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Lysosomal diseases and enzyme replacement therapy

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Abstract

Lysosomal diseases are genetic disorders caused by enzyme deficiencies that lead to substrate accumulation within lysosomes. Key conditions treated with enzyme replacement therapy (ERT) include Gaucher disease, Pompe disease, Fabry disease, alpha-mannosidosis, and mucopolysaccharidoses types I (MPS I) and II (MPS II). ERT involves administering exogenous enzymes to partially restore their function, reduce substrate accumulation, and improve clinical symptoms. While ERT has shown benefits in slowing disease progression and enhancing quality of life, it faces challenges such as immunogenicity, limited biodistribution, and high costs. This work examines the characteristics of these diseases, advances in ERT, and future perspectives for improving its effectiveness and accessibility.

Keywords: Lysosomal diseases; Enzyme replacement therapy; Genetic disorders; Innovative treatments; Gene therapy

1. Introduction

Lysosomes are membrane-enclosed acidic organelles that function as the cell's main site for catabolism. They play a vital role in numerous cellular processes, such as nutrient storage and autophagy (Figure 1) [1].

They are involved in the degradation of a wide range of molecules, including cellular and extracellular substrates intended for the degradation of compounds such as proteins, glycogen, lipids, and nucleic acids, reach the lysosomes through various pathways, such as endocytosis, phagocytosis, autophagy, or direct transport [2].

Due to the critical roles that lysosomes play in cellular metabolism, cell proliferation and differentiation, immunity, and apoptosis, any alteration or dysfunction in lysosomes can disrupt the normal homeostasis of the cell and the organism, potentially causing or exacerbating human diseases [3].

The discovery of lysosomes had a significant impact on medicine, as functional defects in lysosomes were linked to a group of genetic diseases known as lysosomal storage disorders [4].

There are more than 50 clinical variants of lysosomal storage diseases (LSD), which are characterized by the progressive accumulation of undigested material within the lysosomes, leading to cellular dysfunction in various organs, including the brain, muscles, bones, skin, heart, and spleen.

Most LSDs are caused by mutations that reduce the enzymatic activity of a specific lysosomal hydrolase, resulting in a blockage of a particular catabolic pathway and the accumulation of storage material [5].

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Table 1 Most common lysosomal diseases and their main characteristics

Disease	Description	Involved gene	Phenotype	Therapy used
Fabry	It is a genetic lysosomal storage disorder associated with the X chromosome that causes the accumulation of glycosphingolipids in the body's tissues [7]. It manifests in multiple systems, leading to progressive organ damage and reduced life expectancy, resulting in significant morbidity and mortality [8].	GLA gene 300644, located on chromosome Xq22 [9].	301500 [9].	Multidisciplinary symptomatic treatment, enzyme replacement therapies (agalsidase alpha and agalsidase beta), and chaperone treatment with migalastat [8].
Gaucher	The condition arises from a deficiency in the lysosomal enzyme glucocerebrosidase, leading to the accumulation of various substrate-related compounds in cellular lysosomes. This causes visceral manifestations such as hepatomegaly and splenomegaly, as well as cytopenias and bone issues. In addition to the enlargement of the liver and spleen, progressive neurological findings are also observed over time [10].	Biallelic mutations in the GBA1 gene, on chromosome 1q22 [11].	230800, 230900, 231000 [12,13,14].	Inhibitory chaperones Non-inhibitory chaperones Ambroxol [15].
Krabbe	This lysosomal storage disorder results from a deficiency in the enzyme galactocerebrosidase, leading to the accumulation of psychosine, a toxic compound. This buildup primarily affects the nervous system, causing widespread neurological symptoms [16].	A mutation that is either homozygous or compound heterozygous in the galactosylcerami-dase GALC; 606890 gene on chromosome 14q31 [17].	245200 [17].	Hematopoietic stem cell transplantation. Umbilical cord blood stem cell transfusion. Supportive or symptomatic therapy [16].
Pompe	Autosomal recessive disorder caused by mutations leading to a deficiency of the enzyme acid alpha-glucosidase. Two clinical presentations are considered: infantile-onset Pompe disease and late-onset Pompe disease [18].	Glycogen storage disease type II, caused by a mutation in the GAA gene 606800, which encodes acid maltase, located on chromosome 17q25 [19].	232300 [19].	Enzyme Replacement Therapy Gene Therapies; Regeneron, Amicus, licensed by Sarepta from Lacerta, Abeona, Erasmus MC, AVROBIO, JCR Pharma [20].
Cystino-	Rare autosomal recessive lysosomal storage disorder caused by mutations in the gene that encodes the cystine protein. It has	Gene CTNS,	219800,	Systemic therapy with cysteamine.

