

Causal Therapies in Mucopolysaccharidoses: Enzyme Replacement Therapy

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Abstract

Enzyme replacement therapy (ERT) for mucopolysaccharidoses (MPS) is the treatment of choice for patients, since it specifically addresses the underlying cause of the disease. Intravenous weekly infusions of recombinant enzymes for MPS I, II, IVA, VI, and VII have proven to be safe and efficacious for somatic symptoms. ERT has been shown to decrease urinary glycosaminoglycan levels and organomegaly, while improving stamina of patients, respiratory function, and quality of life. Although early administration of ERT optimizes outcomes, adult patients still benefit from treatment. ERT has been successfully used as combination therapy with hematopoietic stem cell transplant for patients with MPS I and MPS II, improving patient's cognitive outcomes. Although patients can receive benefit from ERT, current challenges include lack of improvement of neurological manifestations, limited effect on bone disease, development of immune response toward the infused enzyme, and high cost. We will discuss the milestones achieved by intravenous ERT for MPS diseases as well as the current challenges.

Keywords

- enzyme replacement therapy
- mucopolysaccharidoses
- blood–brain barrier
- skeletal disease

Introduction

Mucopolysaccharidoses (MPS) are a group of genetic diseases that are caused by deficient lysosomal enzymes involved in the breakdown of glycosaminoglycans (GAGs), resulting in the accumulation of enzyme substrates.¹ Although all of these diseases have the same cause—a deficient enzyme—the degree to which the enzyme is deficient is highly variable, and thus the patient population suffering from MPS is heterogeneous in its symptomatology and clinical presentation.

Patients suffering from these diseases have historically been managed with supportive care; however, with the

advent of enzyme replacement therapy (ERT), patients are offered a route of treatment that can target the underlying pathology itself. ERT has been successfully used for many MPS patients. ERT relies on the delivery of exogenous enzyme to lysosomal membranes and utilizes the mannose-6-phosphate ligand and insulin-like growth factor II receptor to target the enzyme to lysosomes.² The utilization of the mannose-6-phosphate ligand in delivering ERT is unique to lysosomal storage diseases (LSDs), and is important for the utility and efficacy of ERT.

MPS I (Hurler syndrome), the most common MPS, was the first MPS to receive Food and Drug Administration (FDA)

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approval for ERT in 2003. The ERT for MPS I, known as Aldurazyme, was developed by BiMarin and is now approved in more than 60 countries worldwide. ERT approved for MPS VI (Maroteaux–Lamy syndrome) in 2005, known as Naglazyme, is used in the United States as well as many European countries. In 2006, Elaprase was approved for use in MPS II (Hunter) syndrome. Elaprase was developed by Shire Pharmaceuticals and it is used in the United States, Canada, and many European countries. The most recent ERTs that have been FDA approved are Vimizim and Mepsevii, which were approved in 2014 and 2017, respectively. Vimizim is used for MPS IVA (Morquio A syndrome) patients; Mepsevii, which was only approved on November 15, 2017, is used for MPS VII (Sly syndrome) patients (►Table 1).

In this review, we will discuss achievements and challenges of intravenous (i.v.) ERT administration for MPS diseases.

Achievements with Enzyme Replacement Therapy

Although manifestations of MPS are highly varied in their clinical presentation, there are certain features that are common among patients. Three major organ systems have shown to be particularly susceptible to GAG accumulation: brain, connective tissue, and the reticuloendothelial system. Thus, common symptoms in MPS patients include organomegaly, mental retardation, heart disease, skeletal disease, and respiratory issues.

Hurler, Hurler–Scheie and Scheie Syndromes, MPS I

α -L-iduronidase is a lysosomal acid hydrolase, which cleaves iduronic acid residues from the nonreducing ends of dermatan sulfate and heparan sulfate.¹ Initial *in vitro* studies in cultured fibroblasts determined that the intracellular half-life of this enzyme was ~5 to 7 days, which suggested administration of α -L-iduronidase on a weekly basis.^{3,4}

In 1997, BioMarin Pharmaceutical Inc. established the safety and efficacy studies of laronidase ERT in an open label phase I/II clinical study with 10 MPS I patients. In 2001, 45 MPS I patients were enrolled in a randomized, double-blind, placebo-controlled, international, multicenter, phase III study.⁵ This pivotal clinical trial paved the way to other ERT studies. Laronidase was approved by the FDA and European Medicines Agency (EMA) in 2003. Currently, lar-

onidase (Aldurazyme) is administered as a weekly i.v. infusion at a dose of 0.58 mg/kg body weight; it is manufactured by BioMarin and commercialized by Genzyme Corporation.

