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Therapy for the mucopolysaccharidoses

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Abstract

Better understanding of disease pathophysiology, improved supportive care and availability of disease-specific treatments for some of the mucopolysaccharidosis (MPS) disorders have greatly improved the outlook for patients with MPS disorders. Optimal management of these multisystemic disorders involves a multidisciplinary team and regular, comprehensive follow-up. Enzyme replacement therapy (ERT) is now available for MPS I (Hurler, Hurler–Scheie and Scheie syndromes) (laronidase), MPS II (Hunter syndrome) (idursulfase) and MPS VI Maroteaux–Lamy (galsulfase), and is in development for MPS IV (Morquio syndrome) and MPS VII (Sly syndrome). Benefits of ERT can include improved walking ability, improved respiration and enhanced quality of life. Haematopoietic stem cell transplantation (HSCT) can preserve cognition and prolong survival in very young children with the most severe form of MPS I, and is under investigation for several other MPS disorders. Better tissue matching techniques, improved graft-*vs*-host prophylaxis and more targeted conditioning regimens have improved morbidity and mortality associated with HSCT.

Key words: Mucopolysaccharidosis type I, Mucopolysaccharidosis type II, Mucopolysaccharidosis type III, Mucopolysaccharidosis type IV, Mucopolysaccharidosis type VI, Enzyme replacement therapy, Haematopoietic stem cell transplantation, Laronidase, Idursulfase, Galsulfase.

Introduction

The mucopolysaccharidoses (MPSs) are lysosomal storage disorders caused by the accumulation of sulphated carbohydrate polymers in the lysosomes leading to a cascade of multisystemic disease manifestations. The sulphated polymers are composed of a central core protein attached to disaccharide branches deriving from sulphate monosaccharides or glycosaminoglycans (GAGs). The primary storage products are: dermatan sulphate, chiefly a constituent of conjunctive tissues; heparan sulphate, chiefly a constituent of cellular membranes; and keratan sulphate and chondroitin sulphate, found abundantly in the cartilages and in the cornea. GAG excretion in urine allows screening for MPSs quantitatively (elevated urinary GAG) and qualitatively (characteristic profile of sulphate derivatives) [1, 2].

Catabolic enzymes responsible for GAG degradation are defective in MPS disorders. Eleven enzymatic deficits are known to be responsible for seven different diseases (MPS I, II, III, IV, VI, VII and IX). All MPS disorders are progressive, multivisceral diseases that involve the musculoskeletal system (bones and joints), heart, lungs, eyes (cornea, retina and optic nerves), liver and spleen, and in some of the diseases, the CNS [1, 2].

During the last several decades, the outlook for patients with MPS disorders has improved considerably, with better understanding of their pathogenesis and natural history, advances in supportive care and finally, the availability of disease-specific treatments for some of the disorders. Table 1 summarizes current disease-specific treatment options for all of the MPS disorders. The two primary treatment modalities are enzyme replacement therapy (ERT) and haematopoietic stem cell transplantation (HSCT), both of which offer substantial benefit but do not cure the disease.

Due to the progressive nature of these diseases, early diagnosis and early therapeutic intervention is of major importance. Early treatment is supported by the pathophysiological mechanisms: disease progression is associated with organ damage that occurs through multiple, complex secondary pathways involving GAGs, rather than just GAG accumulation. This secondary damage is often irreversible. Clinical evidence also points to improved outcome with early intervention for MPS I and VI. Sibling case studies of MPS I, II and VI demonstrate much better

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Table 1 Current therapies for the MPS disorders[a]

