American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Mucopolysaccharidosis VI (MPS 6): Current Treatment and Future Perspectives with Focus on Enzyme Replacement Therapy, Gene Therapy and Glycosaminoglycans Clearance Therapy in Utero and After Delivery

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To Cite This Article: *Stefan Bittmann. Mucopolysaccharidosis VI (MPS 6): Current Treatment and Future Perspectives with Focus on Enzyme Replacement Therapy, Gene Therapy and Glycosaminoglycans Clearance Therapy in Utero and After Delivery. Am J Biomed Sci & Res. 2022 - 15(6). AJBSR.MS.ID.002167.* DOI: 10.34297/AJBSR.2022.15.002167

Received: March 03, 2022; **Published:** March 22, 2022

Introduction

Mucopolysaccharidosis (MPS) VI, also known as Maroteaux-Lamy syndrome, is a momentous, progressive and heterogeneous disease with severe pathologies affecting multiple organs which includes 2-18% of all mucopolysaccharidoses [1-3]. It was first described in 1963 by Pierre Maroteaux and Maurice Lamy [4]. It results from deficient activity of arylsulfatase B (ASB), the enzyme that degrades the glycosaminoglycans (GAGs) dermatan sulfate and chondroitin sulfate. Nearly 130 missense, nonsense or intronic mutations were described to date [3,5-9]. The gene locus was found on chromosome 5 (5q13-5q14) on 8 exons [9,10]. The incidence is described as 1:250000-500000 newborns [2,11-13]. An autosomal recessive hereditary pattern was found [1-3,5-7,11-21]. The disease can be found early after delivery [22]. Intellectual deficit is normally absent or mildly present, which is in contrast to other MPS forms [11]. Although MPS VI has a wide variety of phenotypic forms, disease progression in patients is often described as rapid or slow. Rapidly progressive MPS VI is characterized by early onset usually before the age of 2 or 3 years with cardiac involvement [16,18,23]. If untreated, most affected individuals do not reach adulthood (second and third decades of life). Affected individuals with slowly progressive disease usually show first symptoms as adolescents or young adults. Regardless of the rate of progression, untreated MPS VI can progress for years. MPS VI is a clinically heterogeneous disorder that can either become pronounced in patients as early as the first year of life or gradually lead to symptoms during a slow disease course. However, it should be noted that the symptoms of MPS VI increase continuously over time, i.e., no fixed parameters can be used for progression classification. The rapidly progressive form of MPS VI, which was defined in the cross-sectional study by *Swiedler, et al.* as urinary GAG levels (uGAG) of more than 200 µg/mg,3 can manifest itself in nonspecific symptoms already in the first year of life [19]. The slowly progressive form of MPS VI, defined as uGAG levels as low as 200 µg/mg, may not appear clearly, delaying the diagnosis and making it at a later time [19,24]. Regardless, patients develop significant morbidity that can be life-shortening and life-threatening. Neither the rapidly nor slowly progressive forms of MPS VI usually elicit neurocognitive deficits, although physical limitations may affect patient learning and development. The clinical manifestations associated with MPS VI are heterogeneous; however, disease progression occurs in all patients. The treatment options in MPS VI are manyfold, but, to date, not curing. Different therapies were performed since many years, enzyme replacement

