinical trials have not yet started in MPS I.

Early discussions are underway for planning a study in MPS I.

RNA converts the instructions in the gene to produce enzyme.

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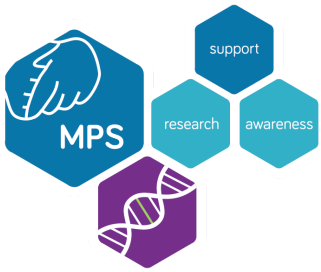

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This document was prepared by Rare Disease Research Partners* for the MPS Society.

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