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Advancements in the Treatment of Mucopolysaccharidoses: From Established Therapies to Gene Therapy

1. Joanna Wanat

Medical University of Lublin

Aleje Racławickie 1, 20-059 Lublin

asiawanat2000@gmail.com

ORCID: 0009-0009-3349-3618

2. Wojciech Homa

Wojewódzki Szpital Specjalistyczny

al. Kraśnicka 100, 20-718 Lublin

wojciech.homa2@gmail.com

ORCID: 0000-0003-2177-8818

3. Aleksandra Warunek

Medical University of Lublin

Aleje Racławickie 1, 20-059 Lublin

warunek.aleks@gmail.com

ORCID: 0009-0000-7542-6522

4. **Gabriela Gronowicz**

Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
gabagronowicz@gmail.com
ORCID: 0009-0009-4034-1284

5. **Izabela Dzikowska**

Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
dzikowskaizabela2@gmail.com
ORCID: 0009-0006-5539-3771

6. **Agata Siejka**

Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
agata.siejka12@gmail.com
ORCID: 0009-0009-2332-0115

7. **Daria Stefaniak**

Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
dariastefaniak18@gmail.com
ORCID: 0009-0002-2207-4177

8. **Weronika Zielińska**

Medical University of Lublin
Aleje Racławickie 1, 20-059 Lublin
w09290929@gmail.com
ORCID: 0009-0007-0707-9590

9. **Michał Chról**

Medical University of Lublin

Aleje Racławickie 1, 20-059 Lublin

michuGBE@gmail.com

ORCID: 0009-0005-7776-6260

Abstract

Introduction and purpose

Mucopolysaccharidoses (MPS), a subset of inborn errors of metabolism (IEM), are genetic disorders requiring pediatricians to recognize non-specific symptoms and carefully monitor newborns. Early diagnosis is essential for optimizing therapeutic outcomes. In recent years, significant progress has been made not only in the diagnostic process but also in the development of therapies. Established treatments, such as hematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT), have been improved, while advancements in gene therapy have opened new possibilities.

State of knowledge

Numerous studies and clinical trials suggest that novel therapies could be game-changers in managing MPS. Among the promising new treatments are: blood-brain barrier (BBB)-penetrable enzyme replacement therapy (ERT), substrate reduction therapy, nonsense suppression therapy, and mRNA engineering. However, the most advanced treatments, that are currently under investigation are in-vivo and ex-vivo gene therapy.

Conclusions

This article aims to review treatment options for MPS I (Hurler syndrome), highlighting the evolution from established therapies to innovative approaches.

Keywords:

Gene therapy; Mucopolysaccharidoses; Hurler syndrome; Hematopoietic stem cell transplantation; Enzyme replacement therapy; Inborn errors of metabolism.

Introduction

Inborn errors of metabolism (IEMs), also called inherited metabolic diseases, are a diverse group of genetic disorders that disrupt normal metabolic pathways [1]. IEMs may be rare

individually, but together they are more common than most people think. Their symptoms can closely resemble those of other illnesses, which significantly complicates the diagnosis process [2]. These conditions can appear at any age but are particularly significant in newborns, where they often manifest with neurological symptoms such as seizures, lethargy, or developmental delay [1]. The variability in IEM presentations highlights the importance of recognizing their signs and symptoms. Increased awareness and early identification are essential since timely diagnosis and intervention can significantly improve patient outcomes [3].

Mucopolysaccharidoses (MPS) are a group of IEMs characterized by deficiencies in specific lysosomal enzymes. These deficiencies result in the accumulation of glycosaminoglycans (GAGs) in various tissues and organs, leading to progressive multi-systemic manifestations [4]. This article focuses on treatment strategies for MPS with a primary emphasis on MPS I (Hurler syndrome). It highlights established therapies while presenting emerging advancements in the field. By providing a comprehensive overview of current approaches and innovative methods, the article aims to bring attention to promising developments that could improve patient outcomes.

