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A Review of Recent Research in Treatment Approaches of Mucopolysaccharidosis (MPS)

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Mucopolysaccharidosis (MPS) is caused by accumulation of the glycosaminoglycans in all tissues due to decreased activity of the lysosomal enzyme. Patients exhibit multisystemic signs and symptoms in a chronic and progressive manner, especially with changes in the skeleton, cardiopulmonary system, central nervous system, cornea, skin, liver, and spleen. In the past, treatment of MPS was limited to enzyme replacement therapy (ERT). The outcome for affected patients improved with the introduction of new technologies as hematopoietic stem cell transplantation, relegated to specific situations after ERT became available. Intrathecal ERT may be considered in situations of high neurosurgical risk but still it is experimental in humans. New insights on the pathophysiology of MPS disorders are leading to alternative therapeutic approaches, as gene therapy, inflammatory response modulators and substrate reduction therapy. In this paper, we will highlight the recent novel treatment and clinical trials for MPS and discuss with the goal of fostering an understanding of this field.

Keywords: MPS, Mucopolysaccharidosis, Clinical trials, Enzyme replacement therapy

Introduction

Mucopolysaccharidoses (MPS) is an inherited congenital metabolic disorder brought about by defects on a lysosomal enzyme necessary for degrading Glycosaminoglycans (GAGs), also previously called mucopolysaccharide. As these enzymes are deficient, glycosaminoglycans are incompletely degraded and thus accumulate in the cell and are excessively excreted through the urine. This causes neurological regression and the functional disorder of multiple organs. According to the standardized typing of deficient enzymes, MPS can be categorized under types I, II, III, IV, VI, VII and IX.

Treatment of Mucopolysaccharidoses

There are many potential treatments for MPS, such as hematopoietic stem cell transplantation (HSCT), enzyme replacement therapy and gene therapy, with HSCT being the only available standardized treatment at the moment. Until the end of the 1980s, supportive care is the only treatment offered for MPS patients. However, since the 1990s, HSCT has been attempted and applied to various lysosomal storage diseases such as MPS I (2001), MPS II (2002) and MPS VI (2004). Moreover, therapeutic drugs for Hunter Syndrome (MPS II, 2012) and Gaucher's disease (2013) have been developed by a domestic pharmaceutical company[1].

1. Pros and cons of treatment options

1) Hematopoietic stem cell transplantation (HSCT)

As HSCT utilizes enzymes released from transplanted cells, its therapeutic effects continues after a single transplant. However, the transplantation itself is of high-risk and donor-determination also takes time. In addition, during HSCT, there is great challenge in the engraftment of cartilage, bone and heart tissues. Despite these disadvantages, HSCT remains actively utilized as a treatment option for disorders including MPS types I, II, VI and VII, which utilizes blood marrow cells derived from the placenta[2].

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Table 1. Current status of domestic and external clinical research on mucopolysaccharidosis

Type	Research title	Treatment method	Ages Eligible for Study / participants	Phase	Responsible country and agency
I	Ascending dose study of genome editing by the zinc finger nuclease therapeutic SB-318 in subjects with MPS I	Gene therapy/SB-318	18 years and older (adult, senior)/ 9 participants	Phase 1 in progress (2017.03.24–2022.01)	U.S (Sangamo Therapeutics)
II	The long-term safety study of idursulfase-beta in MPS II patients	Drug: Hunterase® (idurasulfase-beta)	No limitation/ 34 participants	Phase 3 in progress (2014.1–2020.01)	Korea (Green Cross Corporation)
II	Open, observation study of intracerebrovascular ERT using Hunterase in patients with MPS II	Drug: Hunterase® (idurasulfase-beta) (ICV)	1.5–15 years/ 8 participants	In progress (2016.06–2020.03)	Japan, Korea (AnGes-MG Inc., Green Cross Corporation)
II	Ascending dose study of genome editing by the zinc finger nuclease therapeutic SB-913 in subjects with MPS II	Gene therapy/ SB-913	>18 years/9 participants	Phase 1 in progress (2017.05.11–2022.2)	U.S (Sangamo Therapeutics)
II	Randomized, double blind, dose escalation observation study in patients with MPS II	Drug: Hunterase® (idurasulfase-beta)	5–65 years/20 participants	Phase 2 in progress (2016.12–2020.6)	Korea (Green Cross Corporation)
II	Safety and dose ranging study of insulin receptor MoAb-IDS fusion protein in patients with MPS II	Drug: AGT-182	≥18 years/8 participants	Phase 1 in progress (2015.04–2017.10)	U.S, Germany, Netherlands, Philippines (ArmaGen, Inc)
IIIA	Phase I/II gene transfer clinical trial of scAAV9.U1a.hSGSH	Gene therapy /scAAV9.U1a. hSGSH	≥2 years/16 participants	Phase 2 in progress (2016.03–2020.12)	U.S, Austrailia, Spain (Abeona Therapeutics, Inc)
IIIB	A open label study in previously studied, SBC-103 treatment naïve MPS IIIB subjects to investigate the safety, pharmacokinetics, and pharmacodynamics/ efficacy of SBC-103	Drug: SBC-103 (rhNAGLU)	5 participants	Phase 2 in progress (2015.09–2018.12)	U.K (Alexion)
IIIB	A treatment study of MPS IIIB	Drug: BMN 250	1–10 years/ 33 participants	Phase 2 in progress (2016.04–2019.03)	Germany, Spain, Taiwan, U.K (Biomarin)
IVA	A multicenter, multinational, observational MPS IVA registry study (MARS)	Drug: Vimizim® (elosulfase alfa)	No limitation/ 583 participants	Phase 3 in progress (2014.09–2024.09)	Multinational (BioMarin Pharmaceutical)
VI	Gene therapy in patients with MPS VI	Gene Therapy/ AAV2/8.TBG. hARSB	4–65 years/10 participants	Phase 2 in progress (2017.7.17–2022.06.01)	Italy (Fondazione Telethon)
I, II	Study to evaluate the safety and efficacy of adalimumab in MPS I and II	Drug: Humira® (adalimumab)	>5 years/14 participants	Phase 2 in progress (2017.06.05–2020.6)	U.S (LA Biomedical Research Institute)
I, VI	Study of human placental-derived stem cell transplantation	Drug: Human placental derived stem cell	<55 years/30 participants	Phase 1 in progress (2013.04–2019.12)	U.S (New York Medical College)

