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Review Article

What is the Clue to Cure Pompe Disease in Childhood?

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Abstract

Pompe disease, acid maltase disease, is a rare, autosomal recessive inherited metabolic disorder from the group of lysosomal storage diseases, which is based on a genetically caused deficiency of an enzyme and is treatable by substitution of this enzyme. Pompe disease is also known as myopathy due to acid maltase deficiency, α-1,4-glucosidase deficiency or acid α-glucosidase deficiency, glycogen storage disease type II or glycogenosis type II. It is inherited in an autosomal recessive manner. When each parent carries one copy of the mutated gene the child will be affected by Pompe disease. Pompe disease is one of the metabolic myopathies and is a glycogen storage disease. The incidence of Pompe disease is estimated to be approximately 1:40,000-1:200000. The disease is due to a genetic deficiency or complete absence of the lysosomal Enzyme Acid α-glucosidase. GAA degrades glycogen to glucose, particularly in the lysosomes of muscle tissue. Due to the lack of enzyme, glycogen derived from autophagy accumulates in the lysosomes. As with other lysosomal storage diseases, the cells are affected in their function first, and increasingly as the disease progresses, the entire muscle tissue is affected. Once damage has occurred, it is usually irreversible. Three different types are known, an infantile form (IOPD), a non-classic IOPD without cardiac involvement and a late onset LOPD. IOPD patients show a GAA enzymatic activity of 1-3 %, in LOPD patients an enzyme activity of 2-40 % of GAA is present. Diagnosis will be confirmed by GAA enzyme analysis prenatally in amniotic fluid and postnatally by alpha 1-4 glucosidase activity in the blood. The later the disease appears the better it can be treated. This manuscript focuses on the present therapeutical options to treat Pompe disease in children and shed light on present molecular research curing the disease.

Keywords: Pompe, Children, Glucosidase, Enzyme deficiency, Treatment

Introduction

The disease was named after the Dutch pathologist Pompe, who first described the disease-related abnormalities in 1932. In 1963, the enzyme, acid alpha-glucosidase, was described and its absence was found to be responsible for the disease. Pompe disease is an inherited, autosomal recessive, so-called lysosomal storage disease. Lysosomes are smallest cell components in which certain substances are stored and degraded. Among other things, the enzyme alpha-glucosidase is necessary for the degradation of stored glycogen. Genetic alterations in the gene of acidic alpha-glucosidase lead to reduced formation or activity of the enzyme and thus to impaired degradation of glycogen in the lysosomes. The excessive storage of glycogen then leads to dysfunction in several organs, especially the muscles and the heart. The disease is divided into an infantile form with onset in infancy and a type with onset in adolescence or adulthood. The onset of symptoms, the symptoms themselves and the course of the disease are extremely variable and fluid. The onset of the disease in the newborn, in the first weeks of life, is just as possible as in adolescence. Severe muscle weakness, respiratory and cardiac dysfunction can occur shortly after birth, In Pompe disease, a distinction is made between an early form of the disease, which can already cause symptoms in infancy, and a late manifestation, in which the symptoms appear in childhood or even in adulthood. In the early form of the disease, newborns are characterized by weak drinking and failure to thrive, as well as muscle weakness, reduced muscle tone and low motor activity. In addition, there is marked myocardial damage that, if untreated, leads to death in the first year of life. In the foreground of the late manifestation is progressive muscle weakness and muscle wasting. The muscles of the pelvic and shoulder girdles are particularly affected. Patients often have a conspicuous gait pattern, and the walking distance is limited. They

have difficulty rising from a lying position or rising from a chair. When the arms are involved, overhead work is hardly possible, and there are increasing difficulties in everyday life. Due to the involvement of the respiratory muscles, lung function steadily decreases and patients may require non-invasive ventilatory support. Underlying the disease process is abnormal storage of glycogen in muscle cells. Glycogen, the storage form of glucose in animal cells, is normally degraded by the enzyme alpha-1,4-glucosidase.

Therapeutical Targets to Treat Pompe Disease

Enzyme Replacement Therapy

Alglucosidase Alpha (Myozyme): Alglucosidase alfa, also known as Myozyme, is a drug used for the treatment of Pompe disease, a rare lysosomal storage disorder. It is an enzyme replacement therapy that replaces the deficient enzyme in patients with Pompe disease. It was approved for medical use in the United States in 2006 and is the first drug available to treat this disease. Alglucosidase alfa is indicated for people with Pompe disease and has been approved for the treatment of infantile-onset Pompe disease in children under eight years of age. Common side effects include pneumonia, respiratory complications, infections, and fever, while more serious reactions can include heart and lung failure and allergic shock. The high cost of the drug has led to some health plans refusing to subsidize it for adults. In 2015, Lumizyme, a brand of alglucosidase alfa, was ranked as the costliest drug per patient, with an average charge of over $600,000.