Materials and Methods:

A comprehensive literature review was conducted using PubMed, focusing on articles and research papers published between 2001 and 2024. Search terms included "mucopolysaccharidosis," “Hurler syndrome”, "gene therapy," "hematopoietic stem cell transplantation," "enzyme replacement therapy," and "inborn errors of metabolism."

What are mucopolysaccharidoses specifically?

MPS are a group of lysosomal storage disorders (LSDs) characterized by widespread systemic involvement. The most common type of MPS differs across regions and ethnic groups, suggesting a potential association with geographic and genetic factors [5].

When it comes to clinical presentation, it varies depending on the specific enzyme deficiency involved. The most common symptoms of MPS include short stature, facial dysmorphism, chronic joint pain resembling inflammatory rheumatism, axial and peripheral bone abnormalities, hepatosplenomegaly, and early-onset carpal tunnel syndrome. Additional manifestations may include coarse facial features, cognitive impairment, hernias,

kyphoscoliosis, and corneal clouding. Depending on the specific type, the disease can also involve alterations in the brain, or heart [5,6]. Although the symptoms of different MPS overlap significantly, some forms exhibit distinct characteristics. For instance, while MPS I and MPS II have many shared features, they differ in severity and disease progression. MPS III is characterized by prominent neurological deterioration, whereas MPS VII is often associated with hydrop fetalis [5].

Early and accurate diagnosis of MPS even in the asymptomatic stage, is important for achieving better treatment outcomes. The diagnostic process begins with screening, typically through the analysis of urinary GAGs followed by confirmatory tests such as enzyme activity assays and genetic analysis to identify the specific subtype [7]. Novel diagnostic tools, including advanced urinary and blood GAG testing, enzyme assays, and genetic testing have enhanced the precision of MPS diagnosis and subtype determination [8]. Recognizing MPS is essential not only for effective patient management but also for family screening and counseling [9,10].

MPS I

Hurler syndrome (MPS IH) is an autosomal recessive disorder caused by a deficiency in the enzyme α-L-iduronidase, leading to the accumulation of GAGs such as chondroitin sulfate, heparan sulfate, dermatan sulfate in lysosomes in tissues, including the liver, spleen, heart, and connective tissue [11]. This condition, part of the MPS I spectrum, includes three clinical entities: Hurler syndrome (severe), Scheie syndrome (mild), and Hurler-Scheie syndrome (intermediate) [4,7]. Hurler syndrome, the most severe form, typically results in death by the second decade of life. Its prevalence is approximately 1 in 100,000 births, with no preference for sex or ethnicity [12]. MPS II (Hunter syndrome) typically progresses more slowly than MPS I and is characterized by the absence of corneal clouding. Additionally, MPS II is less common compared to MPS I [7]. Hurler syndrome is usually diagnosed between 6 and 24 months of age, presenting with coarse facial features, a prominent forehead, macroglossia, hepatosplenomegaly, corneal clouding, skeletal abnormalities, joint rigidity, short stature, cardiomyopathy, and gradual lenticular enlargement. Increased intracranial pressure due to communicating hydrocephalus is also a common finding [13].

Standard therapies in Hurler Syndrome

Allogeneic hematopoietic stem cell transplantation (HSCT)

HSCT is the primary treatment for Hurler syndrome (MPS I), significantly improving symptoms and extending life expectancy. Early intervention, ideally before the age of 2 and the onset of cognitive decline, is critical for achieving optimal outcomes [14,15]. HSCT improves facial features, joint mobility, and reduces complications such as sleep apnea, cardiac issues, and hearing impairment [14]. Early procedure can stabilize neurocognitive function, although outcomes depend on the effectiveness of engraftment. Despite its benefits, HSCT has limitations, such as its inability to correct skeletal defects or improve issues in less accessible tissues like the cornea, cardiac valves, or central nervous system (CNS) [14,16,17].

Advancements in conditioning regimens, such as the use of fully ablative protocols with busulfan or fludarabine, are essential for successful engraftment. However, these regimens may lead to toxicity, including infertility and other long-term side effects [15,18]. Reduced-intensity regimens and antibody-based therapies aim to minimize these risks, although they can increase the likelihood of graft failure [18]. The implementation of strict donor hierarchies and improved supportive care has significantly reduced HSCT-related mortality [14,15]. Nevertheless, complications such as graft-versus-host disease (GvHD), infections, and pulmonary issues, particularly during the first year post-transplant, remain significant challenges [14,15].

