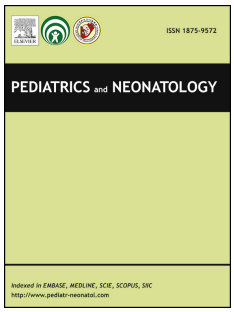

Current and new therapies for mucopolysaccharidoses

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Current and new therapies for mucopolysaccharidoses

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ABSTRACT

The mucopolysaccharidoses (MPSs) are a subset of lysosomal storage diseases caused by deficiencies in the enzymes required to metabolize glycosaminoglycans (GAGs), a group of extracellular heteropolysaccharides that play diverse roles in human physiology. As a result, GAGs accumulate in multiple tissues, and affected patients typically develop progressive, multi-systemic symptoms in early childhood. Over the last 30 years, the treatments available for the MPSs have evolved tremendously. There are now multiple therapies that delay the progression of these debilitating disorders, although their effectiveness varies according to MPS sub-type. In this review, we discuss the basic principle underlying MPS treatment (enzymatic "cross correction"), and we review the three general modalities currently available: hematopoietic stem cell transplantation, enzymatic replacement, and gene therapy. For each treatment type, we discuss its effectiveness across the MPS subtypes, its inherent risks, and future directions. Long term, we suspect that treatment for the MPSs will continue to evolve, and through a combination of early diagnosis and effective management, these patients will continue to live longer lives with improved outcomes for quality of life.

Keywords: mucopolysaccharidoses (MPS), enzyme replacement therapy (ERT), gene therapy (GT), hematopoietic stem cell transplant (HSCT), glycosaminoglycans, lysosomal storage disease

INTRODUCTION

The lysosomal storage diseases (LSDs) represent a broad class of metabolic disorders with multisystemic features, reflecting the critical role of the lysosome in intracellular turnover, nutrient sensing, and calcium storage[1]. Although individually rare, LSDs likely affect greater than 1 in 5,000 live births[2], making this class of monogenic diseases as prevalent as some disorders with far more complex genetic architectures (ex: Systemic Lupus Erythematous[3]). First described in 1917[4], the mucopolysaccharidoses (MPSs) represent a sub-class of LSDs that affect the degradation of glycosaminoglycans (GAGs), a group of extracellular heteropolysaccharides that provide structural support for a variety of tissues[5–7], in addition to playing more complex roles in neurodevelopment[8], inflammation[9], and tumor progression[10]. MPSs are caused by a deficiency in one of the 11 lysosomal acid hydrolases required for the intracellular degradation GAGs[11]. This subsequently leads to an accumulation of GAGs in various tissues, ultimately causing a range of systemic, often progressive symptoms (including skeletal, cardiopulmonary, hematologic, ocular, auditory, and neurocognitive abnormalities). The precise symptoms observed vary according to the enzyme affected and the severity of the biochemical deficiency[12], but to simplify diagnosis and management, MPSs are generally categorized into one of seven sub-types based on the enzyme involved and the GAGs that accumulate (**Table 1**).

Treatment for the various MPSs lagged their discovery for many decades. However, in 1968, Elizabeth Neufeld and colleagues made a critical observation: culturing fibroblasts from MPS I and MPS II-affected patients in medium isolated from unaffected cells could normalize intracellular GAG levels[13,14]. This finding indicated that the deficient enzyme, when provided exogenously, could correct the metabolic defect in MPS-affected cells. Importantly, this result suggested that MPS progression could be delayed or potentially even terminated by providing the deficient enzyme to affected patients. This hypothesis, also known as “cross-correction,” provides the framework for the modern MPS therapies, each of which uses a different modality to exogenously provide the deficient enzyme. In this review, we summarize the three different modalities for MPS therapy: hematopoietic stem cell transplantation

(HSCT), enzyme replacement therapy (ERT), and gene therapy (GT). For each, we briefly review its history, efficacy, challenges, and future directions.