	MPS I (Hurler, Hurler–Scheie and Scheie)	MPS II (Hunter)	MPS III (Sanfilippo Types A–D)	MPS IV (Morquio Types A and B)	MPS VI (Maroteaux–Lamy)	MPS VII (Sly)
Deficient lysosomal enzyme	α-L-iduronidase	Iduronate sulphatase	A: heparan *N*-sulphatase B: α-*N*-aceytylglucosaminidase C: acetyl-CoA: α-glucosaminide acyltransferase D: *N*-acetylglucosamine-6-sulphatase	A: galactose 6-sulphatase B: β-galactosidase	Arylsulphatase B	β-Glucuronidase
Substrate accumulated	Dermatan sulphate, heparan sulphate	Dermatan sulphate, heparan sulphate	Heparan sulphate	Keratan sulphate	Dermatan sulphate	Dermatan sulphate, heparan sulphate
Cognitive status	Varies from severe to no impairment	Varies from severe to no impairment	Impaired	Normal	Normal	Mildly impaired
Inheritance	Autosomal recessive	X-linked recessive (most patients are male)	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive
Estimated incidence (varies with population)	∼1 : 100 000 [39, 73–75]	∼1 : 100 000 [7, 73, 75]	∼1 : 25 000–75 000 [7, 75]	1 : 40 000–200 000 [7, 75]	1 : 240 000–400 000 [34, 75]	Not known
Available treatments						
ERT	Laronidase, somatic benefits [17–21]	Idursulfase, somatic benefits [22–24]	Clinical trials underway for Type A and in development for Type B	Clinical trials underway	Galsulfase, somatic benefits [27–33]	In development
HSCT	Recommended for Hurler patients before 2 years of age; can preserve cognition [7, 41]	Few data, mixed results, neurocognitive benefit unclear [7, 42]	Few data, mixed results, neurocognitive benefit unclear [7, 76–78]	Few data, mixed results [7, 79]	Few data, mixed results [7, 13, 43]	Few data, mixed results, neurocognitive benefit unclear [45]

[a]MPS IX, hyaluronidase deficiency [80], is not included as it is extremely rare. Although the molecular defect has been elucidated, there are no current therapies.

TABLE 2 Symptom-based interventions for MPS disorders

Symptoms	Management/treatment
Behavioural problems (in children with MPS III and severe MPS II)	Medications (mixed results [81, 82]) Create a safe environment by childproofing the home Address contributing issues such as poor hearing and lack of sleep
Bone	Orthopaedic surgery to correct spinal deformities, acetabular hip dysplasia, genu valgum
Cardiac valve disease	Valvular replacement Catheter balloon valvuloplasty
Carpal tunnel and trigger finger	Neurosurgical decompression surgery
Corneal clouding	Corneal transplant Corrective lenses
Deafness	Hearing aids Myringotomy with placement of ventilating tubes
Dental	Antibiotics and analgesics [74] Gum massage
Endocrine function	Human growth hormone (effects unproven) [11]
Gastrointestinal problems	Diet modification Gastronomy tube Pharmacological treatment with loperamide hydrochloride [82]
Joints	Physical therapy for strength and stiffness Hydrotherapy for stiffness and pain Splints to position joints and prevent flexion deformities
Language problems	Hearing aids and speech therapy
Learning disabilities	Standard interventions considering the patient's auditory, visual and motor issues
Hydrocephalus	Ventriculoperitoneal shunt
Spinal cord compression	Decompression surgery
Obstructive sleep apnoea/ airway obstruction/ respiratory involvement	Tonsillectomy Adenoidectomy Continuous positive pressure ventilation (CPAP and BiPAP) with oxygen enrichment Tracheotomy Asthma medications Antibiotics Nasal decongestants or isotonic or hypertonic saline solution
Otitis media	Myringotomy with placement of ventilating tubes
Umbilical and inguinal hernias	Hernia repair surgery

outcome for younger siblings diagnosed at birth and started on ERT in the first 6 months of life [3–6]. Earlier transplant is also associated with better outcome (lower mortality and morbidity [7], improved cognitive status [8, 9] and a lower incidence of CTS [10] in children with MPS I).

