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Mini Review

Hematopoietic Stem Cell Therapy and Novel Approaches for Mucopolysaccharidoses

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Abstract

Mucopolysaccharidoses (MPS) are a group of inherited genetic linked enzyme deficiency lysosomal storage disorders. The deficiency of the enzyme is caused by a gene mutation that leads to the accumulation of harmful Glycosaminoglycans (GAGs) in the cells, tissues and blood. Disease-mutation leads to abnormal accumulation of GAGs: Dermatan Sulfate (DS), Heparan Sulfate (HS), chondroitin sulfate, and keratan sulfate resulting in clinical manifestations of varying severity. Recent advances have shown abnormal HS involvement in Central Nervous System (CNS) dysfunction. Therapeutic options vary according to the type of MPS. In severe MPS I patients, the best therapeutic approach is Hematopoietic Stem Cell Transplantation (HSCT). Unlike in other MPS, when it is performed in MPS I patients, HSCT has the ability to continuously produce the deficient enzyme that crosses the blood-brain barrier, a useful effect for CNS defects and *in fine* for mitigating cognitive and developmental delays. Pharmacological options include Enzyme Replacement Therapy (ERT). Three recombinant human enzymes have so far been approved by the US Food and Drug Administration (FDA) for the treatment of MPS: laronidase for MPS I, idursulfase for MPS II, and galsulfase for MPS VI. However, some of the results of ERT are still controversial. Finally, novel therapeutic avenues (i.e., substrate reduction therapy) have been recently proposed. We review here the different therapeutic approaches proposed in MPS, focusing on MPS I, the MPS that is benefiting most from HSCT so far.

Keywords: Mucopolysaccharidosis; Stem cell therapy; Bone marrow transplantation

Introduction and Epidemiology

Mucopolysaccharidoses (MPS) are a group of genetic-linked metabolic diseases that lead to significant morbidity and fatality in children and adults. MPS are a category of lysosomal storage disorder and comprises of seven clinical types (I, II, III, IV and VI, VII, IX) with specific gene mutations in eleven different lysosomal enzymes. The incidence of MPS has an estimate of 1:50,000 to 1:250,000 with MPSIII (Sanfillippo Syndrome), the most common and MPS VII (Sly disease) the rarest [1]. MPS are autosomal recessive with the exception for MPS II (Hunter Syndrome), which is X-linked. They are due to enzymatic deficit resulting in cellular damage with clinical features of varying degrees of severity [2,3]. In the case of MPS I patients, genetic mutations in the alpha-L-Iduronidase (IDUA) gene (located on chromosome 4p16.3) can be homozygous or heterozygous and are the causative mutation in 95% of cases [4]. According to the Human Gene Mutation Database, MPS I has 110 mutations in the IDUA gene with the majority of nonsense, missense mutations, splicing or small deletions/insertions [5,6]. In MPS I patients, there are more than 30 polymorphisms or nonpathogenic sequence variants within the iduronidase gene that modify the severity of the clinical disease presentation with a pathogenic allele [6,7]. MPS I alleles have variations among different ethnic populations with two nonsense mutations W402X and Q70X alleles found in majority of Europeans (61 to 72% mutations). The mutations found in the European population are rare among Japanese, Koreans, or Moroccan patients [6,8]. Specifically, in the Japanese population, there are two types of missense mutations that are conserved in patients displaying mild MPS I (Scheie) phenotype, while in India, other mutations are responsible for mild forms of MPS I [2]. Patients displaying the more severe phenotype of MPS I (Hurler), are usually homozygous for a nonsense allele or two different nonsense alleles, while milder MPS I forms (Hurler-Scheie and Scheie) have around 1 missense or null mutations [6,7]. Gene locations of other MPS are indicated in Table 1.

MPS are progressive in nature with clinical presentations of multisystemic, chronic and severe complications [3]. MPS features are presented in Table 1. For example, MPS I is separated into three different diseases based on their clinical presentation: Hurler (severe), Hurler-Scheie syndrome (intermediate) and Scheie syndrome (milder) [6]. According to their type, MPS I can be apparent in utero, in children or adults. MPS I am caused by the deficiency of lysosomal enzyme, IDUA, with subsequent improper degradation of Dermatan Sulfate (DS) and Heparan Sulfate (HS) [6]. The clinical manifestations of MPS I include progressive cardiac and pulmonary disease, inguinal and umbilical hernias, corneal clouding and musculoskeletal disease. Patients with MPS I (Hurler), the most severe phenotype, suffer from a progressive intellectual decline with CNS involvement, cognitive abnormalities and limited life expectancy [6]. Diagnoses are based on the accumulation of GAGs in the urine, a sensitive, but nonspecific, test. A more precise diagnosis involves the analysis of the deficient IDUA activity in the fibroblasts, leukocytes, serum or blood spots

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Table 1: Mucopolysaccharidosis: clinical signs, genetic and molecular abnormalities.