Hematopoietic stem cell transplantation

Based on the seminal work of Neufeld and colleagues[13–15], it was hypothesized that bone marrow transplantation (BMT) could be used to treat the mucopolysaccharidoses through a process called "cross-correction." More specifically, after undergoing BMT or another form of hematopoietic stem cell transplantation (HSCT), an MPS patient's native hematopoietic cells are replaced by a graft, which produces functional enzyme. This graft then circulates throughout the body, filling the various niches vacated by the patient's native immune system. These niches include tissue-resident macrophages, particularly within the central nervous system (CNS). These engrafted cells then secrete the functional enzyme, which is endocytosed by native, local cells[16]. In this manner, BMT provides exogenous enzyme for MPS patients, bypassing their inherited metabolic defect.

The first BMT to treat a form of MPS was performed in 1981[17]. The patient was a 1-year-old male with Hurler Syndrome, who was diagnosed based on multiple clinical findings (skeletal anomalies, course features, corneal clouding, hepatosplenomegaly) in the setting of conclusive biochemical evidence (deficient alpha-L-iduronidase enzymatic activity plus elevated urine dermatan and heparin sulfate). Following successful engraftment, near-normal levels of alpha-L-iduronidase enzymatic activity were detected in the patient's leukocytes, and urine GAG concentrations fell accordingly. Overall, these findings were consistent with the secretion of functional enzyme by the patient's transplanted hematopoietic cell lines. Clinically, the patient's corneal clouding and hepatosplenomegaly resolved, and other disease findings (ex: macrocephaly, intellectual disability) appeared to arrest[17]. Since this successful proof-of-principle, HSCTs have been performed in hundreds of MPS patients, and positive clinical outcomes have been reported for several of the sub-types[16].

HSCT has proven most successful for the treatment of the most severe form of MPS I, often referred to as Hurler Syndrome (MPS IH). Since the first successful BMT in 1981[17], well over 200 MPS

IH patients have received HSCTs, and the positive clinical outcomes are well documented[18–23]. The survival benefit among HSCT-treated MPS IH patients is striking. Prior to the introduction of this treatment, MPS IH was generally fatal in early childhood. Following successful HSCT, MPS IH patients can now survive well into adulthood. In one cohort, over 50% of MPS IH patients were alive 10 years after transplant, with most of the mortality occurring within the first year[20]. Given improvements in HSCT protocols over the last three decades, it's likely that the long-term survival among transplanted MPS IH is now much higher[24,25]. Furthermore, the benefits observed among transplanted MPS IH patients are not limited to life expectancy. Consistent with the ability of transplanted monocytes to cross the blood-brain-barrier, neurocognitive outcomes among transplanted MPS IH are substantially improved[18,23], although most patients show some degree of neurodevelopmental delay. Other organ systems are also positively impacted in transplanted MPS IH patients including the musculoskeletal, ophthalmologic, cardiac, and pulmonary. There still remains substantial disease burden necessitating frequent medical interventions[18,21,22]. Nevertheless, HSCT is now considered the first-line therapy for MPS IH, in particular because of its positive impacts on neurocognition.

The utility of HSCT has been demonstrated for other MPS subtypes as well. HSCT was first performed for MPS II (also known as Hunter Syndrome) in 1986[26]. Since then, at least one hundred patients with Hunter Syndrome have been successfully transplanted with clear improvement in biochemical disease markers and somatic symptoms[27,28]. Early studies suggested HSCT did not alter neurocognitive outcomes in this disorder[29,30], so when enzyme replacement therapy was approved by the FDA in 2006, it largely supplanted HSCT as the standard of care due to its overall lower risk for morbidity and mortality. However, more recent analyses suggest some potential benefits from HSCT for neurocognitive outcomes in MPSII[27,31–33], although the evidence is mixed. HSCT is used as the primary treatment for neuronopathic MPS II in China due to ERT access limitations, and in Japan[28], and it is an optional therapy provided that the procedure is performed early in the disease course[34].