Avalglucosidase Alfa (Nexviazym): Avalglucosidase alfa is a recombinantly produced acidic alpha-glucosidase, a glycogen-degrading enzyme used in the lysosomal storage disease Pompe disease, in which genetic alterations result in a deficiency of alpha-glucosidase. Avalglucosidase alfa (Nexviadyme) is a recombinantly produced acid α-glucosidase, a glycogen-degrading enzyme that is insufficiently produced or has reduced activity in Pompe disease due to genetic alterations. Nexviadyme has been approved for long-term enzyme replacement therapy in patients with Pompe disease with late manifestation.Avalglucosidase alfa is administered as an intravenous infusion. The action of avalglucosidase alfa aims to compensate for the deficiency of acid α-glucosidase (GAA), which is required for the degradation of lysosomal glycogen, present in Pompe disease. Avalglucosidase alfa is a human recombinant acid α-glucosidase that provides an exogenous source of GAA. Avalglucosidase alfa is a modification of alglucosidase alfa in which approximately 7 hexamannose structures, each containing 2 terminal fragments of mannose-6-phosphate (Bis-M6P), are conjugated to oxidized sialic acid residues on alglucosidase alfa. Compared with alglucosidase alfa, avalglucosidase alfa increases the number of M6P fragments 15-fold, allowing enhanced uptake into diaphragm and skeletal muscle.

Cipaglucosidase Alfa/Miglustat (small molecule chaperone): Cipaglucosidase alfa, also known as Pombiliti, is a medication used in combination with miglustat for the treatment of glycogen storage disease type II, also known as Pompe disease. It is a recombinant human acid α-glucosidase enzyme replacement therapy that provides an exogenous source of acid α-glucosidase. Common side effects include chills, dizziness, flushing, sleepiness, chest discomfort, cough, swelling at the infusion site, and pain. Cipaglucosidase alfa was approved for medical use in the European Union in March 2023. In the UK, it is available under the Early Access to Medicines Scheme. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has recommended the granting of a marketing authorization for Pombiliti for the treatment of Pompe disease. The applicant for this medicinal product is Amicus Therapeutics Europe Limited.

Gene Therapeutical Attempts of Pompe Disease (PD)

Another potential alternative to ERT for the treatment of PD is gene therapy. PD is a monogenic disorder, making it an ideal candidate for gene replacement strategies. In vivo gene therapy involves the administration of a gene delivery vector, either viral or non-viral, directly into the patient's cells. This approach is currently being developed for the treatment of genetic disorders. Studies using Adeno-Associated Virus (AAV) and retroviruses have shown promising results for gene therapy in PD. AAV vectors can be administered into the bloodstream to indirectly target the muscle, liver, or multiple tissues. They can also be injected directly into the muscle or cerebral ventricles to target the central nervous system. Recent advancements in the production of AAV vectors and positive results in preclinical studies have encouraged the use of AAV vectors with muscle-specific expression cassettes for the GAA transgene. This approach has shown efficient clearance of glycogen storage in muscle and improvement in muscle, cardiac, and respiratory functions. However, one limitation of targeting muscles through the systemic route is the need for high doses of the vector, which can increase the risk of immunotoxicity due to the development of anti-GAA antibodies. Another strategy for gene therapy in PD involves the stable expression of GAA in the liver. Adenoviral GAA transfer has been shown to mediate cross-correction in skeletal muscles, but the major limitation of this approach is the lack of long-term persistence of hepatic gene transfer. In the era of genome editing, another potential therapeutic strategy for PD is based on the CRISPR/CAS technology. This system involves the delivery of Cas9 protein and a RNA guide sequence to target and edit mutations in the genome. The gene can be edited through Non-Homologous End Joining (NHEJ) or Homology-Directed Repair (HDR). However, NHEJ-mediated CRISPR strategies would not be able to correct the site-specific mutations found in PD, where restoring a functional full-length GAA protein is preferred. Site-specific corrections through HDR or other methods, such as base editors, would be necessary. However, HDR-mediated CRISPR strategies are not very efficient in muscle cells due to low expression of DNA repair proteins required for HDR. The development of a one-time curative treatment for Pompe disease is desired by both patients and clinicians. Gene therapy is being explored as a potential cure, following successful applications in other diseases. Multiple gene therapy approaches are being considered for Pompe, including ex vivo approaches