Type	Common name	Incidence	Gene	Locus	Deficient enzyme	Accumulated products	Symptoms
MPS IH	Hurler syndrome	1:100,000	IDUA	4p16.3	α-L-iduronidase	Heparan sulfate Dermatan sulfate	Cardiomyopathy,mental retardation, coarse facial features, macroglossia, corneal clouding, micrognathia
MPS IH/S	Hurler-Scheie syndrome						
MPS IS	Scheie syndrome or MPS type V						
MPS II	Hunter syndrome	1:250,000	IDS	Xq28	Iduronate sulfatase	Heparan sulfate Dermatan sulfate	Mental retardation
MPS IIIA	Sanfilippo syndrome A Sulfamidase deficiency	1:280,000-1:50,000	SGSH	17q25.3	Heparansulfamidase	Heparan sulfate	Motor dysfunction, developmental delay, spasticity, hyperactivity, deathy by second decade
MPS IIIB	Sanfilippo syndrome B NAGLU deficiency		NAGLU	17q21.2	N-acetylglucosaminidase		
MPS IIIC	Sanfilippo syndrome C		HGSNAT	8p11.21	Heparan-α-glucosaminide N-acetyltransferase		
MPS IIID	Sanfilippo syndrome D		GNS	12q14.3	N-acetylglucosamine 6-sulfatase		
MPS IVA	Morquio syndrome A	1:75,000	GALNS	16q24.3	Galactose-6-sulfate sulfatase	Keratan sulfate Chondroitin 6-sulfate	Motor dysfunction, skeletal dysplasia, short stature
MPS IVB	Morquio syndrome B		GLB1	3p22.3	β-galactosidase	Keratan sulfate	
MPS V	MPS IS		IDUA	4p16.3	α-L-iduronidase	Heparan sulfate Dermatan sulfate	See MPS I
MPS VI	Maroteaux-Lamy syndrome ARSB deficiency		ARSB	5q14.1	N-acetylgalactosamine-4-sulfatase	Dermatan sulfate	Kyphosis, motor dysfunction, heart defects, skeletal dysplasia, short stature
MPS VII	Sly syndrome GUSB deficiency	1:250,000	GUSB	7q11.21	β-glucuronidase	Heparan sulfate Dermatan sulfate Chondroitin 4,6-sulfate	Developmental delay, short stature, corneal clouding, hepatomegaly, skeletal dysplasia
MPS IX	Natowicz syndrome Hyaluronidase deficiency		HYAL1	3p21.31	Hyaluronidase	Hyaluronic acid	Painful swelling of nodular soft-tissue masses around joints

[6,9-11]. Prenatal screening is done through enzyme and DNA testing and early diagnosis such as newborn screening can improves disease outcome [6]. Diagnosis of MPS I patients are made between 4 and 18 months based on orthopedic and visceral signs. Births are usually normal but infants can present a giant mongoloid spot; cognitive dysfunction is the hallmark, but can be normal or slightly impaired according to the MPS I phenotypes [1].

Clinical manifestations and types of accumulated products of other MPS are featured in Table 1.

GAGs

The different GAGs involved in MPS, with their corresponding diseases, are featured in Table 1. GAGs are large protein polymers consisting of multiple branches of carbohydrates. They are components of proteoglycans that provide the structural support to the Extracellular Matrix (EM) and structures that are cartilaginous in nature, such as heart valves and joints. GAGs are also involved in the communication and regulation of cellular components. In MPS, inborn defects in the production of lysosomal enzymes result in a progressive accumulation of undegraded or partially degraded GAGs. Consequently, a destabilization of the lysosome occurs, leading to the disturbances of normal cell function and metabolism in the peripheral organs and CNS. Disease-mutation causes harmful accumulation of GAGs in cells, connective tissue and blood [1,3,11].

The main GAGs found in MPS are Heparan Sulfate (HS), Dermatan Sulfate (DS), Keratan Sulfate (KS) or Chondroitin Sulfate (CS). The lysosomal enzyme, alpha-L-iduronidase is involved in the degradation of certain GAGs such as Heparan Sulfate (HS) and Dermatan Sulfate (DS) [2]. It is not completely understood how the accumulation of GAGs that is due to specific enzyme deficiency leads to clinical symptoms. Both primary and secondary effects of the deficiency of HS/DS breakdown and altered cellular function respectively underlie disease manifestations. DS is a component of both connective tissue and skin and HS is involved in angiogenesis and associated with CNS dysfunction [6]. HS and DS are involved in MPS I, II, III, V, VI, VII, and we will describe them in further details.