MPS disorders are best managed by a multidisciplinary team coordinated by a physician with experience in the treatment of these complex disorders. Both supportive and disease-specific treatments, if available, are important. Regular follow-up is essential to monitor disease progression and response to treatment [11–13]. It is also important to be aware of the considerable psychosocial burden of these chronic, debilitating and progressive conditions. Family and individual counselling can be helpful. Additionally, patient societies may provide invaluable networking opportunities for patients and families to share information and connect with others experiencing the same challenges.

Supportive, symptom-based treatments

Coordinated by an experienced physician, a comprehensive team of specialists such as neurosurgeons, orthopaedic surgeons, cardiologists, pneumologists, otorhinolaryngologists and physiotherapists is necessary to address the many comorbidities of these progressive diseases [11, 12]. Common MPS symptoms are listed in Table 2 along with supportive treatments.

Many complications of MPS disorders require surgical intervention. These include common surgeries such as hernia repair, adenotonsillectomy, carpal tunnel release and myringotomy as well as less common procedures such as heart valve replacement, decompression of cervical spinal cord, ventriculoperitoneal shunt and orthopaedic procedures to correct skeletal defects. Unfortunately, patients with MPS disorders are in general at high risk of anaesthetic and surgical complications

because of airway compromise due to GAG accumulation, enlarged tongue, joint stiffness, skeletal anomalies (short, stiff, unstable neck; odontoid dysplasia; spinal instability), susceptibility to respiratory infections, restrictive lung disease and cardiac disease [14]. Thus, it is recommended that general anaesthesia be avoided when possible and that when unavoidable, it be done by an anaesthesiologist with MPS experience [11, 12].

Disease-specific treatments

Today, ERT and HSCT are the standard of care worldwide for certain MPS diseases. The rationale for both treatments is to provide the patient with active enzyme to replace the enzyme that is deficient. In the case of ERT, it is supplied exogenously through regular infusions, and in the case of HSCT the enzyme is supplied endogenously through synthesis by the transplanted stem cells. An important distinction between these two treatments is that HSCT can treat the brain in some MPS disorders, especially if done early in the course of the disease, as stem cells can engraft and differentiate in the CNS. In contrast, infused ERT is too large a protein to cross the blood–brain barrier easily.

Clinical data on the effects of these two treatment approaches come from clinical trials, clinical and rare disease registries, and case series and case reports. When evaluating clinical trial data for rare disorders, it is important to recognize that the small number of patients available, the heterogeneity of disease expression and the short duration of most trials limit the kinds of analysis that can be performed [15]. Clinical registries such as the European Group for Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplant Research provide data on HSCT outcome. As longitudinal data amass, rare disease registries, such as the MPS I Registry [16] founded in 2003 and the Hunter Outcome Survey founded in 2006, will increasingly be a resource for long-term outcome analyses. Finally, case reports and case series can provide a valuable adjunct to clinical trial data by articulating benefits or drawbacks for patients and families not captured by trial end points. Case reports and case series also provide information about patient populations not included in clinical trials (e.g. patients who are diagnosed and treated pre-symptomatically due to family history or patients whose disease is too advanced to qualify for inclusion in a trial).

As these are progressive genetic diseases, response to any form of treatment is influenced by the severity of the disease phenotype (dictated by genetic and other factors) and the degree of disease progression at treatment initiation. Potential clinical benefit for these progressive diseases includes prevention, stabilization and retardation of disease progression, in addition to improvements in clinical status. Some benefits of treatment in certain MPS disorders, such as reduction of liver and spleen size and reduction of sleep apnoea typically occur within months of treatment initiation, whereas others occur more gradually (increased joint range of motion, mobility, endurance, decreased pain and improved quality of life) [17].

ERT

The treatment regimen for ERT involves i.v. infusions of the recombinant human enzyme weekly or every other week. ERT is a life-long therapy, and each infusion takes 1–4 h depending on the enzyme and the dose. There is the potential for severe infusion reactions; life-threatening anaphylaxis has occurred in some patients receiving ERT. Most infusions are given in a hospital setting because of this risk, but home infusions are reported to be feasible and safe for some patients. The feasibility of home therapy for any MPS patient should be based on a risk–benefit evaluation by the treating physician, the patient and the patient's care giver.