using transduced stem cells, in vivo gene therapy to directly correct muscles, and in vivo gene therapy to cross-correct muscles through transduced liver and other tissues. AVR-RD-03 is an ex vivo gene therapy approach that uses transduced bone marrow-derived stem cells to produce a fusion protein of hGAA and an IGF2 peptide for cross-correction of muscles. This approach is currently in the pre-clinical stage of development. In vivo gene therapy approaches using recombinant adeno-associated virus (rAAV) are also being evaluated. AAVB1-GAA has shown promising results in transducing and expressing hGAA in various muscles, including the heart, gastrocnemius, tongue, and diaphragm. AAV8-LDes, another in vivo gene therapy, has demonstrated broad hGAA expression in liver, cardiac and skeletal muscles, and the spinal cord. These approaches aim to produce therapeutic levels of hGAA for direct correction of muscles or cross-correction through systemic delivery. In vivo rAAV-based gene therapies for cross-correction of muscles are also being developed by various biopharmaceutical companies. These therapies involve systemic delivery of rAAV gene therapies to transduce the liver and other tissues to produce and secrete hGAA for cross-correction of muscles. Some of these gene therapies are also being developed for immunotolerization to minimize the impact of anti-GAA antibodies in patients receiving Enzyme Replacement Therapy (ERT). The success of these gene therapies depends on factors such as the serotypes of rAAV capsids used, promoters, codon optimization, and signal sequences for better protein expression and secretion. However, current in vivo gene therapy approaches may face challenges in terms of poor biodistribution, low interstitial enzyme levels, and inefficient phosphorylation of hGAA, which limits its cellular uptake in skeletal muscles. It is uncertain if these approaches can modulate carbohydrate processing to increase levels of bis-phosphorylated oligosaccharides on hGAA, which are necessary for cellular uptake. Therefore, high doses of rAAV may be required to compensate for these limitations and achieve glycogen clearance in skeletal muscles. Further research is needed to determine the efficacy and safety of these gene therapy approaches in higher species, including non-human primates and humans.

CRISPR-Cas9 Technology: In a study by Kan et al. was aimed to create a mouse model that recapitulates the human form of the disease caused by a specific mutation (c.1935C>A) in the GAA gene [1]. Researchers used CRISPR-Cas9 technology to introduce the c.1935C>A mutation into the mouse genome. They also created a myoblast cell line carrying the same mutation [1]. The study then goes on to describe the various molecular, biochemical, histological, physiological, and behavioural characteristics of the Gaaem1935C>A mice. The results showed that the Gaaem1935C>A mice had normal levels of GAA mRNA expression but significantly reduced GAA enzymatic activity. They also exhibited increased glycogen storage in tissues and impaired autophagy. At three months of age, the mice showed skeletal muscle weakness and hypertrophic cardiomyopathy, but they did not experience premature mortality [1]. Overall, the Gaaem1935C>A mouse model closely resembles the human form of Pompe disease caused by the c.1935C>A mutation [1]. The researchers suggest that this model can be used to evaluate potential therapies for infantile-onset Pompe disease, including personalized approaches that aim to correct the underlying genetic mutation and restore GAA activity [1].

Liver Gene Depot Therapy in LOPD: The study of Smith et al. published in 2023 focuses on the use of gene therapy with an Adeno-Associated Virus Serotype 8 (AAV8) vector to potentially replace Enzyme Replacement Therapy (ERT) in patients with Late-Onset Pompe Disease (LOPD) in a phase 1 study based on a liver gene depot [2]. The researchers conducted a 52-week open-label, single-dose, dose-escalation study to assess the safety and bioactivity of gene therapy [2]. In the study, three patients received the first dose of the AAV8-LSPhGAA vector. After 26 weeks, the patients discontinued biweekly ERT based on the detection of elevated serum GAA activity and the absence of clinically significant declines. Prednisone was administered as immunoprophylaxis for the first four weeks, followed by an 11-week taper [2]. The results showed that all subjects maintained sustained serum GAA activities ranging from 101% to 235% of baseline trough activity two weeks after the preceding ERT dose. There were no serious adverse events related to the treatment, and no subject experienced a decrease in transgene expression due to anti-capsid T cell responses. Muscle biopsy at week 24 showed no significant changes in muscle glycogen content in two out of three subjects [2]. However, at week 52, muscle GAA activity for the cohort significantly increased. Based on these initial findings, the researchers concluded that AAV8-LSPhGAA gene therapy is safe and bioactive in patients with LOPD [2]. The study also demonstrated the safety of withdrawing ERT, the success of immunoprophylaxis, and supports further clinical development of AAV8-LSPhGAA therapy for Pompe disease [2].