sis	three known forms of presentation: infantile (nephropathic), juvenile (intermediate and late onset), and adult (benign, ocular, and non-nephropathic) [21].	within the deletion interval on chromosome 17p13.2 [22].	219900, 219800, 219750 [22].	Topical ophthalmic therapy with cysteamine. Use of prostaglandin inhibitors Treatment of complications and comorbidities.Kidney transplant [21].
Danon	Danon disease is an X-linked dominant genetic disorder that presents as a clinical triad, including cardiomyopathy, skeletal myopathy, and intellectual disability [23].	A mutation occurs in the LAMP2 gene 30906, which encodes the lysosome-associated embrane protein 2, located on chromosome Xq24 [24].	300257 [24].	There is no established treatment. The disorder is managed symptomatically, aiming to control physiological cardiac irregularities [23,25].
Mucopo-lysaccha-ridosis	This is a group of genetic disorders that includes seven types and 13 subgroups, characterized by an inherited enzyme deficiency that affects the degradation of glycosaminoglycans [26]. The absence or malfunction of lysosomal enzymes leads to the accumulation of these compounds, which, over time, causes progressive damage to cells, tissues, and organs [27].	MPS I- gene encoding alpha-L-iduronidase IDUA; 252800 on chromosome 4p16 [28]. MPS II- Mutation in the gene encoding iduronate 2-sulfatase IDS; 300823 on chromosome Xq28 [29]. MPS III A- Mutation in the gene encoding N-sulfoglucosamine sulfohydrolase SGSH; 605270 on chromosome 17q25 [30]. MPS III B- Mutation in the gene encoding N-	MPS I-607014 [28]. MPS II-309900 [29]. MPS III A-252900 [30]. MPS III B-252920 [31]. MPS III C-252930 [32]. MPS III D-252940 [33]. MPS IV A-253000 [34].	Enzyme Replacement Therapy (ERT) IDUA (Aldurazyme) AAV Gene Therapy Substrate Reduction Therapy (Rhodamine) [27,36].

		alpha-acetylglucosaminidase NAGLU; 609701 on chromosome 17q21 [31]. MPS III C- Mutation in the HGSNAT gene 610453, encoding heparan acetyl-CoA:alpha-glucosaminide N-acetyltransferase, on chromosome 8p11 [32]. MPS III D- Mutation in the gene encoding N-acetylglucosamine-6-sulfatase GNS; 607664 on chromosome 12q14 [33]. MPS IV A- Mutation in the GALNS gene 612222, which encodes galactosamine-6-sulfate sulfatase, on chromosome 16q24 [34]. MPS IV B- Mutation in the gene encoding beta-galactosidase GLB1; 611458 on chromosome 3p22 [35].	MPS IV B-253010 [35].	
Tay-Sachs	It is a neurodegenerative disorder caused by the deficiency of the enzyme hexosaminidase-A, leading to progressive neuronal damage. The disease manifests in three variants: infantile, juvenile, and adult, with the infantile form being the most severe.	Mutation in the alpha subunit of the hexosaminidase A gene HEXA;	272800 [38].	Therapies are used to manage symptoms, especially for the late