The success of HSCT is closely tied to achieving full donor chimerism and normal enzyme levels, as reflected in reductions of GAGs in the blood and urine [14]. However, complete normalization is rarely achieved, as residual GAGs persist in poorly vascularized tissues like cartilage, corneas, and heart valves. GAG biomarkers such as heparan sulfate and dermatan sulfate are used to monitor the effectiveness of the therapy [19]. Animal studies have demonstrated significant enzyme activity and GAG reduction in organs like the liver and spleen but minimal improvement in bone and cartilage. Similarly, in human patients, early HSCT prevents severe disease progression but has limited effects on skeletal abnormalities, which often necessitate surgical correction [14,20].

Skeletal disease is one of the most challenging aspects of MPS I and tends to progress even after HSCT due to the enzyme's limited penetration into avascular tissues and early-onset irreversible damage [21]. Research in animal models suggests that combining neonatal HSCT with ERT may improve bone outcomes. However, challenges remain, and as patients live longer due to better treatments, addressing skeletal complications becomes increasingly

important. Developing targeted therapies for persistent issues like bone disease is a critical area for future research [20].

MPS I is typically diagnosed earlier, around 12 months of age, compared to MPS II, which is usually identified later, at approximately 3.5 years. This difference in timing is a key reason why HSCT is not the standard recommendation for children with MPS II [22]. Since HSCT can prevent severe cognitive decline in most cases, it could potentially benefit MPS II patients as well if early diagnosis becomes possible through the newborn screening in the future [22,23].

Enzyme replacement therapy (ERT)

ERT involves weekly intravenous infusions of laronidase, a recombinant form of human iduronidase. While ERT is considered safe and effectively reduces urinary GAG levels and hepatosplenomegaly, lengthy infusions can be exhausting for patients [14,24]. Additionally, the enzyme cannot penetrate avascular tissues, so brain function, visual acuity, and bone abnormalities do not improve [14]. Pulmonary function and endurance may improve with ERT [25]. Patients may develop IgG antibodies to laronidase, which can interfere with the treatment. Due to these limitations, ERT is not recommended as the sole treatment for Hurler syndrome. However, ERT can be effectively used before HSCT, as it does not lower engraftment rates. It is a valuable option for patients awaiting a suitable donor, while post-HSCT ERT addresses residual deficiencies [14,25].

Hampe et al. compared the effects of HSCT and ERT on specific clinical manifestations of Hurler syndrome. The main findings are summarized below:

-HSCT stabilizes cognitive decline but does not restore lost cognitive functions. In contrast, a combination of HSCT and ERT may provide short-term improvements.
- Both HSCT and ERT help reduce hypertrophy and stabilize ventricular function; however, their effects on valvular disease are limited.
- Both therapies can alleviate upper airway obstruction and sleep apnea, although the long-term effectiveness may decrease over time.
- HSCT initially stabilizes corneal clouding, but progression is a common issue. ERT has little impact on corneal clouding.

- HSCT can lead to partial improvements in hearing, particularly with sensorineural loss, while ERT shows inconsistent effects on hearing [14].

ERT when initiated early, may help prevent bone disease in MPS I [25]. An even better prospect is a modification of ERT, which involves chemically altering the enzyme to prolong its circulation time or targeting iduronidase to the bone through a hydroxyapatite binding site [20]. It is also important to develop strategies that enhance enzyme delivery to the central nervous system (CNS) and other resistant tissues. Efforts to promote immune tolerance ERT represent a significant focus for future therapeutic advancements [14].