Initially, up to half of patients treated with ERT experience mild to moderate infusion-associated reactions (IARs) such as headache, flushing, fever and/or rash. These reactions usually can be managed by pre-treatment with anti-pyretics and/or anti-histamines and may decrease with time. The development of IARs generally coincides with an immune response to the enzyme protein and tends to occur more frequently as dosage increases [18].

ERT for MPS I (Hurler, Hurler–Scheie and Scheie syndrome)

Laronidase (recombinant human α-L-iduronidase; Genzyme Corporation, Cambridge, MA and BioMarin Pharmaceutical, Inc., Novato, CA, USA) was the first ERT approved for treatment of an MPS disorder and has been available in the USA and Europe since 2003. Four clinical trials have been conducted, encompassing patients of all phenotypes and an age range of 0.8–43 years (Table 3) [17–21]. Clinical benefits noted in the drug label include increased distance walked in the 6-min walk test, improved per cent predicted forced vital capacity (FVC), decreased liver volume and decreased (but not normalized) urinary GAG levels. Additional benefits experienced by the majority of patients in the pivotal randomized placebo-controlled trial and extension include stabilized or improved joint range of motion, stabilized or decreased sleep apnoea, decreased left ventricular hypertrophy and improved quality of life [17, 21]. A dose optimization study found that the labelled dose [0.58 mg/kg (100 U)/kg/week] appeared to offer the most favourable risk–benefit ratio, but that a double dose every 2 weeks could be an acceptable alternative regimen for patients who have difficulty receiving weekly infusions [18]. Approximately half of all patients experience at least one IAR and >90% of patients develop antibodies to laronidase. Life-threatening anaphylactic reactions have occurred in a small number of patients.

Two case series providing data from siblings who began treatment at different ages suggest that initiation of laronidase treatment in infancy, before the development of significant disease manifestations, may improve

Table 3 Clinical trial of enzyme replacement with laronidase for MPS I

	Phase 1/2 and extension [19, 83]	Under 5 years [20]	Dosing trial [18]	Phase 3 and extension [17, 21]
Study type	Open label	Open label	Randomized, open-label, dose-optimization	Randomized, double-blind, placebo-controlled with open-label, 3.5-year extension
Participants (*n*)	10 → 5	20	33	45 → 40
Phenotype distribution	80% Hurler–Scheie 10% Hurler 10% Scheie	20% Hurler–Scheie 80% Hurler	49% Hurler–Scheie 30% Hurler 21% Scheie	84% Hurler–Scheie 16% Scheie
Mean age at baseline, years	12.4 (range 5–22)	2.9 (range 0.8–5.1)	8.9 (range 1.4–20.7)	15.7 (range 6.3–43.3)
Dose	0.58 mg/kg (100 U)/kg/week	0.58 mg/kg (100 U)/kg/week	0.58 mg/kg (100 U)/kg/week 1.2 mg (200 U)/kg/week 1.2 mg (200 U)/kg/every 2 weeks 1.8 mg (300 U)/kg/every 2 weeks	0.58 mg/kg (100 U)/kg/week
Duration of study	1 year with 5-year extension	1 year	6 months	6 months with 3.5-year extension
Trial purpose/ end points	Safety Overall efficacy	Safety Global assessment of clinical status	Safety Dosing Urinary GAG Hepatomegaly	Change in per cent predicted FVC Distance walked in 6-min walk test
Other clinical measures evaluated	Urinary GAG Hepatomegaly Growth Shoulder flexion Apnoea/ hypopnoea NYHA class	Urinary GAG Hepatomegaly LVF Apnoea/hypopnoea Growth Cognition	6-min walk test	Urinary GAG Hepatomegaly Joint flexion Apnoea/hypopnoea index Visual acuity Quality of life Left ventricular hypertrophy Valvular disease Growth

outcome with respect to musculoskeletal disease [5], cardiac valve disease [5] and brain MRI abnormalities [4].