While the benefits of HSCT in MPS IH and MPS II are clear, a role for this therapy in other forms of MPS is less certain[16]. For example, MPS III (also known as Sanfilippo Syndrome) is primarily

characterized by progressive neurocognitive decline without substantial somatic symptoms. Early studies showed that HSCT had no impact on MPS III-related neurodegeneration[35], but more recent work suggests that a positive response may be possible[36,37], particularly when the transplant is performed early. The evidence for positive outcomes after HSCT for the other forms of MPS (MPS IV, MPS VI and MPS VII) is similarly sparse and conflicting[16], but it suggests that symptomatic improvement can occur. However, it remains unclear which patients stand to benefit most relative to the risks of morbidity and mortality, and therefore, HSCT is not often performed for these other forms of MPS.

Long term, HSCT will likely continue to play a prominent role in the treatment of MPS. Many of the risks associated with the procedure such as graft rejection, graft vs host disease, and overall mortality have been reduced over the last 20 years through innovations in HSCT protocols[23,24,36,38,39], although mortality remains in the 5-10% range even in highly experienced centers[20]. Nevertheless, the role of HSCT as a primary therapy for MPS will likely decrease as other modalities like enzyme replacement and gene therapy evolve, particularly as these therapies become more effective at crossing the blood-brain-barrier. As other therapies improve, HSCT may play more of an adjunctive role in the treatment of MPS. For example, as patients develop immune intolerance to certain enzyme replacement or gene therapies, HSCT can be performed to re-induce tolerance[40]. There is also limited evidence to suggest a synergistic effect between HSCT and other treatment modalities[27,41]. Finally, autologous hematopoietic stem cells can even serve as the mechanism of delivery for gene therapy[42]. Therefore, HSCT will likely continue to play a prominent role in the treatment of MPSs, even as alternative therapies become more effective.

Enzyme replacement therapies

Enzyme replacement therapies (ERTs) constitute first-line treatment for several of the mucopolysaccharidoses. The principle behind this approach is to replace the missing enzyme by periodically providing it intravenously (or intrathecally). Each enzyme is produced with recombinant DNA technology. A clone DNA (cDNA) construct for the gene (*IDUA*, for example) is introduced into a host (human fibroblasts or animal cell lines). The host is then cultured to produce multiple copies of the

incorporated DNA fragment. The recombinant enzyme is then purified from the host, yielding a supply of missing enzyme that can be exogenously provided to patients[43,44] . Currently, ERTs have been approved for use in most of the MPSs, including MSP I, MSP II, MSP IVA, MSP VI and MSP VII[44,45].

The first human ERT trial for MPS began in 1997. It was led by Dr. Emil Kakkis, Dr. Elizabeth Neufeld, and colleagues. Similar to HSCT, it targeted MPSI[46]. Ten patients, aged 15-22, were treated with recombinant α-L-iduronidase, and outcomes were measured over one year. The results from this benchmark study showed a significant improvement in peripheral (non-CNS) systemic symptoms. Treated patients showed improvements in mobility, increases in linear growth velocity, reductions in liver volume, and reduced urine glycosaminoglycans. Recombinant Iaronidase (Aldurazye®) was subsequently approved by the FDA in 2003. Since then, ERTs have also become available for MPS II (Hunter syndrome; 2006), MPS VI (Maroteaux-Lamy syndrome; 2005), MPS IVA (Morquio A syndrome; 2014) and MPS VII (Sly syndrome; 2017) (**Table 2**)[44,45,47–51].

For ERT to be successful, it must be delivered to the affected tissues. The enzymes have a short half-life in circulation, but they quickly bind to mannose-6-phosphate receptors for cellular uptake, and previous studies have demonstrated that these enzymes effectively penetrate visceral organs like the liver, spleen, and kidney. As a result, ERT administration results in clinical and biochemical improvement for patients with MPSs, resulting in significant improvements to their quality of life[44]. However, these enzymes tend be less effective at penetrating bone, cartilage, and ocular tissues[44], which in part explains the limited clinical improvement in the skeletal symptoms observed in MPS patients, even after long-term ERT. Moreover, ERT does not readily penetrate the blood-brain barrier, making it an ineffective treatment for central nervous system (i.e. neuronopathic) disease.