therapy, hematopoietic stem cell transplantation, and gene therapy (gene editing). Liver transplantation was performed in animal studies [13]. Treatment options concentrate on enzyme replacement of defect enzyme to diminish cellular accumulation of GAG in different organs. Early diagnosis and early treatment is of upmost importance [25]. To date, only symptomatic therapy of MPS VI is possible [1-3,5-7,11-21]. Galsulfase, as enzyme replacement therapy, is a form of the human enzyme N-acetylgalactosamine-4-sulfate sulfatase and is genetically engineered using recombinant DNA technology [17,12,21,26-28]. It is used in enzyme replacement therapy for mucopolysaccharidosis VI [12,17,21,27-30]. After intravenous infusion, galsulfase is rapidly cleared from the bloodstream and taken up by cells into lysosomes, most likely via mannose-6-phosphate receptors. As with all lysosomal storage diseases, treatment should be started as early as possible, especially in severe forms, to avoid irreversible clinical manifestations. In particular, young patients under five years of age with severe forms of the disease should be treated, even though no patients under five years of age have been enrolled in the phase III study to date. The recommended dosing regimen for galsulfase is 1 mg/kg body weight, given once weekly as an intravenous infusion over four hours. The initial infusion rate is adjusted so that approximately 2.5% of the total solution is infused during the first hour and the remainder (approximately 97.5%) is infused over the next three hours. The three clinical trials conducted with galsulfase focused on evaluating the systemic manifestations of MPS VI such as performance, joint mobility, joint pain and stiffness, upper airway obstruction, manual dexterity, and visual acuity. The safety and efficacy of galsulfase was evaluated in a randomized, double-blind, placebo-controlled Phase III study of 39 MPS VI patients aged five to 29 years. At presentation, the majority of patients were of short stature, had limited functional capacity, and exhibited symptoms of the musculoskeletal system. Patients received either 1 mg/kg galsulfase or placebo each week for a total of 24 weeks. The primary efficacy endpoint was the number of meters walked in 12 minutes at week 24 compared to meters walked at baseline. The secondary efficacy endpoints were the speed at which stairs were negotiated in three minutes and the urinary glycosaminoglycan excretion of treated patients compared with placebo-treated patients at week 24. Subsequently, 38 patients were enrolled in an open-label extension study in which they received 1 mg/kg galsulfase each week. After 24 weeks of therapy, the distance walked in 12 minutes improved by 92 ± 40 m in galsulfase-treated patients compared with placebo-treated patients. Treated patients improved by 5.7 steps per minute in the three-minute stair climbing test compared with placebo-treated patients. Glycosaminoglycan excretion decreased to near normal levels in treated patients. In relation to gene therapy, the results of various studies show the efficacy of a causal therapy of MPS VI in the mouse model by gene transfer of the human ASB gene into the hematopoietic system. Different genome editing have been developed in the last decade. Only ZFN`S or CRISPR-CAS9 gene scissors were used to develop strategies to cure MPS VI. They were used in animal studies but are to date in clinical stages in humans [31-33]. But overall, it will be the future treatment option for MPS VI in early stages. Moreover, an innovative aspect of intrauterine gene therapy of the disease in the unborn is an aspect of future treatment. Replacing the original DNA sequence on chromosome 5 is of upmost interest to cure the disease. GAG clearance therapy focus on a beta-D xylosid analogon application reducing the intracellular pool of GAG in fibroblasts from MPS VI patients. Odiparcil is one of a new drug to treat patients to diminish the storage of GAG in different tissues of the body [14,20].

In conclusion, Maroteaux-Lamy syndrome (MPS VI) is a congenital metabolic disorder of mucopolysaccarides and is one of the lysosomal storage diseases. The syndrome is caused by a genetic mutation of the enzyme arylsulfatase B (ASB, N-acetylgalactosamine-4-sulfatase). Complete absence or deficiency of this enzyme results in dermatan sulfate storage. In the course of time, this storage in healthy cells and organs limits their function more and more. The syndrome is caused by a new mutation or is inherited in an autosomal recessive manner. The disease is mainly manifested by its external appearance. Severe cases are characterized by an enlarged head with a relatively short neck, widened nose, prominent cheekbones, enlarged lips, enlarged tongue and short stature. In addition, a number of other typical symptoms may occur during the course. These include corneal opacity, respiratory infections, hearing loss, sleep apnea, various hernias, hepatosplenomegaly, as well as thickening of the heart valves and consequent cardiomyopathies. In mild cases, often only a few symptoms appear. Depending on the severity, the first symptoms may appear in infancy or only in advanced adulthood. The severity of the disease increases with age. The suspected diagnosis by clinical appearance and pedigree analyses, can be confirmed by laboratory diagnostics. This involves determination of dermatan sulfate in urine and activity of arylsulfatase B enzyme in leukocytes. In affected pregnant women, prenatal diagnosis by chorionic villus sampling or amniocentesis is possible. The disease is currently incurable. In addition to supportive symptom-guiding therapy, enzyme replacement therapy with galsulfase (Naglazyme®) can curb disease progression.

A central role in supportive therapy is played by speech therapy, occupational therapy and physiotherapy with respiratory therapy, exercise therapy and massage. In addition, depending on the severity of symptoms, further therapy may be necessary, such as nocturnal CPAP ventilation for sleep apnea syndrome or heart

valve replacement for valve stenosis. In addition, aids such as hearing aids can make patients' daily lives easier. Affected patients should undergo regular orthopedic, cardiological, neurological, ophthalmological and dental follow-up. Future therapeutic perspectives should focus on gene editing therapy as early as possible. Furthermore, any intrauterine treatment option like early gene therapy in utero or interuterine enzyme replacement therapy should be discussed applicated in any device. The damage by defect enzyme activity is represented in utero and in pregnancy so therapy should focus not only on treatment after delivery but by fetal surgery or fetal enzyme replacement, otherwise by as early GAG clearance therapy in utero.

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