ERT for MPS II (Hunter syndrome)

Idursulfase (Shire Human Genetic Therapies, Inc., Cambridge, MA, USA), a recombinant form of human I2S, has been commercially available since 2006. Four clinical trials of idursulfase have been conducted in patients with MPS II, encompassing an age range of 5–53 years [22–25] (Table 4). No patient in the trials had baseline cognitive impairment. Benefits noted in the drug label are improved walking capacity, along with decreased liver and spleen volume and reduction (but not normalization) of urinary GAG levels [24]. In the pivotal trial, there was also a statistically significant improvement in a composite end point combining walking and respiratory benefits as measured by changes in per cent predicted FVC [24]. IARs occurred in over half of clinical trial participants and antibodies developed in 50% [22–24]. An analysis of 124 MPS II patients <6 years of age from the Hunter Outcome Survey who were treated with idursulfase identified no new safety concerns [26]. Life-threatening anaphylactic reactions have occurred in some patients during idursulfase infusions as well as biphasic anaphylactic reactions [23].

ERT for MPS VI (Maroteaux–Lamy)

Galsufase (Biomarin, Novato, CA, USA), a recombinant form of human arylsulphatase B, has been available since 2005. Three clinical trials of galsulfase have been conducted in patients with severe disease manifestations ranging in age from 5 to 29 years [27–33] (Table 5). Clinical benefits noted in the drug label are improvements in walking and stair climbing capacity and reductions (but not normalization) of urinary GAG excretion. Additional analyses of combined data from all three trials also found pulmonary benefit and improvements in growth [27–33]. In the clinical trials, over half of the patients experienced at least one IAR and 16% of patients experienced an IAR that was judged anaphylactoid (allergic type reactions that recurred during multiple infusions) [28]. Almost all patients develop antibodies to galsulfase [34]. A sibling case–control study suggested that early, pre-symptomatic intervention with galsulfase in infancy may improve outcome with respect to development of scoliosis, joint movement, cardiac valve disease and facial morphology [4].

Immune tolerance

Most MPS patients receiving ERT develop antibodies, as patients with these disorders have absent or very low residual enzyme activity and thus the normal active protein

Table 4 Clinical trials of enzyme replacement with idursulfase in MPS II patients

	Phase 1/2 trial [23]	Phase 2/3 trial and extension [24–25]	Japan Elaprase study [22]
Study type	Randomized, double-blind, placebo-controlled, followed by open-label study	Randomized, double-blind, placebo-controlled	Open-label, compassionate use
Participants (*n*)	12 males, no cognitive decline at baseline, all with moderately advanced disease	96 males, no cognitive decline at baseline, all with moderately advanced disease	10 men, all with advanced, attenuated disease
Mean age at baseline, years	14	14 (range 5–31)	Range 21–53
Dose	0.15 mg/kg/every other week 0.5 mg/kg/every other week 1.5 mg/kg/every other week	0.5 mg/kg weekly 0.5 mg/kg every other week	0.5 mg/kg weekly
Duration of study	6-month double-blind with 6-month open-label extension	1 year	1 year
Purpose/end point(s)	Safety Change from baseline in urinary GAG excretion	Composite end point of 6-min walk test and per cent predicted FVC based on the sum of the ranks of change from baseline	Urinary GAG levels 6-min walk distance Change in per cent predicted FVC
Other clinical measures evaluated	6-min walk distance Liver and spleen volume	Individual components of composite end point Liver and spleen volume Passive joint range of motion Quality of life	Joint range of motion Left ventricular mass index Ejection fraction Cardiac valve disease Sleep study oxygen desaturation index