Table 1. Continued

Type	Research title	Treatment method	Ages Eligible for Study/ Participants	Phase	Responsible country and agency
I, II, VI, VII	Study of impact on allogenic hematopoietic stem cell transplantation and conditioning Regimen for inherited metabolic disease	Hematopoietic stem cell transplantation	<55 years/ 100 participants	Phase 3 in progress (2014.07–2019.09)	U.S (Masonic Cancer Center)
II	A study of JR-141 in patients with MPS II	Drug: JR-141	≥6 years/ 12 participants	Termination (2017.03.30–2017.10.04)	Japan (JCR Pharmaceuticals Co., Ltd.)
VI	Multicenter, multinational open expansion study using recombinant human N-acetylgalactosamine 4-sulfatase (rhASB)	Drug: N-acetylgalactosamine 4-sulfatase	≥7 years/ 39 participants	Termination (2004.02–2006.10)	U.S (BioMarin)
I	Multicenter, multinational, randomized study using Aldurazyme® (Laronidase)	Drug: Aldurazyme	No limitation/ 34 participants	Termination (2004.12–2006.01)	Brazil, Canada (BioMarin/ Genzyme LLC
IIIA	Observational study of intracerebral administration of SAF-301	Drug: SAF-301	4 participants	Termination (2014.1–2017.06)	France (LYSOGENE)
VII	An open-label phase 1/2 study to assess the safety, efficacy and dose of study drug UX003 recombinant human beta-glucuronidase enzyme replacement therapy in patients with MPS VII	Drug: UX003	5–30 years/ 3 participants	Termination (2013.10–2016.07)	U.K (Ultragenyx-Pharmaceutical)

2) Enzyme replacement therapy (ERT)

Sufficient clinical experience and effectiveness of ERT have been documented in previous literature. However, enzymes are not well distributed in tissues such as the bone or heart valves, cannot pass through the blood brain barrier, and are thus less effective in the central nervous system. The use of Hunterase, an ERT developed in Korea for MPS II treatment, has shown dramatic efficiency for several abdominal and musculoskeletal tissues[1,3,4]. In addition, Hunterase is undergoing a Global Phase 3 Clinical Study on Chinese patients with MPS II.

3) Substrate reduction therapy (SRT)

Oral administration of SRT has been shown to improve quality of life; however, less clinical experience and long-term stability is known.

4) Pharmaceutical chaperone therapy (PCT)

PCT results in a good distribution of treatment, including the containment of degenerative neural tissues in patients with lysosomal storage disease. Although oral administration enhances the quality of life, clinical experience remains minimal and long-term stability is still unknown.

5) Gene therapy

Studies involving the injection of intravenous AAV2/8TBG-I2S viral particles into rats with MPS II have reduced urine GAG to the normal range, with an observable improvement in the skeletal system[5]. Although gene therapy can be used to treat primary diseases through a single procedure, it has little clinical experience and is still in the developmental stage. Other studies related to gene therapy using AAV are also under development in MPS I, IIIA and VI patients[6].

2. Other approaches aside from intravenous enzyme replacement therapy for improvement of the CNS

Because Idursulfase hardly passes through the blood-brain barrier, it is difficult to expect improvement in the central nervous system for patients with severe syndromes[7]. Besides IV treatment, intrathecal transfer of enzymes to the spinal fluid is also attempted, either through lumbar puncture or cisterna magna puncture. In addition, these various methods have been reported to be effective for the recovery of CNS damage in MPS I, IIIA and VI patients.

In particular, the effects of intrathecal ERT using BMN-250 are currently being investigated in MPS IIIA, which presents with serious neurological regression[8]. Research on intracerebrovascular ERT targeted for severe types of MPS II has been conducted in collaboration with Japan and Korea, and interim results are encouraging.

3. Current clinical trials on MPS (I, II, IIIA, IIIB, IVA, VI) are listed in Table 1[6,8-12]

Results

Recently, novel treatment approaches are being developed such as various substrate reduction therapies, gene therapies and intrathecal ERT to overcome the limitations of conventional ERT. Successful clinical research is expected to produce positive results in the future as it may lead to the resolution and improvement of major issues, such as poor quality of life due to the regression in neurological functions, shorter life expectancies and chronic complications.

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