Beyond reduced efficacy for some manifestations, ERT has other downsides that reduce its clinical utility. First, it is a life-long therapy that requires weekly (or bi-weekly) intravenous infusions, which often take somewhere in the range of 3-5 hours to administer. Although most patients tolerate the infusions well, this treatment certainly places a burden on patients and their families. Infusions generally need to be started in a hospital setting to monitor adverse events. Once deemed safe, patients can be

transitioned to home infusions. In addition, ERT can cause immune reactions in some patients, which are often managed with pre-medications and/or changes to the infusion protocol. However, rare patients develop neutralizing or cell uptake blocking antibodies to the infused enzyme, decreasing its efficacy over time.

To improve the efficacy of ERT for MPS, there are active efforts to develop therapies with improved penetration for high-risk tissues, in particular the skeletal and central nervous systems[52–54]. Regarding the central nervous system, there are several completed and active clinical trials evaluating different strategies for ERT delivery to this tissue. For example, one possible approach is to provide the enzyme directly to the target tissue, either via intrathecal or intracerebroventricular delivery. A phase II/III clinical trial investigated the efficacy of intrathecal idursulfase to treat patients with neuronopathic MPS II[54]. Although the primary endpoint was not met (a significant improvement in cognitive function), there was a trend toward cognitive benefits in some patients. Recently, a phase I/II trial showed that idursulfase beta delivered via the intracerebroventricular route effectively increased developmental age[53], resulting in its approval for use in neuronopathic MPS II in Japan.

Alternatively, there are several therapeutics in active clinical trials that use novel fusion proteins to drive a peripherally delivered enzyme directly across the blood-brain-barrier (BBB). This method, also called the “Trojan-Horse” hypothesis, was first proposed by Dr. William Pardridge[55]. The exogenous enzyme is fused to an antibody or peptide that binds to an endothelial receptor, which facilitates its transfer across the blood-brain-barrier. Different companies have since leveraged this idea to produce new recombinant enzymes potentially capable of treating neuronopathic forms of MPS. For example, recombinant fusions enzymes that bind the insulin receptor were developed by Armagen, Inc. for MPS I and MPS II[56,57], but clinical efficacy was never demonstrated. Since then, both JCR pharmaceuticals and Denali have developed exogenous iduronidate-2-sulfatase fused to peptides that bind the transferrin receptor. Phase I/II studies for these therapeutics are currently underway (trial NCT04227600), NCT03128593, NCT04251026) and Phase 2/3 studies have been initiated in U.S. and Europe. A phase 2/3 study in Japan of recombinant iduronate-2-sulfatase, Pabinafusp-Alfa (IZCARGO®), for the

treatment of MPS II resulted in local drug approval after 28 patients experienced significant reductions of heparan sulfate concentrations in cerebrospinal fluid. The study also supported improvement in somatic symptoms[58].

In summary, ERT has dramatically changed the treatment of MPSs. Hundreds of patients around the world are receiving these medications, and as a result, have improved systemic symptoms and quality of life. Given its efficacy and overall positive safety profile, ERT will continue to be an effective option for systemic disease in amenable MPS patients. However, despite great advances, there continue to be a lack of treatment options for some forms of MPSs, especially those with CNS manifestations. In addition, there continues to be demand for MPS therapeutics that do not require lifelong treatment.