Table 5 Clinical trials of enzyme replacement with galsulfase in MPS VI patients

	Phase 1/2 [31]	Phase 2 [29]	Phase 3 and extension [27–28]
Study type	Randomized double blind	Open label	Randomized, double blind, placebo controlled with open-label extension
Participants (*n*)	6	10	56
Mean (S.D.) age at baseline, years	12.0 (3.8) Range: 7–16	12.1 (5.3) Range: 6–22	Treated: 13.7 (6.5) Placebo: 10.7 (4.4)
Dose	0.2 mg/kg/week 1.0 mg/kg/week	1.0 mg/kg/week	1.0 mg/kg/week
Duration of study	48 weeks	48 weeks	24 weeks followed by 96-week extension
Purpose/end points	Safety Dosing Pharmacokinetics Urinary GAG excretion	Evaluation of efficacy variables of endurance, mobility and joint function	Distance walked in a 12-min walk test Number of stairs climbed in a 3-min stair climb Urinary GAG excretion
Other clinical measures evaluated		Distance walked in a 12-min walk test Number of stairs climbed in a 3-min stair climb Urinary GAG Shoulder range of motion FVC, forced expiratory volume	Growth [33] Pulmonary function [30]

infused by ERT is perceived as foreign. However, unlike some patients with Pompe disease (a lysosomal storage disease caused by a deficiency of the enzyme acid α-glucosidase) who lack cross-reactive immunologic proteins to recombinant enzyme (CRIM-negative) and some patients (also CRIM-negative) with haemophilia, patients with MPS disorders do not appear to develop neutralizing antibodies that negate the efficacy of the infused protein. Clinical trial data have not found a relationship between clinical outcome and antibody titre, although in some

severely affected patients with MPS I, antibody titre is inversely related to the reduction in urinary GAG level achieved. Data from the MPS I dog model suggest that immune tolerance might enhance treatment efficacy of laronidase. This possibility is being explored in an ongoing immune tolerance trial of MPS I Hurler patients who have not undergone transplantation and have two nonsense mutations (Clinicaltrials.gov identifier: NCT00741338), predicting a completely non-functional enzyme protein and a maximal immune response.

HSCT

The first successful bone marrow transplant for a patient with MPS I was done in 1980 [35], and since then, hundreds of patients with the severe phenotype of MPS I, Hurler syndrome, have undergone HSCT. There has been considerable progress in addressing the two major challenges associated with HSCT—the difficulty of finding compatible stem cell donors and the high morbidity and mortality associated with the procedure. Stem cell sources now include umbilical cord blood, which has been proved safe and effective [36], is much more readily available than bone marrow and requires a less strict HLA match than bone marrow transplantation. Better tissue matching techniques, improved graft-*vs*-host prophylaxis, and more targeted conditioning regimens have improved survival and decreased transplant-related morbidity. However, the mortality associated with the procedure is still considerable; a recent risk factor analysis of cord blood transplantation among 93 Hurler patients reported a 3-year overall survival rate of 77% [37]. This risk is similar for patients with other MPS disorders who undergo HSCT [7].

HSCT involves a toxic ablative conditioning regimen to eliminate the patient's own stem cell population, followed by immunosuppression and semi-isolation for up to 12 months. Approximately 60% of MPS I patients report transplant-related complications [38], such as mild graft-*vs*-host disease. Most of the clinical experience with HSCT for MPS disorders comes from North America and parts of Europe. The procedure is not widely available in all parts of the world.

HSCT for MPS I

HSCT is the recommended treatment for severely affected MPS I patients (Hurler phenotype) under 2 years of age with a developmental quotient $\geqslant$70% of normal [12]. When successful, HSCT significantly prolongs survival from a median of 6.8 years for untreated Hurler patients to 20 years and beyond [39]. Most importantly, HSCT may preserve neurocognition. Although many transplanted patients have some learning issues or deficits, they do not experience the relentless neurocognitive decline that occurs without transplantation. Cognitive outcome is improved with earlier transplant [7, 36, 40]. Somatic improvements include resolution of hepatosplenomegaly, reduction of sleep apnoea and upper airway disease, preservation of hearing and greater mobility of upper extremities. Urinary GAG excretion is also reduced. However, musculoskeletal disease continues to progress, vision usually worsens, cardiac valve disease persists and often progresses and growth is stunted, although a successful transplant may slow down the progression of some of these disease manifestations [7, 41].

