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CLINICAL TRIALS OF NEW THERAPIES FOR MUCOPOLYSACCHARIDOSES

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A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: Mucopolysaccharidoses (MPS) are a group of rare genetic diseases with a metabolic etiology. Currently, there are no effective methods of treating MPS, and new ways of treating patients are constantly being sought.

Aim of the study: The purpose of this article is to review the available literature concerning clinical trials involving new treatments for MPS.

Material and methods: The review of research literature published between 1999 and 2023 was conducted, with a specific focus on the last ten years. The literature for this article was selected from publications available online in databases such as Google Scholar or PubMed. The research was based on keywords such as mucopolysaccharidoses, clinical trials, gene therapy, and MPS.

Results: A total of 104 publications were considered in the study, including 95 scientific articles and 9 clinical trial reports (consisting of 1 FDA approval). Out of those 104 articles, 82 discussed potential future therapies for patients with MPS. Among them, as many as 51 focused on gene therapy.

Conclusions: The only currently approved treatments for MPS are enzyme replacement therapy and hematopoietic stem cell transplantation, which are not suitable for all types of MPS and have their limitations. In addition, there is no single therapy for all types of MPS, as they are the result of mutations in different genes and result from the deficiency of different enzymes. Numerous preclinical and clinical studies are being conducted on therapies for MPS. These include therapies that allow manipulation of cellular pathways, substrate reduction, and gene therapy, which is the most promising form of treatment. Some of the studies have successfully passed the first and second phases of research.

KEYWORDS: mucopolysaccharidoses, MPS, clinical trials

Background

Mucopolysaccharidoses (MPS) are a group of rare genetic diseases with a metabolic etiology. Under physiological conditions, glycosaminoglycans (GAGs) are digested in lysosomes, resulting in complete degradation of their long chains. MPS result from a deficiency or lack of activity of lysosomal enzymes responsible for the degradation of GAGs present in the extracellular space of connective tissue [1]. Disruption of the GAG metabolic process leads to their accumulation in body tissues and causes damage to multiple organs [1,2].

MPS are progressive diseases that make it difficult for patients to function in daily life, cause pain, and shorten longevity. There are 7 types of MPS, of which types I, III, and IV are further divided into subtypes [3]:

– Type I (Hurler, Hurler-Scheie and Scheie syndromes),

– Type II (Hunter syndrome),

– Type III (Sanfilippo syndrome, with 4 subtypes: A, B, C, D),

– Type IV (Morquio syndrome, with 2 subtypes: A and B),

– Type VI (Maroteaux-Lamy syndrome),

– Type VII (Sly syndrome),
– Type IX (Natowicz syndrome).

MPS have certain features that distinguish them from other lysosomal storage diseases (LSDs), e.g., primarily disorders of the osteoarticular system, including diffuse ossification disorders, also known as dysostosis multiplex, enlargement of the internal organs, including the liver, spleen, and tongue; there is also often progressive deterioration of vision and hearing and thickening of the facial features. As the disease progresses, valvular defects, cardiomyopathy, and enlargement of the heart muscle are observed, as well as thickening of the structures of the respiratory system, leading to sleep apnea and breathing difficulties [1–3]. Mental retardation is characteristic in severe Hurler, Hunter, and Sly syndromes, and in particular, Sanfilippo syndrome, in which neurodegenerative symptoms are most severe and distressing [1,2,4].

The differences between the types of MPS are caused by mutations in other genes and the accumulation of different GAGs [1,2]. This feature of MPS allows the diagnosis of specific types based on examination of the presence of individual GAGs in urine, blood, or cerebrospinal fluid samples [5].

Diagnosing MPS is often delayed due to its rarity and late-appearing symptoms [6]. At the same time, early diagnosis is crucial for the successful initiation of enzyme replacement therapy (ERT) or hematopoietic stem cell transplantation (HSCT), the only currently approved treatments for MPS [7,8]. ERT is available for patients with MPS types I, II, IVA, VI, and VII and consists of administering an intravenous replacement enzyme to patients. This form of treatment has a positive effect on the changes in the respiratory and musculoskeletal systems. Unfortunately, the replacement enzymes do not cross the blood-brain barrier and, therefore, do not affect the progression of damage to the nervous system [8,9]. HSCT is recommended for patients younger than 2 years of age because it must be performed before significant mental retardation develops. It is a highly effective method to prevent progressive osteoarticular deformities and mental retardation; however, the procedure itself carries a high risk of mortality and may have negative side effects [8].