HS, abundantly present on the cell surface and in the EM, interacts with growth factors, growth factor binding proteins, extracellular proteases, protease inhibitors, chemokines, and adhesive proteins. HS regulates the activity, gradient formation and the stability of ligand-receptor interactions in different cells [12-16]. HS is also involved with the formation of new blood vessels during embryonic development and facilitates the action of pro- and anti angiogenic factors during vascular formation as shown in studies using zebra fish and mouse models. Studies in animal models showed a HS-based modulation of the signaling of growth factors like VEGF-A [16,17], PDGF-B [16,18-20] and TGF-β [16,21,22] in order to promote steps in angiogenesis [16].

Excess accumulation of HS severely affects the CNS by inducing cerebral dysfunctions, deregulating major cell migrations, axon

guidance, neuritogenesis, synaptogenesis, and structural plasticity of neuronal cells [1,3,23]. Studies in MPS I mice showed an increase in HS accumulation, lysosomal storage, neuroinflammation, astrocytosis, microgliosis [23]. Lipid accumulation is present in the brains of Hurler patients with mental retardation but is not found in Scheie patients with normal intelligence. The accumulation of GAGs may be associated with the infiltration of macrophages of the arachnoid villi and thickening of the leptomeninges in the brain. The increased thickness of leptomeninges may be a result of defective pacchionian granulations, causing slowly progressive communicating hydrocephalus. MRIs in MPS I patients show abnormal thickening of the leptomeninges in the brain, enlargement of ventricles, subarachnoid space and Perivascular Spaces (PVS). The enlargement of the PVS is due to a meshwork of fibrous tissue and cells with abnormal storage of GAGs which may result to a disorder of the movement and absorption of cerebrospinal fluid [1,24].

Dermatan Sulfate (DS) is a GAG mainly found in tendons, blood vessels, heart valves, skin and lungs. DS has different roles in fibrosis, coagulation, infection, wound repair, cardiovascular disease and carcinogenesis. An accumulation of DS in the mitral valve can lead to a myxomatous degeneration of the leaflets and finally to mitral valve prolapse into the left atrium and cardiac insufficiency (mainly by left heart failure).

Keratan Sulfate (KS) can be found in cartilage, bone and cornea. KS can also be found in the CNS where it is involved in brain development and glial scar formation following an injury. KS are large molecules acting as cushions to absorb mechanical shocks. The amount of KS depends on the tissue where it is found: KS is 10 times more abundant in cornea than in cartilage and 2-4 times more in cornea than in other tissues.

Chondroitin Sulfate (CS) is part of cartilage and provides resistance to compression. CS interacts with proteins of EM. In the brain, CS levels are increased after injury and act to prevent regeneration of damaged nerve endings. CS is also involved in cortical development where it acts as a stop signal for neurons migrating from the ventricular zone. In chondrocytes, CS reduces IL-1beta-induced-NF kappa B translocation. Role of proteoglycans of CS are not yet as well understood compared to the ones HS.

Treatments of MPS

Non-pharmacological therapies: Hematopoietic stem cell transplantation (HSCT)

Transplantation of Hematopoietic Stem Cells (HSCs) can significantly increase survival rates in MPS patients, more specifically in severe MPS I (Hurler) patients [6,25]. HSCT therapy has been performed for years in both animal models and human patients. HSCT is based on the transplantation of Bone Marrow (BM), Peripheral Blood Stem Cells (PBSC) or Umbilical Cord Blood (UCB). HSCT has had major challenges involving finding compatible stem cells, HLA match for bone marrow transplantation and high morbidity and mortality rates associated with the failure to achieve complete engraftment. Graft-Versus-Host Disease (GVHD) is another complication related to stem cell or BM transplantation. To address HSCT challenges, umbilical cord blood uses safe and effective source of stem cells [26,27]. Umbilical cord blood is more readily available and requires less strict HLA matching as bone marrow transplantation. Better tissue matching techniques involving graft-versus-host prophylaxis have been a major improvement in reducing transplant-related morbidity and mortality rates.