Discussion

Pompe's disease belongs as acid maltase deficiency to the group of glycogen storage diseases and is classified as type II of this group [3-14]. The gene is found on 17q25.3 chromosome region [1-57]. This rare, prevalence of 1:18,702 births, hereditary metabolic disease is predominantly manifested by muscle weakness and is therefore also classified as a myopathy [15-17]. The prevalence of the adult form is estimated at 1:57,000 and that of the infantile form at 1:138,000 [3-14]. In Germany, at least 300 people are currently diagnosed; worldwide, it is assumed that 5,000-10,000 people are affected. The disease is named after the Dutch pathologist Joannes Cassianus Pompe (1901-1945), who first described the symptoms in 1932. The disease was classified as glycogen storage disease type II by G.T. Cori in 1954. In 1963, H.G. Hers discovered the absence of lysosomal α-glucosidase as the cause of the disease. The adult form was first described by A.G. Engel in 1969. As early as 1973, a therapeutic trial was conducted with alpha-glucosidase, which at that time was obtained from placenta. The disease can occur at all ages and is divided in three types, into the early (IOPD, infantile onset Pompe disease), the non-classic infantile PD without cardiac involvement and the late (LOPD, late onset Pompe disease) courses depending on the severity and time of onset of the first symptoms [3-14]. In infants it is usually fatal in the first year of life

due to heart failure in the setting of hypertrophic cardiomegaly [18-19]. The best results of treatment are found when treated in the first days of life and diagnosed very early [3-14]. It is usually fatal in the first year of life due to heart failure in the setting of hypertrophic cardiomegaly [18-19]. The infantile form begins before 3 months of age with severe muscle hypotonia, weakness in sucking and swallowing, hypertrophic cardiomyopathy, and progressive liver enlargement [1-57]. The adult form is characterized by progressive limb-girdling myopathy that begins in the lower limbs and also affects the respiratory problem. Respiratory problems may be the first symptom. A whole spectrum of intermediate forms exists between these two extremes. The diagnosis is confirmed by the detection of the enzyme deficiency in fibroblasts, lymphocytes, dried blood or in chorionic villus sampling [1-57]. Differential diagnoses of the infantile form are primarily Werdnig-Hoffmann disease and metabolic or idiopathic cardiomyopathy. When the disease has a later onset, it is reminiscent of Danon disease (see there). Differential diagnoses of the adult form are the other myopathies. If both mutations have been investigated in the patient, heterozygote testing can be performed in the family and prenatal diagnosis in further pregnancies of the mother. In very rare cases, prenatal diagnosis is complicated by pseudo deficiency alleles. A complex transposon, a transponible element insertion as a novel cause of Pompe disease was described on intron 15 recently [20].

The development of next-generation ERTs and gene therapies for Pompe disease is crucial in order to address the limitations of current treatments and provide more effective options for patients [1,2,21-37]. These advancements aim to overcome challenges such as poor distribution to muscles, reduced muscle uptake, interference from antibodies, and limited penetration of the blood-brain barrier. Promising developments have been made with neoGAA and AT-GAA, which have reached the pivotal stage of clinical development. The breakthrough therapy designation granted to AT-GAA by the FDA indicates its potential for substantial improvement over existing therapies [1,2,21,24-26,33,35]. Gene therapy, as a single-administration curative treatment, holds great promise for Pompe disease based on preclinical data [1,2,21,24-26,33,35]. However, there are still significant challenges and questions that need to be addressed. These include replicating preclinical efficacy in humans, ensuring durable transgene expression, and establishing long-term safety and efficacy. Clinical studies comparing gene therapy to current standard of care and demonstrating long-term safety and gene expression will be necessary [1,2,21,24-26,33,35]. Additionally, the manufacturability of rAAV gene therapies at large scale and the improvement and standardization of analytical assays will need to be addressed.

Therapy with pluripotent stem cell lines shows compromising results in the treatment of Pompe disease and further research is necessary to produce clearer data towards efficacy and tolerability [12,32,33,38].

The biopharmaceutical industry plays a crucial role in developing effective medicines and providing treatment options for rare genetic diseases like Pompe. It is unlikely that one treatment will be optimal for all patients, and different factors such as tolerability, convenience, and individual circumstances may influence treatment choices. Combining therapies may also be considered for optimal outcomes, such as using next-generation ERTs for peripheral symptoms and intrathecal administration of gene therapy for neuronal aspects. Continual development of more effective therapies is necessary to properly manage Pompe disease and provide treatment options for patients [39-57].

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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SB wrote the article, LB made suggestions and corrections of the references, GV checked the information details and references, EL worked on manuscript, and EMA checked the references in detail.

Conflict of Interest

None.

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