Delayed therapy initiation may shorten life, emphasizing the need for new diagnostic methods, especially prenatal [10,11], and effective therapies for all MPS types to enhance patients' quality of life.

Aim of the study

This study aimed to analyze and review the current scientific knowledge regarding the future of MPS treatment.

Material and methods

A systematic literature search was conducted using Google Scholar, clinicaltrials.gov, and PubMed databases. The search was focused on identifying studies concentrated on MPS and current clinical tri-

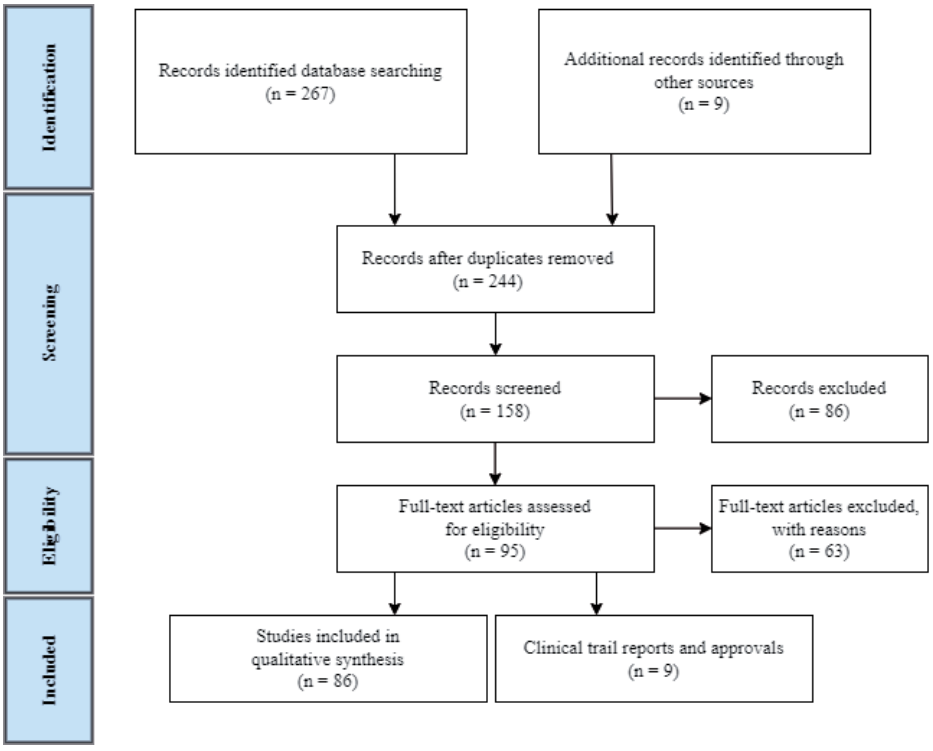

Figure 1. Flowchart of study selection [12]

als to find the best treatment. Keywords used for the research included: "mucopolysaccharidoses", "MPS", and "glycosaminoglycans". A total of 273 articles were identified and, after excluding duplicate articles, 244 were included for review. Another 86 articles were excluded because they did not meet the inclusion criteria for this topic, which included articles about currently used methods, mandatory payment to access the article, or a small number of citations, leaving 158 articles for the following analysis. Out of these, 63 articles were excluded because of small patient groups and used procedures or drugs that did not pass preclinical trials. At this point, 86 articles, 8 clinical trial reports, and 1 FDA drug approval remained and were included in the review (Figure 1).

Results

Therapies in clinical trials

Due to the problems in performing ERT and HSCT in patients and the lack of effective therapies for patients with MPS types III and IX, research is constantly being conducted to find safe treatments that could not only increase patient comfort but also allow full recovery in the future. It was one of the conditions to eliminate articles about currently approved methods. Studies and clinical trial reports used in this analysis focused on substrate reduction therapy, manipulation of pro-inflammatory signaling pathways, and gene therapy.

Substrate reduction therapy

Substrate reduction therapy, an investigational treatment for MPS, aims to inhibit GAGs synthesis, reducing their body levels [8]. This method, utilizing small molecules that cross the blood-brain barrier, shows potential advantages in addressing central nervous system symptoms [13,14].