There have been many MPS I patients that have been successfully treated with ERT. This treatment has shown to be effective in reducing urinary GAG (uGAG) levels, decreasing organomegaly, and increasing stamina of patients as evidenced by 6-minute walk test (6MWT) improvement.^{3,5} A meta-analysis of studies evaluating the effectiveness of ERT in adult MPS I patients, who initiated treatment as adults, concluded that ERT improved uGAGs and liver volume, with moderate improvement in 6MWT.⁶ This study addresses a key factor with ERT: early initiation of treatment has been associated with better outcomes. This study supports the premise that though early initiation of ERT optimizes outcomes, initiation of ERT for adults still provides major benefits to patients.⁶

While ERT has become a mainstay for many MPS patients, hematopoietic stem cell transplant (HSCT) is the gold standard therapy for MPS-IH (Hurler syndrome) patients younger than 2.5 years of age.⁷ However, ERT has been shown to be effective as an adjunct therapy along with HSCT for MPS-IH patients.⁸ Utilizing ERT for MPS-IH patients waiting on HSCT has shown to reverse cardiomyopathy and severe heart failure. Additionally, there have been no deleterious side effects of ERT on engraftment success. While ERT may be useful in MPS-IH patients who have yet to undergo HSCT, there is no evidence which justifies ERT use years after transplant. A case study of a HSC-transplanted 2.5-year-old patient who had respiratory failure at the age of 14 was started on weekly ERT for 24 months, along with non-invasive ventilation, and showed great improvement in respiratory functions and quality of life.⁹

Hunter Syndrome, MPS II

Iduronate-2-sulfatase is deficient in patients with MPS II leading to the accumulation of dermatan sulfate and heparan sulfate in cells and tissues.¹ Unlike other recombinant enzymes used for ERT, idursulfase was produced in a human cell line (HT-1080 fibrosarcoma cell line) to ensure similarities in glycosylation profile with the human endogenous form.¹⁰ Idursulfase tissue half-life was estimated as 1 to 2 days after *in vivo* studies.¹¹ In 2001, a randomized, double-blind, placebo-controlled, dose-finding, phase I/II ERT study was initiated by Transkaryotic Technologies with 12 MPS II patients. In 2003, a worldwide, randomized, double blind,

Table 1 FDA^a approved enzyme replacement therapies

Disease	Product	Company	Year of FDA ^a /EMA ^b approval
MPS I	Laronidase (Aldurazyme)	BioMarin & Genzyme Corporation	2003/2003
MPS II	Idursulfase (Elaprase)	ShireHGT	2006/2007
MPS IVA	Elosulfase alfa (Vimizim)	BioMarin	2014/2014
MPS VI	r-arylsulfatase alfa (Naglazyme)	BioMarin	2005/2006
MPS VII	Vestronidase alfa (Mepsevii)	Ultragenyx	2017

^aFood and Drug Administration.

^bEuropean Medicines Agency.

placebo controlled phase II/III trial was initiated with 96 patients.^{12,13} On the basis of these studies, idursulfase was approved by the FDA in 2006 and EMA in 2007. Currently, idursulfase (Elaprase) is administered i.v. with a weekly dose of 0.5 mg/kg body weight and is manufactured by Shire.

While HSCT remains the gold standard therapy for MPS I patients, it has not been shown to improve clinical status of MPS II patients.¹⁰ Thus, ERT remains the sole treatment strategy for them. Since ERT was approved for use in MPS II patients in 2006, there is a decade of data that now exists. A study of 17 MPS II patients who underwent ERT shows that there have been improvements in forced vital capacity (FVC) as well as a reduction in left-ventricular mass (LVM).¹⁴ The improvement in FVC is thought to be due to improved musculoskeletal and cardiovascular functions rather than an improvement in skeletal or laryngeal-tracheal deformities. Of the five cognitively normal patients, four of them had clear improvement in 6MWT with improved quality of life. Additionally, the hearing of six patients in this study improved with ERT, making this the first study to provide data on hearing improvement with ERT, although this may have been due to decreased mucous production.¹⁴