HSCT provides normal and bone-derived cells that allow the continuous release of the deficient enzyme available for uptake by cells, which consequently reduces excess accumulation of GAGs in tissues [11,28,29]. The success of monocyte-derived cells is associated with the ability to cross the blood-brain barrier, incorporate in microglia and secrete enzyme in neurons [29-34]. The first successful treatment of allogeneic HSCT was performed on a patient with MPS I in 1980 [26,27]. Thirteen months after treatment, there was a decrease in IDUA in plasma, reduction of hepatosplenomegaly and corneal clouding and an arrest in the developmental deterioration. Twenty years later, the patient had full engraftment and an improved intelligence [35]. Since then, hundreds of severe MPS I (Hurler syndrome) patients have undergone HSCT treatment, primarily from bone marrow, but increasingly from umbilical cord blood [6,36].

To optimize successful engraftment in MPS I patients, pre-transplantation preparation involves sufficient immunosuppression and myeloablation [11]. HSCT is effective, but there are limits to the treatment of bone involvement due to cartilage cells deriving from mesenchymal stem cells and HSCT does not provide sufficient amounts of enzymes to cartilage. This occurs because cartilage is a vascular and it is difficult for circulating enzymes to reach growth plates and cartilaginous tissues. Moreover, the rate of diffusion is affected because of the large molecular weight of lysosomal hydrolases [37-41].

Overall, HSCT is useful in significantly improving progressive degeneration of the CNS and in reducing cognitive dysfunction in patients with severe MPS I [25]. The treatment is most effective during early administration at beginning of disease onset and developmental deterioration. Efficacy of treatment at the CNS level is associated with early treatment and with graft-cells producing deficient enzyme partly in microglia cells [6,11]. HSCT also significantly reduces complications in the peripheral organs of MPS I patients. The effectiveness of HSCT may be due to the local presence of graft-derived cells (Kupffer cells in the liver) or the uptake of the deficient enzymes [11].

In severely affected MPS I (Hurler) patients under 2 years with developmental quotient of less than 70% normal, the recommended treatment option is HSCT. However, HSCT is not recommended for patients above 2, due to the lack of compatible donors, graft rejection, and GVHD [11]. Successful HSCT therapies significantly improve survival years from 6.8 years to 20 years and beyond. Importantly, when HSCT is performed early in Hurler patients, neurocognition stops declining and improves overtime [25-27,36]. There are also improvements in the resolution of hepatosplenomegaly, reduction in sleep apnea and upper airway disease, preservation of hearing, upper extremities movements and a reduction of GAGs in the urine. However, MPS I patients treated with HSCT continued to have a decline in musculoskeletal disease, worsened vision, cardiac valve disease and stunted growth. [27,39]. In other milder MPS I types, HSCT results are not as effective in neurocognitive involvement as in severe MPS I (Hurler) patients [25,27,35,42-45].

Unlike in Hurler syndrome, HSCT may not be effective in the other MPS diseases in which diagnosis is made in children older than 2 years. At that time, CNS disease may be irreversible, especially in MPS III patients, who show developmental delay and motor dysfunction around age 3 with very little somatic disease [27,45]. The efficacy of HSCT in MPS II is still debated [3]. Other MPS disorders including MPS IV (Morquio) and VI (Maroteaux-Lamy) present normal cognitive function and development but present somatic disorders. In these MPS, HSCT would not be the best treatment option because of the increased morbidity and mortality rates due to this procedure, which outweighs the benefits of treating the somatic complications [3,27].

Pharmacological therapies

Partly because of the side effects of HSCT, Enzyme Replacement Therapy (ERT) has been proposed for the treatment of MPS. Three recombinant human enzymes have been approved so far by the US Food and Drug Administration (FDA) for the treatment of MPS: laronidase (Aldurazyme®) for MPS I, idursulfase (Elaprase®) for MPS II, and galsulfase (Naglazyme®) for MPS VI. Once injected intravenously, these enzymes are internalized to reach their target in lysosomes to replace the defective enzymes. ERT can control somatic manifestations of MPS, including joints abnormalities, organ enlargement and pulmonary insufficiency. However, there are currently two limitations of ERT: first, enzymes cannot cross the blood-brain barrier and consequently, ERT cannot correct brain abnormalities; secondly, heart valves and bones are relatively resistant to ERT.