The process of GAG synthesis is regulated by the epidermal growth factor (EGF) receptor pathway, as EGF-mediated signal transduction regulates the expression of genes encoding specific enzymes involved in GAG production. To inhibit EGF receptor tyrosine kinase activation, genistein, a soy isoflavone showing structural similarity to 17β-estradiol, has been used [15–18].

Thus, it was the first molecule proposed as a potential drug for substrate reduction therapy in MPS patients, especially those with neurological manifestations. In this way, gene expression-targeted isoflavone therapy (GET IT) was introduced into clinical trials in patients with Sanfilippo syndrome [14]. The expected effect of substrate reduction therapy on the patient's cells is shown in Figure 2.

Initial pilot studies show promising results, as oral administration of 5 mg/kg/day of genistein to patients with MPS type III showed a reduction in GAG urinary excretion along with improvement in behavior and reduced progression of neurological changes. It was hypothesized that higher doses might produce a better effect [18,19,20].

However, doubling the genistein dose in a subsequent trial involving 30 patients did not translate into clinical improvement [21]. Safety studies with doses up to 150 mg/kg/day were conducted, revealing uncertain clinical efficacy, and requiring further investigation [22]. An interesting observation was made by Dr. Marucha's team, who used genistein in seven patients with Hunter syndrome who were not eligible for ERT. The administration of isoflavones increased the elasticity of the connective tissue and, in particular, improved the range of motion of the joints [23].

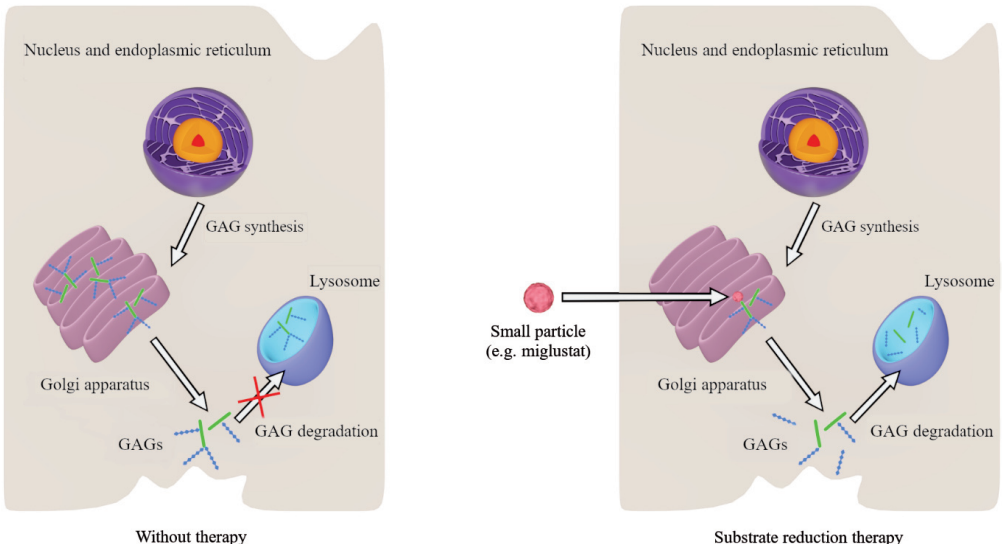

Figure 2. Diagram of the action of substrate reduction therapy on a cell [8]

Although genistein has not yet shown significant improvements in neurological outcomes, substrate reduction therapy remains an attractive approach for the treatment of MPS. It is possible that the identification of new drugs (e.g., inhibitors of specific steps in GAG synthesis) could provide better results.

A critical aspect of new therapy research involves secondarily stored substrates, previously considered clinically irrelevant. However, lipids, glycosphingolipids, phospholipids, and cholesterol have been recognized as inflammation indicators during excessive storage, influencing the disease's pathogenesis [24,25]. Accordingly, an attempt was made to treat patients with miglustat (N-butyl-deoxynojirimycin, NB-DNJ), an iminosugar that inhibits the synthesis of glucosylceramide, a precursor to the synthesis of gangliosides Gm1 and Gm2. The therapeutic goal was to reduce the secondary storage of gangliosides in patients with severe central nervous system involvement. Miglustat is a drug approved for the treatment of Gaucher and Niemann-Pick type C diseases. The initial studies conducted in animal models confirmed a reduction in Gm2 gangliosides and neuroinflammation, as well as an improvement in the animal's behavior [26].