Sanfilippo Syndrome, MPS III

MPS III is a group of diseases characterized by the deficiency of one of four lysosomal enzymes: *Type A*—heparan *N*-sulfatase, *Type B*— α -*N*-acetylglucosaminidase, *Type C*—acetyl CoA α -glucosaminide acetyltransferase, and *Type D*—*N*-acetylglucosamine-6-sulfatase.^{1,15} Deficiency of any of these enzymes leads to the systemic accumulation of heparan sulfate characterized by variable developmental delay and central nervous system (CNS) dysfunction.¹ Clinical trial for MPS IIIB was initiated by Synageva which was later acquired by Alexion Pharmaceuticals, Inc. Results of phase I/II (i.v. administration of SBC-103 at 0.3, 1, or 3 mg/kg every other week) for 24 weeks), showed that in the neurocognitive assessments of the 3 mg/kg group, three out of four patients had an increase in both mental age equivalent (AEq) and developmental quotient (DQ) compared with baseline. In the 1 mg/kg group, two out of four patients had an increase in both AEq and DQ compared with baseline, and in 0.3 mg/kg group, one out of three patients had an increase in both AEq and DQ compared with baseline. Overall, response profiles among the 3 mg/kg treatment groups suggested a potential dose effect as compared with the 0.3 mg/kg and 1 mg/kg groups.¹⁶ Although the results were promising, in February of 2017 Alexion Pharmaceuticals, Inc. decided to suspend further development of its MPS drug candidate, SBC-103.¹⁷ After disappointing termination of the MPS IIIB as well as MPS IIIA (recombinant human Heparan-*N*-sulfatase administration via an intrathecal drug delivery device by Shire) programs by two different companies, questions remain whether ERT is the best approach to treat these diseases.¹⁸

Morquio A Syndrome, MPS IVA

Patients with MPS IVA have a deficiency of *N*-acetylgalactosamine-6 sulfate sulfatase (GALNS) leading to the systemic

accumulation of chondroitin-6-sulfate and keratan sulfate.^{1,19} GALNS has been shown to be stable in serum around ~200h *in vitro*²⁰ and to have a circulation half-life of 2.9 minutes.²¹

ERT for MPS IVA was developed by Biomarin Pharmaceutical Inc. and was approved for use in 2014 by the FDA. A review of elosulfase alfa (Vimizim) efficacy discusses the outcomes of the clinical trials of Morquio A disease.²² A phase III, randomized, double-blind study (MOR-004) showed that there were improvements in 6MWT in the group receiving weekly infusions, but not in the biweekly or placebo-infused patients. There was no improvement in 3-minute stair climb test (3MSCT), pulmonary function, or quality of life. Another phase III study (MOR-005), a continuation of the previous study (MOR-004), showed improvement in 6MWT and 3MSCT.²² A double-blind, randomized clinical trial in a pediatric population has shown that elosulfase alfa is effective for improving the respiratory function and bone growth in younger children compared with placebo.²³ Currently, elosulfase alfa is administered i.v. weekly at a dose of 2.0 mg/kg body weight.

Maroteaux-Lamy Syndrome, MPS VI

N-acetylgalactosamine-4-sulfatase (arylsulfatase B) is deficient in patients with MPS VI, resulting in the intracellular accumulation of dermatan sulfate and chondroitin-4-sulfate.¹

Arylsulfatase B (galsulfase, Naglazyme) is produced in genetically engineered Chinese Hamster Ovary cells.²⁴ ERT for MPS VI was developed by BioMarin Pharmaceutical Inc. and was approved for use in 2006 by the FDA. A case series assesses the efficacy of long-term ERT for nine Taiwanese MPS VI patients.²⁵ After 6.2 to 11.2 years of long-term ERT, six of the patients experienced improvement in 6MWT by a mean of 150 m. Four patients had improved cardiac diastolic function. All patients in this study showed increased shoulder range of motion as well as decreased liver and spleen sizes as measured by abdominal ultrasonography. Additionally, there was a mean overall 69% decrease in uGAG excretion. This study suggests that long-term ERT was beneficial for a wide range of clinical functional assessments as well as reducing uGAGs. A second study focuses on growth improvement in MPS VI ERT-treated patients.²⁶ This study looks at height data of 141 MPS VI patients who began ERT treatment by 18 years of age. The majority of these patients had high baseline uGAGs at the beginning of treatment. The results showed that the most significant improvement in height was seen in those beginning treatment at a younger age, with those starting treatment between 0 and 3 years old having the most improvement. Patients beginning treatment between 15 and 18 years of age had no improvement.²⁶ Additionally, patients who had low baseline uGAG levels showed no improvement.