Gene therapy

In some ways, ERT and HSCT are imperfect therapies for MPS. They both provide exogenous enzyme to the affected patients, but neither is fully effective. In addition, each is associated with unique challenges and morbidities. Gene therapy (GT) is a promising approach to treat the MPSs, as it could provide a way to permanently replace the deficient enzymes. Gene therapy is a procedure in which genetic material (genomic DNA, coding DNA or RNA) is inserted into human cells to either: 1) correct the underlying molecular error or 2) exogenously express the deficient enzyme. Once done, the patient's own cells begin producing the desired enzyme, bypassing their underlying metabolic defect. The critical hurdle with respect to GTs is delivery. Typically, this is done with therapeutically engineered viruses, for example, a modified adeno-associated virus (AAV)[59]. Such vectors can be delivered directly to the CNS (brain or spinal cord), or into the bloodstream (*in vivo* administration)[60]. Alternatively, the target cells can be removed from the body, transfected with the molecular therapeutic *ex vivo*, and then provided back to the patient[61]. Both strategies are viable, and there are currently multiple ongoing MPS GT trials using both approaches (**Table 3**).

For MPS I, there are two ongoing phase I/II GT trials: one *ex-vivo* and one *in-vivo*. The first is for a therapeutic called RGX-111. RGX-111 is manufactured by REGENEXBIO, and it delivers a copy of α-l-iduronidase (*IDUA*) gene packaged into an AAV-9 vector and administered directly into the CNS. The trial's endpoints are safety, biomarker reduction, and improvements in neurodevelopmental outcomes. Preliminary data is promising. Thus far, 5 patients have been successfully dosed, and no serious drug-related adverse events have been reported. Biomarker and neurodevelopmental assessments also indicate an encouraging CNS response (Press release: https://regenxbio.gcs-web.com/news-releases/news-release-details/regenxbio-presents-positive-initial-data-phase-iii-trial-rgx-111). The other ongoing phase I/II GT trial for MPS I is an ex-vivo therapy (OTL-203) developed by Orchard Therapeutics. OTL-203 is an investigational autologous hematopoietic stem cell approach. Autologous hematopoietic and progenitor cells are transduced *ex vivo* with a lentiviral vector encoding the *α*-l-iduronidase (*IDUA*) gene. Following transfection, the genetically engineered cells are re-administered to the patient via an autologous HSCT. This therapy was provided to 8 patients with MPS IH after myeloablative conditioning. Interim results showed a safety profile like autologous HSCT: all patients showed prompt, sustained engraftment and supraphysiological blood and CSF IDUA levels. Both urine and CSF GAGs decreased appropriately, and patients showed stable neurocognitive performance with ongoing motor development[42].

For MPS II, RGX-121 is an investigational, one-time GT designed to deliver the gene that encodes the iduronate-2-sulfatase (I2S) enzyme using an AAV-9 vector. A trial for this therapeutic is currently underway. At this time, the primary endpoint is to evaluate safety only, but secondary and exploratory endpoints include α-iduronate-2-sulfatase (I2S) enzymatic biomarkers (in the CSF, serum and urine), neurodevelopmental assessments, and caregiver reported outcomes. RGX-121 is administered directly to the central nervous system (CNS). Thirteen patients have been enrolled so far, and preliminary results were presented at the annual WORLDSymposia (Press release: https://www.prnewswire.com/news-releases/regenxbio-presents-additional-positive-interim-data-from-phase-iii-trial-of-rgx-121-for-the-treatment-of-mps-ii-hunter-syndrome-at-18th-annual-worldsymposium-2022-301478792.html). Thus far, no drug-related serious adverse events have been reported. Moreover,

patients are reported to have a reduction in CNS-relevant biomarkers, improvement in caregiver reported outcomes, and positive trends in neurodevelopment.

MPS-related GT is a very active area of research with multiple ongoing trials (**Table 3**)[60]. The approach is overall promising and could provide a permanent, more effective approach to treating these diseases. However, GT, like any novel therapeutic, has potential limitations, risks, and unique challenges. For example, engineered AAVs are the most common vector used for *in vivo* MPS-related GT delivery. Rather than modifying a host's genome through insertion (and increasing the risk for genotoxicity), these vectors form stable, intracellular double-stranded DNA episomes, which express the target enzyme using the host cell's transcriptional machinery[59]. Using this technology to express lysosomal enzymes in not necessarily straightforward. The vector needs to be large enough to hold and transport the molecular therapeutic, but must still escape immune clearance, pass through cell membranes, and promote high gene expression. The patient's own immune system presents a particularly unique challenge. The foreign genetic material (including the enzyme itself) can be recognized, attacked, and cleared following administration, causing therapy failure[62]. Not surprisingly, addressing these issues remains a very active area of investigation.