Subsequently, miglustat was administered to patients with Sanfilippo syndrome in a clinical trial; the same doses were used as in patients with Niemann-Pick disease type C, but despite promising evidence, no significantly reduced ganglioside levels in CSF or improvement in neurological impairment were observed [27].

Manipulation of pro-inflammatory signaling pathways

Storage, both primary and secondary, leads to the activation of signal transduction pathways, especially inflammation. Some researchers hypothesize that this mechanism is responsible for the pathophysiology of some of the most devastating symptoms of MPS, including central nervous system or osteoarticular involvement, among others.

In the central nervous system, pro-inflammatory states are associated with the activation of microglia, and secretion of inflammatory cytokines and chemokines, including tumor necrosis factor-alpha (TNF-alpha), interleukins (IL-1β, IL-6), and macrophage inflammatory protein 1-alpha (CCL3), leading to chronic brain inflammation [28,29]. Exploiting these signaling pathways may represent a novel therapeutic target. Of particular interest in this context is the TLR4 signaling pathway [14]. Studies have shown that activation of TLR4 pathways led to altered STAT1 and STAT3 expression, which in turn results in an increase in TNF-α levels in patient tissues. In experimental animal models with MPS, treatment with the anti-TNF-α drug, infliximab, was attempted. In rats with Maroteaux-Lamy syndrome, a reduction in serum TNF-α levels and the number of apoptotic cells in articular cartilage was confirmed [30]. Animals treated with ERT in combination with infliximab showed a significant decrease in TNF-α levels compared to untreated animals. In addition, improvements in bone length and mobility were observed, while rats treated with ERT alone showed weaker treatment effects [31].

Based on the encouraging results of the preclinical study, anti-TNF-α treatment has entered the clinical trial phase in patients with MPS types I, II, and VI. The focus of the study was to test the safety and efficacy of subcutaneously administered adalimumab against osteoarticular symptoms [32]. The positive results will allow for the future introduction of an ERT-based therapy in combination with anti-TNF-α drugs, which could offer the chance to improve osteoarticular symptoms in the most severely affected patients.

Another drug with similar properties is pentosan polysulfate (PPS), a drug approved by the Food and Drug Administration (FDA) as an anti-inflammatory and prochondrogenic agent [33]. It has been shown to improve the clinical signs of disease in ERT-treated rats with MPS type VI, reducing urinary levels of GAGs and IL-8 and TNF-α levels in tissues and the cerebrospinal fluid [31], and was additionally effective in improving clinical outcomes even when the treatment was used as monotherapy [34].

PPS treatment was also useful in improving the vitreous cartilage of the trachea, motor skills were found to improve, and craniofacial and dental changes were reduced, along with a decrease in their typical rough appearance [35]. In addition, the study investigated the safety and efficacy of treating mobility and pain in patients with MPS type I with PPS in combination with ERT [36]. The drug was not only well tolerated but also significantly reduced the amount of GAGs excreted in the urine, improved mobility, and reduced joint pain.

Gene therapy

Gene therapy represents one of the most promising forms of treatment for patients with genetic diseases. The introduction of a therapeutic gene into the patient's cells is designed to correct the expression of defective genes and permanently express lysosomal enzymes. Approximately 5–15% of lysosomal enzyme activity is sufficient to maintain the patient's healthy state, and if the deficient enzyme is produced by one organ, uptake by other organs is possible. In addition, the pathophysiology of MPS is now well understood, which greatly facilitates the development

of therapeutic genes and the vectors needed for them [37–39].

Currently, there are two approaches to treatment with gene therapy: *in vivo* and *ex vivo* therapy. A schematic of how gene therapy works *in vivo* is shown in Figure 3, while *ex vivo* is shown in Figure 4.

The first adeno-associated virus (AAV) gene therapy was approved by the European Medicines Agency in 2012. This was the drug Glybera®, alipogene tiparvovec, produced for patients suffering from lipoprotein lipase deficiencies [40]. Further studies are currently underway in the USA and some European countries, including Poland and Australia. Phase I and II clinical trials are being conducted for patients with MPS types I, II, IIIA, IIIB, and VI [41–48].