Sly Syndrome, MPS VII

β -glucuronidase hydrolyzes glucuronic acid, found in heparan sulfate, dermatan sulfate, and chondroitin 4–6

sulfate. β -glucuronidase was the first enzyme characterized catalytically for any MPS. Studies of cells from the first identified patient had an important impact on the field, which led to the elucidation of the mannose-6 phosphate targeting system on which most of the ERTs are dependent.²⁷

The ERT drug for MPS VII, called Mepsevii, was developed by Ultragenyx Pharmaceutical. The first use of ERT in a MPS VII patient was described in a report from 2015.²⁸ A 12-year-old patient with advanced MPS VII had reached the point where there were no additional options for medical intervention, and experimental ERT was started. Upon initiation of ERT, the patient's uGAG excretion levels decreased by more than half and hepatosplenomegaly was reversed to normal by 24 weeks. Additionally, the ERT was well tolerated and no serious adverse events, infusion associated reactions, or hypersensitivity reactions were observed.²⁸ A phase III clinical trial conducted by Ultragenyx Pharmaceutical was completed in May 2016, and the drug was approved in November 2017.

Challenges of ERT

Neurocognitive Disease

The neurocognitive burden that MPS patients face is one which has yet to be addressed therapeutically. CNS damage tends to be irreversible and the selective permeability of the blood-brain barrier (BBB) limits the extent to which systemic treatments can penetrate the CNS and prevent neurodegeneration.²⁹ ERT remains unsuccessful at improving cognitive function because of its inability to cross the BBB. Efforts to overcome this limitation are being utilized to (1) design novel enzymes that can cross the BBB, (2) use receptors or transporters expressed by cells in the BBB, (3) use different routes of administration of enzyme, and (4) develop new therapies (i.e., gene therapy and small molecules).

Hematopoietic stem cell transplantation and ERT combination therapy has been shown to improve patient's condition before the transplant. In a pediatric cohort of MPS I patients, administration of ERT prior to HSCT has shown improved cognitive outcomes due to increased permeability of the BBB.^{30,31} Another approach is to administer high-dose ERT to facilitate transit of the enzyme across the BBB. Use of high-dose of laronidase (11.6 mg/kg/week for 4 weeks) in the Hurler mouse model showed increased enzyme activity in the mouse cortex to 97% of that in wild-type mice.³² In addition, a preclinical study done in mice utilized a dose-dependent approach in ultimately administering a systemic high-dose in the MPS II mouse model.³³ This study showed that administering a high-dose of enzyme to young mice for a longer period of time was the most effective in improving CNS defects. Parameters utilized in this study to assess CNS improvement were brain GAG levels, brain histopathology for vacuolization, and Lamp-2 staining, all of which were most decreased in the treatment group with the highest dose, longest treatment time, and youngest initiation of therapy.³³ MPS VII studies in mice have also shown that high dose of enzyme could cross the BBB and improve glia and neocortical neurons.³⁴ Thus, early application of high-

dose ERT may play a role in reducing CNS GAG accumulation, and may prove to be a treatment option for MPS patients suffering from CNS involvement.

Systemic administration of chemically modified enzymes in MPS VII mice has been shown to extend circulating half-life and improve clearance of GAG accumulation in several tissues including the brain.³⁵ Also, fusion proteins that could enhance the ability of a large enzyme to cross the BBB have been explored in MPS I, MPS II, and MPS IIIB (i.e., monoclonal antibody against the human insulin or transferrin receptor and insulin-like growth factor-II).^{36–38} Finally, new approaches like direct delivery of ERT via the cerebrospinal fluid by intracerebroventricular or intrathecal injection, or via the parenchyma by intracerebral injections, seem to be, although highly invasive, promising in ameliorating the neurodegeneration in MPS.^{29,39,40}

Cardiovascular Disease

With the increased lifespan of MPS patients, cardiac abnormalities are becoming an increasingly important cause of morbidity. Cardiac abnormalities exist in all MPS types. A study comparing 33 MPS patients with pediatric and adult controls showed that carotid intima-media thickness (as measured by carotid artery ultrasonography) was significantly greater in MPS patients than both pediatric and adult controls.⁴¹ Additionally, this study showed increases in adjusted arterial stiffness measurements such as reduced carotid artery distensibility and compliance.

A study of 28 Taiwanese patients with MPS I, II, IVA, and VI assessed the impact of ERT on their cardiac abnormalities.⁴² While cardiac hypertrophy, as measured by interventricular septum thickness in diastole and LVM index, was effectively reduced in these patients, valvular defects showed little improvement. Additionally, the improvements in cardiac hypertrophy were only observed in those patients starting ERT before 12 years of age. It is thought that GAG removal from cardiac valves is a challenge because the myofibroblasts which compose the valves are supplied with oxygen primarily through diffusion. Thus, it remains difficult for the larger ERT enzymes to access and enter these cells.⁴³ While the impact of MPS on cardiovascular function has been described, the effects of ERT on these parameters are unclear.