Novel therapies

BBB-penetrable ERT

The blood-brain barrier (BBB) poses a significant challenge in delivering high-molecular-weight ERT to the CNS, necessitating innovative approaches to overcome this obstacle. Alternative administration methods, such as intrathecal (IT) and intracerebroventricular (ICV) delivery, have shown promise in addressing CNS symptoms of MPS [22]. For example, IT-administered iduronidase combined with HSCT and intravenous (IV) ERT has successfully reduced markers of disease and inflammation in Hurler syndrome patients [26]. Similarly, idursulfase-IT and idursulfase-beta-ICV have demonstrated significant reductions in cerebrospinal fluid GAGs in MPS II patients [27].

Advancements in enzyme modification are focused on improving the ability of enzymes to cross the BBB which could help address the neurological symptoms of MPS that are not fully treated by standard ERT [22]. Researchers have also developed BBB-penetrable ERT therapies that utilize the receptor-mediated transcytosis, a natural process that allows molecules like insulin and transferrin to cross the BBB by binding to specific receptors on brain endothelial cells [22,28]. By fusing deficient enzymes with antibodies targeting these receptors, the enzymes can be transported into the brain parenchyma, enabling them to reach neuronal cells and exert therapeutic effects [22].

Substrate Reduction Therapy (SRT)

SRT offers an alternative treatment for MPS by inhibiting the biosynthesis of substrates that accumulate due to enzyme deficiencies, rather than directly addressing lysosomal GAG storage like ERT [22]. Products used in SRT:

Miglustat: Approved for mild-to-moderate type I Gaucher disease and later for neurological symptoms in Niemann-Pick disease type C. It inhibits glucosylceramide synthase, reducing glycosphingolipid production [29].
Rhodamine B: A fluorescent known from cosmetics. It has small effects in humans, decreases GAG synthesis in MPS III models [30].
Genistein: A natural isoflavone that reduces GAG storage through tyrosine kinase inhibition. Early studies showed limited success. High-dose trials in MPS III slightly reduced heparan sulfate levels in CSF but failed to show clinical benefits [20,31].
Odiparcil: An orally administered small molecule that modifies GAG synthesis, enabling soluble GAG excretion. A Phase IIa study in MPS VI showed safety and improvements in cardiac, lung function, and corneal clouding, with pediatric trials underway [22,32].
PIKFyve inhibitors: Under development to enhance lysosomal biogenesis by activating transcription factors like TFEB and TFE3 [22].
SRT drugs are orally administered and have shown the ability to effectively reach tissues that are less responsive to treatments like ERT or HSCT, including the brain, cartilage, and eyes [22]. Their non-invasive administration and ability to circulate systemically increase their therapeutic potential, whether used alone or alongside other treatments, positioning them as a promising direction for future MPS management [14,22].

New therapies for MPS I include strategies aimed at accelerating GAG degradation [14]. Resveratrol, which promotes autophagy and can cross the blood-brain barrier, is one such option, reducing GAG accumulation in the body [33]. Another promising approach is anti-inflammatory therapy with pentosan polysulfate, which has been shown to decrease urinary GAG excretion in MPS I patients [14]. This therapy holds the potential for addressing bone disease in MPS I, based on positive results from animal model trials [20]. Additionally, adalimumab, an anti-inflammatory treatment, has demonstrated pain reduction in clinical trials **[14].**

Gene therapy

Gene therapy is a promising approach for treating all IEMs, including MPS [20]. It aims to provide functional copies of deficient genes, either by directly delivering a therapeutic transgene into the patient's cells (in vivo) or by modifying the patient's cells outside the body (ex vivo) before reintroducing them. Both strategies offer the potential for sustained enzyme production and the reversal or slowing of disease progression [20,22].

In vivo - vectors

Adeno-associated virus 9 (AAV9) vectors, such as RGX-111 for delivering the α-l-iduronidase gene in MPS I and RGX-121 for delivering the iduronate-2-sulfatase gene in MPS II, show promise for crossing the BBB [22,34]. Strategies under investigation include temporary disruption of the brain's microvascular endothelial tight junctions and receptor-mediated transcytosis [34]. Intracisternal administration in preclinical and clinical trials has demonstrated improvements in biomarkers and reductions in neurological symptoms. Clinical trials using AAV9 vectors for MPS I in children are currently underway [22].