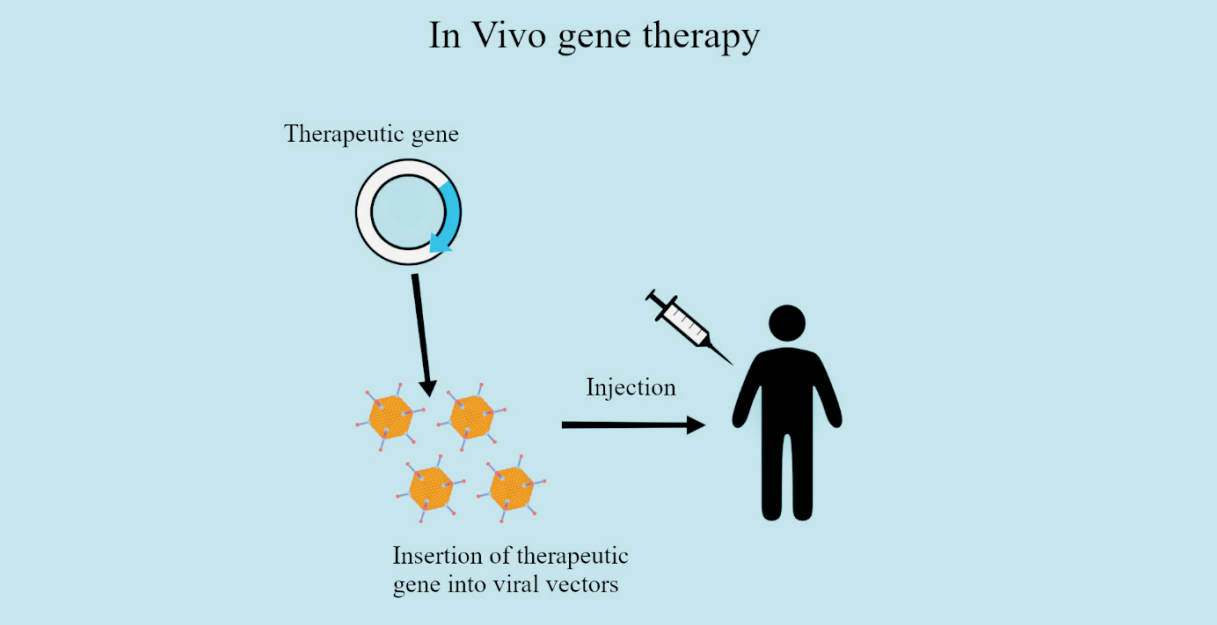

Figure 3. The principle of *in vivo* gene therapy [48]