Other emerging therapies

Although enzymatic "cross-correction" remains the mainstay of modern MPS therapies, there are several new avenues for disease management, which may be used in conjunction with cross-correction (ex: anti-inflammatory medications) or as an alternative approach altogether (substrate reduction). Finally, given age-related differences in efficacy reported for treatments described above, fetal therapeutic approaches are also being explored. These are each reviewed briefly below.

Anti-inflammatory therapy

Historically, the clinical manifestations of the MPSs were attributed directly to the accumulation of GAGs in tissues. However, there is ongoing recognition that GAG accumulation also leads to immune

dysfunction and inflammation[63]. In animal models, GAG continues to accumulate despite ERT, leading to a pro-inflammatory state. Elevated pro-inflammatory cytokines have since been replicated in treated MPS patients[64], suggesting that ongoing symptoms may be due to local and systemic inflammation. Adalimumab, a TNF-α inhibitor, is being investigated as a therapeutic for MPS in a randomized, double-blind, placebo-controlled study. The objective is to determine the effects of this immunomodulator on skeletal disease in children and adults with MPS I, II and VI. A pilot study showed some improvement in physical function and pain[65], and as a result, a phase I/II trial is now ongoing (NCT03153319).

Substrate reduction therapy

Substrate reduction therapy may also be an alternative treatment for MPS patients[66]. Substrate reduction works by inhibiting the synthesis of the compounds that cannot be degraded in patients with enzymatic defects (for example, GAGs in the MPSs). Clinical studies were performed for Genistein, a isoflavone that reduces the synthesis of multiple GAGs[67]. An open-label pilot study evaluating the effectiveness Genistein was completed on 10 patients with MPS IIIA or MPS IIIB. Patients were treated for 12 months with a genistein-rich soy isoflavone extract with no adverse effects and improvements in urinary GAGs and cognitive function[68]. However, follow-up randomized and controlled trials did not replicate these results[69,70]. Therefore, SRT remains a potential therapeutic approach, but currently, no effective medication is known to exist.

Fetal therapies

It is critical for the success of new therapies to be implemented early in the disease course before severe damage occurs. For example, HSCT has consistently been shown to be more effective in younger children. Because fetuses with MPS are at increased risk for perinatal morbidity and mortality, the administration of enzyme therapy in-utero has the potential to improve outcomes. Investigators at the University of California San Francisco are assessing the safety and feasibility of in-utero ERT for MPSs in an ongoing Phase I trial (NCT04532047). In utero ERT may lead to more sustained immunotolerance,

resulting in more effective long-term treatment. It also may lead to improved neurodevelopmental outcomes due to its administration during critical periods of development[71].

CONCLUSIONS

The MPSs are progressive, debilitating diseases that impact the quality of life for patients and their caregivers[72,73]. An increased understanding of MPS pathophysiology and natural history, combined with interventions like HSCT and ERT, have led to improved survival and reduced morbidity. However, several unmet needs remain, particularly therapies that effectively treat the neurodevelopmental and skeletal symptoms. We anticipate that some of the treatments discussed above will soon make headway on this problem. However, there remain MPS sub-types, specifically MPS III, that entirely lack effective therapies. More research is certainly needed to help these patients. Beyond new treatments, improvements in disease diagnosis should also improve outcomes. For example, MPS-related newborn screening is increasingly being implemented. When appropriately administered, this should enable earlier treatment initiation with better results[74]. Moving forward, we believe that multidisciplinary treatment, in conjunction with improved therapies, will result in longer and better lives for our MPS patients.

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Table 1. Mucopolysaccharidoses summary of conditions and available treatments.