+ MPS I

Recently, Enzyme Replacement Therapy (ERT) was used alone or in conjunction with HSCT. Laronidase is an ERT drug that is an analogue of human alpha-L-iduronidase produced in the CHO (Chinese hamster Ovary) cells [25,27]. In the treatment of MPS I, laronidase can be used in conjunction with HSCT for a short term during transplant therapy typically up to 6 weeks, leading up to engraftment [27,35,42,44,45]. This particular recombinant enzyme demonstrated in clinical trials [46-49] to be effective in the reduction of GAGs accumulation in the liver and the urine [27,36]. The use of iduronidase drug therapy has limitations due to the inability to cross the blood brain barrier, which limits its effectiveness in the CNS of patients with Hurler syndrome. The use of HSCT and laronidase is used in combination to improve treatment and clinical status for MPS I patients and is effective during transplant improving the likelihood of the success of the HSCT treatment [27,43,50,51].

ERT should be offered to MPS I patients at the time of diagnosis and continued until severe neuropathy or any other condition appears that may affects prognosis. Laronidase should be given if the patient fulfills one of the following criteria: patient with age > 2 years; patient with age < 2 years but who is expected to have attenuated phenotype; patient with age < 2 years and who is expected to have a severe phenotype with intelligence quotient of less than 70 [6].

+ MPS II

Idursulfase (Elaprase®) is a recombinant human iduronate-2-sulphatase approved for the treatment of MPS II. Clinical trials showed prolonged improvements in forced vital capacity (particularly when ERT is given weekly). Spleen and liver size, and GAGs levels in urine [52,53] were reduced under treatment by idursulfase. Guidelines are still discussed [3].

+ MPS VI

Galsulfase (Naglazyme®) is a recombinant human N-acetylgalactosamine 4-sulfatase (rhASB). It is approved for the treatment of MPS VI. Galfulfase has to be initiated at the beginning of the course of the disease, and continued until neuropathy compromises its efficacy.

Some positive results were noticed in Phase 1/2 and Phase 2 clinical trials [54,55], leading to a Phase 3 study. Primary and secondary endpoints (both involving locomotion) were improved in the Phase 3 trial [56,57]. Beneficial effects were observed during at least 240 weeks. Respiratory function is also improved with galsulfase [58]. Side effects were negligible.

Novel Therapeutic Approaches

+ Substrate reduction therapy

The goal of Substrate Reduction Therapy (SRT) is to reduce and possibly inhibit the synthesis of GAGs using small molecules

Among the molecules used, Genistein, a plant isoflavone, has demonstrated potential for blocking the Epidermal Growth Factor (EGF)-mediated signal transduction responsible for the expression of genes coding for the enzymes synthesizing GAGs. Genistein can reduce GAGs accumulation and neuroinflammation in brains of MPS II [59] and MPS III mice [60]. Clinical trials in small groups of patients with MPS II and III showed improvements in joint movements and cognition respectively [61], but the long term efficacy of Genistein is not totally established yet [3].

The fluorescent dye Rhoda mine B can inhibit the elongation of GAGs chain. Rhoda mine B has been shown to interrupt GAGs synthesis in cell cultures of MPS III and VI. It can also improve cognition in MPS IIIA mice [62]. Possible side effects of Rhoda mine B need further investigations to assess its toxicity [3].

Miglustat (Zavesca®) has been primarily used for the treatment of Niemann-Pick type C disease and Gaucher's disease [63]. Miglustat inhibits the synthesis of glucosylceramide synthase, a precursor of GM_2 ganglioside. Miglustat may play a role in improving neurological deterioration seen in MPS [64]. However, its efficacy has not been fully shown in MPS to date [3].

+ Gene therapy

Gene therapy provides the transfer of relevant cDNA to produce and secrete the deficient enzyme for uptake in cells. Different vectors carrying the missing gene were used in animal models of MPS [65]. Similarly, different ways of gene delivery have been tested so far [66-69].

+ Other therapies

Other treatments include small-molecules therapies such as chaperone molecules, and stop cod on read-through therapies [29]. All available therapeutic approaches use the phenomena of cross reference correction. This allows the reuptake of exogenous enzyme and deliver it to the lysosome via mannose-6-phosphate receptor-mediated process but most are limited by their inability to cross the blood-brain barrier [29,70].

However, other treatment options such as exogenous enzyme replacement therapy, have challenges with severe MPS I patients (Hurler), due to their failure to correct neurocognitive disorder, because of their inability to cross the blood brain barrier [25].

Conclusion

MPS are diseases leading to the harmful accumulation of GAGs in cells, tissues and blood. The accumulation of GAGs has adverse effects with somatic and clinical manifestation, particularly involving the CNS. HSCT has been the most successful approach in treating MPS I, especially Hurler, the more severe phenotype. Even though challenges are present, HSCT efficacy is due to its ability to provide enzymes able to cross the blood-brain barrier, mitigating the decline of cognitive functions and developmental delays, manifestations that were a major challenge to many of the other treatments for MPS patients.

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