HSCT for other MPSs

For other MPS disorders, HSCT experience is limited and results are mixed [7, 42–45]. Most case reports and case series have reported only partial or no neurocognitive benefit. This may be related to the fact that, unlike MPS I Hurler, other MPS disorders typically are not diagnosed in infancy, and thus transplant usually occurs well past 2 years of age, when the CNS disease may be established and irreversible. This is especially a consideration for children with MPS III, who have very little somatic disease and do not begin to regress developmentally until $\geqslant$3 years of age [46]. For MPS IV (Morquio) and VI (Maroteaux–Lamy), disorders with normal cognitive development and for attenuated forms of the other MPS disorders, possible somatic benefits of HSCT have to be weighed against the mortality and morbidity of the procedure. However, if transplant risks continue to decline, HSCT may become a more appealing option for MPS patients who are expected to have normal or near-normal cognition.

In MPS II (Hunter), some somatic but variable neurocognitive benefits have been reported. For MPS III (Sanfilippo), transplantation appears to have little or no neurocognitive benefit; however, a recent series reported a decrease in behavioural problems and better sleeping patterns in transplanted children, and modest cognitive gains in children transplanted before 2 years of age [7]. For MPS VI (Maroteaux–Lamy), benefits of transplantation are similar to those obtained with ERT but with significant morbidity; among 45 MPS VI patients, 1-year survival was 67% [7]. In MPS VII (Sly disease), transplant experience is limited to a handful of case reports [45].

Use of ERT in conjunction with HSCT

An increasing number of MPS I patients who undergo HSCT receive laronidase for a short term during the transplant period (typically beginning at least 6 weeks before transplant and continuing until engraftment is established) [47–54] in an effort to improve patients' clinical status during the interval between diagnosis and transplant and thus enhance the likelihood of successful HSCT. A multivariate analysis of risk factors and outcome in 93 MPS I patients who underwent HSCT with cord blood found that among the 23 patients who received peri-transplant laronidase, engraftment was not affected by exposure to laronidase and there was a trend towards improved event-free survival and a lower incidence of graft-*vs*-host disease [37]. Two single-centre case series have reported >90% survival and engraftment with the use of peri-transplant laronidase in conjunction with a full conditioning regimen [51, 52]. Other multicentre studies have not established a clear benefit of peri-transplant

laronidase except for patients in poor clinical condition [37, 47, 48]. The use of laronidase in transplanted patients beyond the transplant period is currently under investigation; one case report suggests that it may be beneficial in selected patients with MPS I [55].

Emerging therapies

Several new approaches to the treatment of MPS disorders are under investigation, especially to treat the neurological and skeletal manifestations of these diseases [56, 57]. Some of these could be stand-alone therapies, others would likely be used in conjunction with ERT or HSCT to enhance treatment efficacy. Currently under study are small-molecule therapies, gene therapy and novel methods of delivering enzyme directly to the brain.

Small-molecule therapies

Small molecules are oral medications that may have better biodistribution than infused enzyme, including the potential to cross the blood–brain barrier. Unlike ERT and HSCT, the efficacy of small-molecule therapies can depend on the type of mutation that causes the loss of enzyme activity and/or the degree of residual enzyme activity present. Small-molecule therapies under consideration for MPS disorders fall into three categories: chaperone molecules, substrate reduction therapies and stop codon read-through therapies.