Liver-directed vectors

Liver-directed early-stage gene therapy with retroviral vectors in MPS I mice prevented bone disease and other manifestations, while studies in MPS I dogs alleviated but did not completely remove bone abnormalities [20].

Bone-directed modified vectors

Research has explored modifying vectors to increase connection for bone tissues to try to cope with bone defects. Modified gene therapy approaches showed higher enzyme expression in bone in MPS IV mice, indicating the potential for addressing skeletal manifestations [20].

Genome editing technologies

Genome editing tools like Clustered Regularly-Interspaced Short Palindromic Repeats/ CRISPR-associated protein 9 (CRISPR/Cas9) and zinc-finger nucleases (ZFN) directly correct genetic mutations, offering durable solutions [35].

In vivo gene therapy with CRISPR/Cas9 is based on the injection of a liposomal complex that targets the insertion of functional *IDUA* genes into loci, such as ROSA26 [20]. This approach

has demonstrated a sustained, increase in iduronidase (IDUA) activity across serum and most organs, except the brain. The outcomes are noteworthy: respiratory function has stabilized, bone abnormalities have been effectively avoided, and there has been a partial reduction in elastin breaks in the aorta [14,20]. Nevertheless, limitations remain, as no significant functional improvements were observed in heart valves or the brain, highlighting the need for further optimization to address these critical areas [14,20,35].
This treatment was further enhanced with ex-vivo genome editing. Gómez-Ospina et al. genetically modified hematopoietic stem cells using CRISPR/Cas9 to insert the *IDUA* gene into the CCR5 locus [20]. After transplantation into adult MPS I mice, the modified cells secreted elevated levels of IDUA. This approach significantly improved neurological symptoms and nearly fully corrected bone abnormalities in the treated mice [36].

The ZFN technique, another recent advancement in gene therapy, targets the patient's hepatocytes to address enzyme deficiencies associated with MPS I and MPS II. This approach uses AAV vectors to deliver a functional copy of the α-L-iduronidase or iduronate 2-sulfatase gene into the hepatocyte genome, aiming for lifetime therapeutic enzyme production [22,35]. In MPS I mouse models, treatment successfully corrected GAG accumulation and prevented neurological manifestations of the disease. However, its impact on bone abnormalities was not evaluated, leaving this aspect unexplored [20]. Alternative genome editing techniques and delivery approaches are being explored as potential substitutes for AAV-based gene therapies [35].

Ex vivo gene transfer

Ex vivo gene transfer offers a promising approach to addressing the enzyme deficiency in MPS I, with the potential to overcome complications associated with allotransplantation. By genetically modifying autologous hematopoietic stem cells (HSCs), this strategy can achieve higher enzyme expression levels while maintaining access to the CNS [14]. Research using lentiviral vectors to introduce the *IDUA* gene into HSCs and transplant them into MPS I mice has shown promising results with effective enzyme delivery to all affected tissues, leading to a full resolution of disease symptoms, including neurological and skeletal issues, which are resistant to improvement through other treatment methods [14,37]. However, outcomes in MPS I dogs using murine gamma-retroviral vectors have been less successful. Despite high initial *IDUA* expression and successful engraftment, enzyme levels in vivo became

undetectable due to immune responses against the modified cells. These challenges highlight the importance of addressing immune-mediated rejection to improve efficacy [14,37].

Currently, Gentner et al. are conducting a clinical trial in children who received autologous hematopoietic stem and progenitor cells (HSPCs) transduced ex vivo with an IDUA lentiviral vector following a conditioning regimen. Early results indicate stabilization of cognitive function and improvements in skeletal parameters after one year [38].