	Symptoms typically begin within the first six months of life and include motor weakness, developmental delay, and a characteristic "cherry-red spot" in the retina. As the disease progresses, affected individuals experience loss of motor function and vision [37].	606869 on chromosome 15q23 [38].		onset of this disorder; currently, there is no cure for TSD. Efforts have been made to develop enzyme replacement therapies, enzyme enhancement through the use of chaperones, substrate reduction, gene therapy, and stem cell replacement therapy [39].
GM1 Gangliosidosis	A neurodegenerative disease resulting from the deficiency of the enzyme β-galactosidase, which is involved in the cleavage of ganglioside GM1. The accumulation of ganglioside GM1 and other substrates in the lysosome disrupts cellular physiology and precipitates dysfunction of the nervous system [40].	GM1 I, II, III- Mutation in the gene encoding beta-galactosidase-1 GLB1; 611458 on chromosome 3p22 [41,42,43].	GM1 I- 230500 [41]. GM1 II- 230600 [42]. GM1 III- 230650 [43].	There are no treatments available for GM1, and current medications focus on managing symptoms. However, new therapeutic strategies are emerging that aim to replace, mimic, or assist the primary functions of β-galactosidase [44].
Metachromatic leukodystrophy	It is a rare lysosomal storage disease that results from insufficient activity of arylsulfatase A. It follows an autosomal recessive inheritance pattern. This condition is severe and can lead to death within 5 to 6 years in its early-onset form [45].	Mutation in the arylsulfatase A gene ARSA; 607574 on chromosome 22q13 [46].	250100 [46].	Currently, there are no curative treatments available; the therapeutic approach focuses on improving quality of life through symptom management [45].
Neuronal Ceroid Lipofuscinoses	A group of neurodegenerative conditions primarily impacting the gray matter, characterized by seizures, cognitive deterioration, myoclonus, vision problems, and abnormal movements [47].	CLN 1- Mutation in the gene encoding palmitoyl-protein thioesterase-1 PPT1; 600722 on chromosome 1p34 [48]. CLN 2- Caused by mutation in the TPP1 gene 607998 on chromosome 11p15 [49]. CLN 3- Mutation in the CLN3 gene 607042 on chromosome 16p12 [50].	CLN1- 256730 [48]. CLN 2- 204500 [49]. CLN 3- 204200 [50]. CLN 5- 256731 [51].	Enzyme replacement therapy recently approved by the FDA and EMA for CLN2 is still being researched for new treatments [53].

		CLN 5- Mutation in the CLN5 gene 608102 on chromosome 13q22 [51]. CLN 7- Mutation in the MFSD8 gene 611124, on chromosome 4q28 [52].	CLN 7- 610951 [52].	
Alpha-mannosi-dosis	Is a genetic disorder caused by a deficiency of lysosomal α-mannosidase, inherited in an autosomal recessive manner [54]. The clinical symptoms include skeletal abnormalities, cognitive impairment, hearing loss, and frequent infections. In its severe form, the disease leads to death in early childhood, while those with milder forms may reach adulthood [55]. It occurs in two forms: a severe form with liver enlargement and early death due to infections (Type I), and a mild form with hearing loss, mental retardation, and survival into adulthood (Type II) [54].	Caused by homozygous or compound heterozygous mutation in the MAN2B1 gene; 609458 on chromosome 19p13 [56].	248500 [56].	Bone marrow transplant; hematopoietic stem cell transplant.Enzyme replacement therapy; Velmanase alfa, for long-term treatment in adults, adolescents, and children, the recombinant enzyme does not cross the blood-brain barrier, limiting its effectiveness in the central nervous system. rhLAMAN reduces biomarkers and oligosaccharides in patients and stabilizes the disease [57].

With the understanding of various mechanisms associated with lysosomes in the development of diseases, it is reasonable to conduct extensive research focused on lysosomes for therapeutic treatments.

Several strategies have been proposed, such as enzyme replacement therapies and the use of various chemical compounds specifically targeting lysosomal proteins or signaling proteins related to lysosomes to modulate cellular behavior, among others [6].

It is crucial to develop and investigate these options to explore innovative treatments in the coming years.

There is a wide variety of lysosomal storage diseases (Table 1). Some of them will be discussed in more detail, specifically those that have enzyme therapy replacement.