Chaperone molecules are designed to enable inactive enzymes with certain kinds of mutation to regain activity by binding to the active site of the molecule and causing it to fold into the correct three-dimensional structure [58]. Chaperones may also protect incorrectly folded enzymes from rapid degradation by the endoplasmic reticulum and thus promote the processing and trafficking of mutant enzymes to the lysosomes. As a result, the enzyme is still able to fulfil its function, despite the initial misfolding caused by a missense mutation. Examples include 1-deoxyidronojirimycin and 1-deoxygalactonojirimycin, evaluated pre-clinically for MPS I Hurler–Scheie and MPS III, respectively [58].

The goal of substrate reduction therapy is to inhibit production of the stored substrate [59]. Several compounds that reduce substrate synthesis, miglustat (currently used for treatment of non-neuronopathic Gaucher disease when ERT is not an option), rhodamine B and genistein [60], are being investigated for treatment of MPS disorders [46]. Genistein, a naturally occurring plant isoflavone, was evaluated in a 12-month, open-label pilot study of 10 patients with MPS III, where it decreased GAG levels and improved psychological tests of cognitive function [61].

Gentamicin and a less toxic analogue, NB54, are being investigated as potential therapies that could restore enzyme activity in mutant enzyme proteins with premature stop mutations (termed nonsense or null mutations) that halt enzyme synthesis [62]. A similar drug with potential for MPS disorders is PC124 (ataluren) [63–64]. Such drugs could have a role in treating MPS I Hurler, as ~70% of Hurler patients have at least one nonsense allele [65–66].

Gene therapy

Human gene therapy involves the insertion of normal DNA directly into cells to correct a disease-causing genetic defect. The challenge with gene therapy is finding a safe delivery system that results in therapeutic levels of gene expression. Several approaches are being explored, including delivering the corrective gene to the patient's cells via a viral vector, or *ex vivo* approaches involving removing cells from the patient (such as blood cells or stem cells), genetically modifying them to produce the deficient enzyme and then re-introducing the genetically modified host cells by autologous transplant [67–69]. Other *ex vivo* approaches include creation of smart stem cells for HSCT that are genetically engineered to augment enzyme production and/or differentiate into specific cell types.

Strategies for getting exogenous enzyme into the brain

Two MPS I clinical trials involving intrathecal delivery of enzyme are currently underway, one in children undergoing HSCT (in the hope that it will help preserve neurocognition until CNS engraftment occurs) and one in adults with spinal cord compression (in the hope that risky decompression surgery can be avoided). Two case reports describe successful delivery of recombinant enzyme intrathecally in adult patients with MPS I and MPS VI with spinal cord compression [70–71]. In addition, trials of intrathecal enzyme delivery have recently been initiated for patients with MPS II or MPS III. Also under exploration in animal models is delivery of enzyme through the intracisternal route. An alternative approach is to modify the enzyme protein in a manner that enables it to cross the blood–brain barrier through special transport systems that allow certain large molecules to enter the CNS. This includes Trojan horse strategies in which the enzyme is fused to a protein such as the insulin receptor that can cross the blood–brain barrier [72].

Summary and conclusions

Therapeutic options for certain MPS disorders, once considered untreatable, are available for patients with these devastating diseases. ERT is now commercially available for MPS I, II and VI, and in clinical trials for MPS IV. HSCT is now the standard of care for patients with the severe phenotype of MPS I and is being investigated for other MPS disorders. Morbidity and mortality associated with HSCT continue to decline. Both ERT and HSCT, although not cures, have been able to alter the natural history of the disease. Other promising therapeutic approaches are in the pipeline. As MPS disorders are multisystemic, treatment must be multifaceted and involve both disease-specific and supportive care.

Early diagnosis and treatment are essential to optimize outcome. Newborn screening, currently being piloted for MPS I and MPS II, could have a profound impact on the mortality and morbidity of MPS disorders by enabling pre-symptomatic intervention.

Rheumatology key messages

- Disease-specific treatment is now or will soon be available for most MPS disorders.
- Due to the progressive nature of MPS disorders, early intervention is very important.
- Disease-specific treatments for MPSs are not curative but can improve outcome and quality of life.

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