MPS type	Common name	Gene	GAG	ERT /HSCT
MPS I	Hurler, H-S, Sheie	*IDUA*	DS, HS	+/+
MPS II	Hunter	*IDS*	DS, HS	+/-
MPS III	Sanfilippo A,B,C,D	*GNS, HGSNAT, NAGLU, SGSH*	HS	-/-
MPS IV	Morquio A,B	*GALNS* *GLB1*	KS, CS KS	+/-
MPS VI	Marateaux-Lamy	*ARSB*	DS	+/-
MPS VII	Sly	*GUSB*	DS, HS, CS	+/-
MPS IX	Hyaluronidase deficiency	*HYAL1*	HA	-/-

MPS mucopolysaccharidoses, HS Heparan sulfate, DS dermatan sulfate, KS keratan sulfate, CS chondroitin sulfate, HA hyaluronic acid, H-S Hurler-Sheie, ERT enzyme replacement therapy, HSCT hematopoietic stem cell transplant

Table 2. Enzyme replacement therapy summary.

	MPS I	***MPS II***				***MPS IVA***	***MPS VI***	***MPS VII***
Enzyme deficiency (gene)	Alpha-L-iduronidase (IDUA)	Iduronidate-2-sulfatase (IDS)				N-acetylgalactosamine-6-sulphatase (GALNS)	N-acetylgalactosamine-4-sulphatase (ARSB)	Beta-glucoronidase (GUSB)
Drug	Laronidase	Recombinant idursulphase	Recombinant iduronate-2-sulfatase	Recombinant idursulphase-beta	Recombinant idursulphase-beta	Recombinant elosulphase-alpha	Galsulphase	Vestronidase alfa
	Aldurazyme®, Genzyme.	Elaprase®, Takeda.	IZCARGO®, JCR Pharma.	Hunterase® IV, CANbridge	Hunterase® ICV, GC Pharma.	Vimizim®, BioMarin	Naglazyme®, BioMarin	MEPSEVII®, Ultragenyx
	Available since 2003.	Available since 2006.	Available since 2021.	Available since 2012. Approved in Republic of Korea*	Available since 2021. Approved in Japan.	Available since 2014.	Available since 2005.	Available since 2017 in the USA.
Dosage	0.58 mg/kg, once a week. Delivered in 3-4 hours.	0.5 mg/kg, once a week. Delivered over 3 hours, can be shortened to 1 hour if no reactions.	2.0 mg/kg/dose, once every 2 weeks.	0.5mg/kg/dose, once a week	0.5mg/kg/dose ICV, every 4 weeks	2 mg/kg, once a week. Delivered over 4 hours.	1 mg/kg, once a week. Delivered over 4 hours.	4 mg/kg, once every 2 weeks. Delivered over 4 hours.

ICV=intracerebroventricular injection, *Hunterase IV is also approved in more than 10 countries worldwide.

Table 3. Current statuses of ongoing GT clinical trials for MPSs

DISEASE	PRODUCT	COMPANY	VECTOR	INJECTION ROUTE	STATUS (PHASE)	NCT NUMBER
MPS I	OTL-203	Orchard	Ex-vivo HSC/IDUA	IV	I/II	NCT03488394
	RGX-111	Regenxbio	AAV9/IDUA	IC	I/II	NCT03580083
MPS II	RGX-121	Regenxbio	AAV9/IDS	CNS	I/II	NCT04571970
	HMI-203	Homology	AAVHSC/IDS	IV	I	NCT05238324
MPS IIIA	LYS-SAF302	Lysogene	AAVrh10/SGSH	IC	II/III	NCT03612869
	ABO-102	Ultragenyx	AAV9/SGSH	IV	I/II	NCT04360265
	OTL-201	Orchard	Ex-vivo HSC/SGSH	IV	I/II	NCT04201405
MPS VI	AAV8/ARSB	Fondazione Telethon, Italy	AAV8/ARSB	IV	I/II	NCT03173521

CNS = central nervous system, IV=intravenous, IC=intracerebral