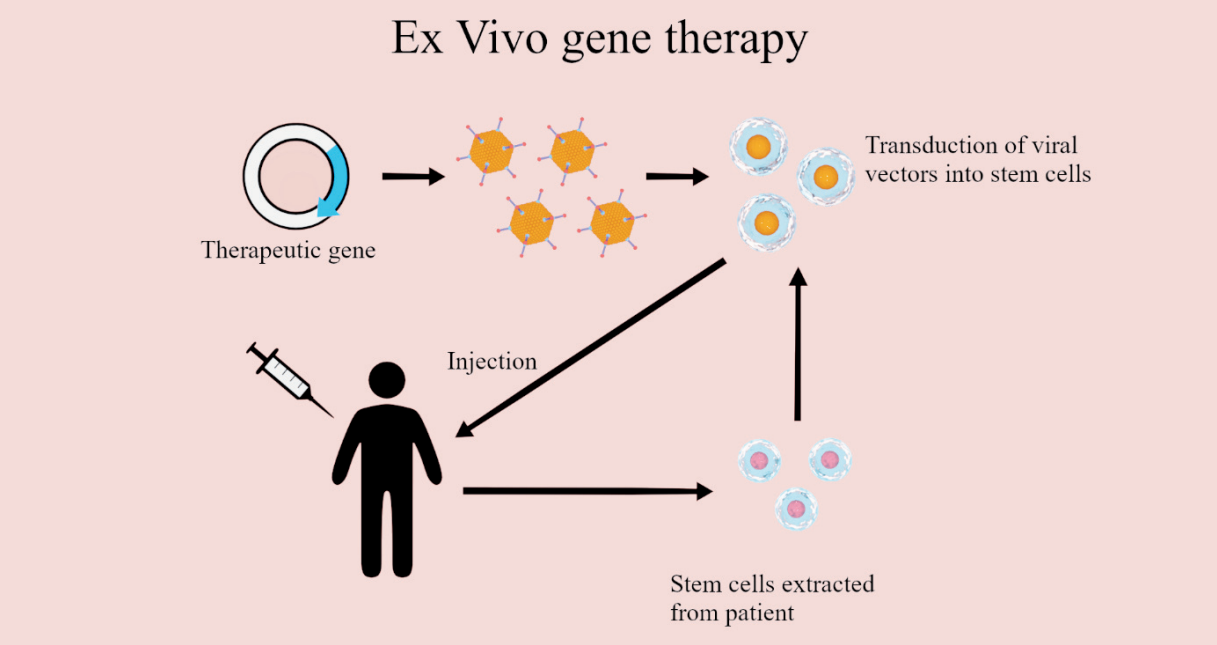

Figure 4. The principle of *ex vivo* gene therapy [48]

For the Hurler syndrome, trials of *ex vivo* gene therapy using stem cells transduced with lentiviral vectors are ongoing [49], while for other MPS, the main clinical trial involves *in vivo* therapy with an AAV vector. It is capable of transducing both dividing and non-dividing cells and promotes long-term ex-

pression in infected cells. Compared to retroviruses and lentiviruses, it has low genotoxicity because the genome of the AAV vector is present as an episome. Additionally, several serotype variants have been identified for humans and primates, and each serotype has a unique pattern of tissue tropism, which has great potential in the context of gene therapy [37,50,51].

However, AAV vector genomes remain episomal in target cells and are rarely integrated into recipient genomes. In comparison, lentiviral and retroviral vectors can integrate stably into host cell genomes, leading to insertional mutagenesis. In addition, AAV is a parvovirus with induced replication defects, so it requires a so-called helper virus for replication. It is also worth noting that antibodies to the AAV2 vector are detected in about 80% of people due to previous infections, potentially reducing efficacy and safety in patients treated with gene therapy [52–55]. Negative effects on liver transduction with the AAV8 vector and reduced positive effects on the skeletal system in a cat model of Sly syndrome have also been confirmed [56]. Among the ways to overcome the host immune response are modifications of the vector and removal of antibodies by plasmapheresis, use of immunosuppressants, and simultaneous administration of empty AAV vectors as bait [57–59].

Gene therapy was supposed to offer hope for a lasting improvement in neurological symptoms. However, as it turned out, even injecting an AAV vector into the body does not overcome the blood-brain barrier. Therefore, the effects after administration of recombinant AAV into the intracerebral space were investigated, which significantly reduced the amount of storage material and improved behavioral pathologies in mouse models of MPS types I, IIIA, IIIB, and VII, but histopathological studies showed improvement only in the area adjacent to the injection site [60–69]. Given these conclusions, studies were then conducted with multisite administration, resulting in the transduction of rAAV vectors into the wider brain space. This resulted in significant improvement in GAG accumulation and cognitive function as well as behavioral symptoms in both rodents and large animals [70,71].

In 2013 and again in 2017, Lysogene completed two clinical trials for intracerebral injection of rAAV in patients with Sanfilippo syndrome types A and B. The company developed the rAAV10 vector expressing the hSGSH and SUMF1 genes, which were administered intracerebrally and had no side effects in patients monitored for one year after administration. In addition, improvements in brain atrophy and behavior were observed in some patients [43,44,72]. Also in 2017, UniQure completed a Phase I and Phase II clinical trial in four children who were administered rAAV2/5 containing the NAGLU gene in 16 interstitial deposits, four of which were in the cerebellum. Subsequently, a NAGLU activity of 15–20% was detected in the cerebrospinal fluid [73].