Skeletal Disease

Currently available ERTs show limited delivery to the skeletal manifestations of the disease. Optimization of enzymes or combination of treatments could be the best approach to reach some improvement in these hard-to-reach tissues.^{31,44}

Although early administration of ERT has been reported to stop the progression of the skeletal disease in patients with MPS and even improve growth,^{23,45–49} some studies have shown that ERT does not have any effect in bone even if the enzyme is administered early.⁵⁰ Interestingly, studies in MPS VI and VII mice indicated that ERT can prevent vertebral and facial bone abnormalities, but cannot reverse progressive deformities.^{51,52} Long-term ERT follow-up may provide answers regarding the effectiveness of ERT on growth for different MPS disorders.

Immune Response to Enzyme Replacement Therapy

While high-dose ERT in mice has not shown significant hypersensitivity responses, there are many adverse effects to consider for application to humans.³² The immune response to ERT seen in some patients, which ranges from mild to life-threatening hypersensitivity reactions, is another challenge in the efficacy of ERT. These immune-mediated reactions include anaphylaxis and type III hypersensitivity responses, both of which present as urticaria, rash, and bronchospasm.⁵³

In addition to the adverse immune responses associated with ERT, there is also the concern for a decrease in ERT efficacy. Immune response to ERT has been extensively studied in other LSDs such as Gaucher disease. Initially, most patients with Gaucher disease who underwent treatment did not have significant antidrug antibodies, which is thought to be due to the presence of residual enzyme activity in these patients that tolerized their immune systems to ERT. However, it has been observed that those patients with the least enzyme activity often have the worst antidrug-antibody reactions to ERT.⁵³ This became evident with the treatment of MPS VI, from which patients had a decrease in their response to ERT due to immune responses.⁵⁴

Current management strategies for immune responses to ERT include a low infusion rate, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), or steroid treatment. However, chronic usage of these drugs, such as NSAIDs, has its own adverse effects. Ultimately, immune response to ERT is an issue that must be addressed for better efficacy and safety of ERT.

Access and Cost of Enzyme Replacement Therapy

Treatment of rare diseases such as ERT is typically extremely expensive due to low prevalence of the indication, small number of patients, expensive surveillance programs imposed by regulatory authorities, and absence of alternative treatments.^{22,55} The average annual cost of ERT for MPS IVA, which affects ~800 people in the United States, is \$555,360. While Medicare Part B and D cover home drug infusion therapies, they do not cover nursing services, supplies, or equipment. Rare disease therapies such as ERT for MPS are challenges for the current state of Medicare and Medicaid. To compound this issue, there is not yet enough data to correctly answer whether or not ERT for certain MPS, such as MPS IVA, is cost-effective, as not enough time has passed to calculate the number of quality-of-life years gained from ERT.

Future of Enzyme Replacement Therapy

Early Initiation of Enzyme Replacement Therapy

Many studies have shown that early initiation of ERT in MPS patients has led to the best outcomes. One sibling study of two Japanese MPS VI patients illustrates the stark difference in outcomes between those patients beginning ERT early in infancy and those beginning later in childhood.⁵⁶ The siblings began ERT at 5.6 years and 6 weeks of age, and both were followed up after 10 years of undergoing treatment.

The report found that the older sibling (began ERT at 5.6 years of age) exhibited significant improvement in shoulder range of motion, but still had typical MPS VI phenotypic features. The younger sibling (began ERT at 6 weeks of age), however, did not exhibit many of the typical symptoms of MPS VI, such as progressive dysmorphic facial features, hepatosplenomegaly, and hearing impairment. The younger sibling was observed to have skeletal deformity, however, suggesting that while early initiation of ERT is effective in slowing MPS VI disease progression, it still has minimal effects on bone symptoms.⁵⁶ This report supports that initiating ERT as early as possible is important in optimizing ERT; thus, newborn screening for MPS would be extremely useful in doing so.

Immune Tolerance Induction

Recently, a method that prevents IgG-mediated immune responses in patients with infantile-onset Pompe disease using immune tolerance induction methods has been developed.⁵³ This is a safer alternative than immunosuppressing patients, or using chronic anti-inflammatory agents. This method, however, is not yet being utilized in other LSDs. Similar efforts to minimize immune response to ERT in MPS patients are ongoing, and will be necessary to increase efficacy of treatment, as well as decrease allergic symptoms. Currently, novel methods to decrease immune response to ERT are being developed.^{57,58}

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