An alternative to viral gene delivery is the Sleeping Beauty (SB) transposon system, which uses a transposase to integrate gene sequences into the host genome [14]. This vector merges the benefits of viruses and free DNA [39]. In MPS I mice, this method successfully induced enzyme expression in the liver, however, the animals' immune reaction led to a later decrease in IDUA levels. GAG levels were reduced to normal in the liver [40]. An SB-based therapeutic approach is also being developed, utilizing autologous human B cells engineered to produce IDUA. In MPS I mice, this strategy demonstrated significant enzyme activity and effectively reduced GAG accumulation, showcasing its potential as a promising treatment option [14].
Another strategy involves combining CRISPR/Cas9 and rAAV vectors to insert the *IDUA* gene into B cells. When these modified B cells were transplanted into MPS I mice, there was a considerable increase in IDUA enzyme activity [14].
New therapeutic approaches are being developed to protect engineered human cells producing high levels of IDUA from immune rejection. In MPS I mice, these cells reduced GAG levels in blood and organs showing promise as a new treatment [14].

Nonsense suppression and mRNA Engineering

MPS I seems to be a perfect candidate for nonsense suppression therapy, particularly when targeting the W402X mutation, the most common mutation associated with the disease [41]. Drugs such as NB84, an aminoglycoside derivative, aim to bypass premature stop codons, enabling the production of full-length IDUA protein. Studies show that prolonged use of the nonsense suppression agent NB84 restored sufficient α-l-iduronidase activity to diminish GAG storage [41]. As a result, improvements in the skeletal system, cardiovascular system, and behavior were observed [14,41].

Therapeutic RNA editing represents another innovative strategy for MPS I. This technique utilizes endogenous or engineered enzymes, such as ADAR or ABEmax, to bypass stop codons or correct genetic mutations. Emerging programs like LEAPER and RESCUE have demonstrated increased IDUA activity and metabolic correction in preclinical models, offering further potential for addressing underlying genetic defects [14].

Kingman et al. focus on small molecule therapies, including already described substrate reduction therapy, but also chaperone therapy, and stop codon read-through therapy. Small molecule therapies offer significant advantages, particularly their superior tissue penetration [20].

Chaperone therapy

Chaperone therapy involves small molecules that assist in improving protein folding or protecting misfolded proteins from degradation. However, this approach may have a limited impact on severe MPS I patients who predominantly have nonsense mutations, resulting in minimal residual enzyme activity [20].

Stop codon read-through therapy

Stop codon read-through therapy targets nonsense mutations common in severe MPS I [20]. Compounds like chloramphenicol, a peptidyl transferase inhibitor capable of inducing read-through, can cross the BBB [42]. This approach allows for the suppression of premature stop codons, enabling full protein translation. Aminoglycoside, like NB54, have shown a similar potential [43]. However, they may pose toxicity risks [42,43].

In Utero Gene Therapy

In utero gene therapy has also been explored as a treatment for MPS I, aiming to provide early intervention during fetal development [14]. While attempts in canine models have shown successful gene delivery, they were unable to maintain enzyme expression [20]. Despite these setbacks, this approach remains a topic of ongoing research due to its potential for early disease modification [14,20].

Conclusion

Mucopolysaccharidoses, particularly Hurler syndrome, exemplify the advancements in medical research and treatment. Current therapies, such as HSCT and ERT, offer significant benefits when administered early, but often fail to address the full spectrum of disease manifestations, including skeletal abnormalities. Gene therapy shows promise as a comprehensive and enduring treatment option with encouraging results in both preclinical and clinical studies. However, despite its potential, these approaches face challenges in translating theoretical success into consistent clinical outcomes, highlighting the need for continued refinement and innovation.

Disclosures

Author's contribution:

Conceptualization: Joanna Wanat
Methodology: Agata Siejka, Daria Stefaniak, Aleksandra Warunek
Formal analysis: Gabriela Gronowicz, Weronika Zielińska, Michał Chról
Investigation: Gabriela Gronowicz, Weronika Zielińska, Michał Chról
Data curation: Joanna Wanat, Agata Siejka, Wojciech Homa, Aleksandra Warunek
Writing - rough preparation: Joanna Wanat, Wojciech Homa, Izabela Dzikowska, Agata Siejka, Aleksandra Warunek
Writing - review and editing: Michał Chról, Weronika Zielińska, Daria Stefaniak, Agata Siejka
Supervision: Joanna Wanat, Izabela Dzikowska
Project administration: Joanna Wanat, Izabela Dzikowska

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