Intrathecal or intravenous administration is one of the less invasive delivery methods that effectively transduce genes to many tissues, including the CNS. The study was performed in large mammals, in which the transduction of different rAAV serotypes into the CNS after administration into the cerebrospinal fluid was compared. This study demonstrates the high transduction efficiency of rAAV9 in extensive CNS lesions [74–76]. Mouse and cat models of MPS types I, IIIA, IIIB, and VII were also observed, in which intrathecal administration of the rAAV9 vector corrected the pathological changes in the central nervous system [77–80]. Furthermore, the efficiency of gene transfer with rAAV9 proved to be significantly better than when rAAV1, 6, 7, or 8 were administered, and additionally, rAAV9 resulted in extensive neuronal transduction in a neonatal mice model. At the same time, rAAV2 and 5 showed the lowest transduction efficiency of the other recombinant viral vectors [81].

It is worth noting that the use of rAAV9 in a single systemic administration resulted in a significant increase in lysosomal enzyme activity, not only in the CNS but also in the visceral organs in mouse models of MPS IIIA and IIIB [82,83]. The positive results of these studies are leading to ongoing clinical trials in patients with Sanfilippo syndrome types A and B, in whom the rAAV9 vector is administered intravenously [45,46].

A continuing challenge for gene therapy remains the delivery of sufficient amounts of lysosomal enzymes for avascular bone and cartilage lesions. To improve the osteochondral components, studies were performed on the insertion of aspartic acid octapeptide (D8) into the C-terminus of tissue nonspecific alkaline phosphatase and the N-terminus of GUS and GALNS into the AAV2 vector, which significantly increased enzyme delivery to bone [11,84,85]. Based on the experimental results, a vector targeting bone with a significantly higher affinity for hydroxyapatite was explored. This was accomplished via an oligopeptide D8 being inserted into the N-terminal region of the VP2 capsid protein. Three months after injection, enzyme activity in bone was 4.7-fold higher than when the unmodified vector was used. After immunohistochemical analysis, it was found that the rAAV2 vector increased GALNS expression and activity in the bones of mice with MPS type IVA [86].

Genome editing, in which DNA or RNA sequences are altered, offers great hope for many patients. The editing process uses nucleases to create double breaks in DNA strands at specific locations in the genome. The resulting breaks are repaired by terminal non-

homologous splicing or homologous recombination. Four families of artificial nucleases include [37,87]:

– meganucleases,

– nucleases with a zinc finger motif (ZFN),

– nucleases based on the transcription-activating effector (TALEN),

– protein 9 – associated with clustered regularly-interspaced short palindromic repeats (CRISPR/Cas9).

Using ZFN, a corrective gene at the albumin locus was inserted into the AAV8 vector so that strong expression of IDUA and IDS was observed in mouse models after administration of the vector. The increase in enzymatic activity of IDS in the blood and other tissues of the mice significantly reduced the amount of stored GAGs in visceral organs. In addition, the concentrations of dermatan sulfate and heparan sulfate in the brain were reduced, leading to an improvement in neurocognitive symptoms [88–90]. Based on the positive results, phase I and II clinical trials are currently being conducted for patients with Hurler and Hunter syndromes [41,42].

The possibility of using CRISPR/Cas9 to treat rare genetic diseases was also investigated. A nanoemulsion containing a recombinant CRISPR/Cas9 plasmid and a donor oligonucleotide was developed. An oligonucleotide homologous to the mutated region (p.Trp402* region) introduced into fibroblast cultures from MPS type I patients was synthesized with the correct nucleotide. Carrying out the genetic modification resulted in a significant increase in the activity of the IDUA enzyme and a reduction in the size of the lysosome [91].

Studies were also conducted on the use of *ex vivo* therapy in animal models with MPS types I, II, IIIA, and IIIB [92–95]. Phase I and II clinical trials were then initiated in Hurler syndrome patients to evaluate the safety, tolerability, and efficacy of IDUA gene-transduced autologous CD34+ lentiviral cells. The endpoint of the study measured the level of IDUA activity in the patient's peripheral blood one year after transplantation [49].

Conclusions

The only currently approved therapies for mucopolysaccharidosis are enzyme replacement therapy and hematopoietic stem cell transplantation.

Currently, there is no single therapy for all mucopolysaccharidoses because they are based on mutations in different genes and result from deficiencies in different enzymes. Therefore, it is important to diagnose the disease at an early stage and tailor the therapy to the specific type of MPS.

Many preclinical and clinical studies are being conducted on therapies targeting mucopolysaccharidoses. Some studies have successfully completed phase I and phase II trials.

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