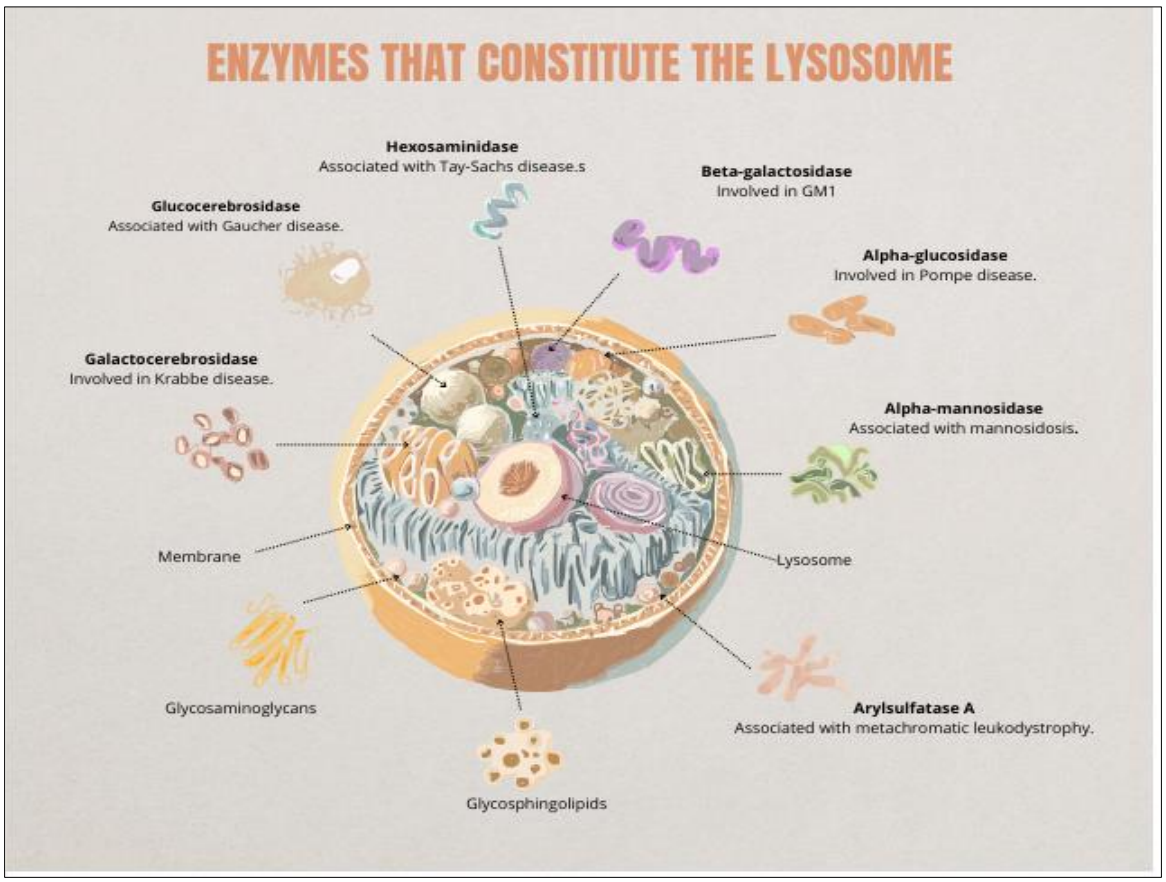

Figure 1 Enzymes involved in lysosomal diseases, present in the lysosome

2. Mucopolysaccharidosis type I (MPS I) – 252800

Mucopolysaccharidosis type I (MPS I) is an autosomal recessive inherited disorder classified among lysosomal storage diseases related to innate metabolic errors. Its global incidence ranges from 0.99 to 1.99 per 100,000 live births, and 20% of MPS I cases present in an attenuated form. The disease is characterized by the accumulation of glycosaminoglycan (GAG) substrates: dermatan sulfate and heparan sulfate, due to a deficiency of the enzyme alpha-L-iduronidase. This deficiency leads to progressive, debilitating, and fatal multi-organ dysfunction. Each type of GAG has primary deposition organs; heparan sulfate primarily causes neurological symptoms, while dermatan sulfate is associated with cardiomyopathy and valvulopathy. Three clinical manifestations are defined, varying in symptom severity and age of onset: Hurler (severe), Hurler-Scheie (moderate), and Scheie (mild) [58].

Most presentations of MPS are inherited in an autosomal recessive pattern; however, MPS II is a genetic disorder linked to the X chromosome [59]. Studies suggest that the average life expectancy for patients with this condition is 11.6 years [60]. The accumulation of GAGs in the cytoplasm of endothelial cells, cardiomyocytes, and fibroblasts in cardiac tissue leads to progressive cardiac thickening, which can result in valvular deformities causing regurgitation or stenosis [61]. It is estimated that around 98.2% of patients exhibit symptoms by six months of age, such as increased head

circumference, feeding difficulties, alopecia, organomegaly, cardiac issues, joint restrictions, or kyphosis [61]. Additionally, research on MPS VI has explored its pathophysiology, diagnosis, and treatment [62], and the early progression of the disease in Hurler syndrome has also been documented [61]. A study in the UK evaluated the prevalence and survival of Hurler, Hurler-Scheie, and Scheie syndromes [58].

3. Enzyme Replacement Therapy (ERT)

Enzyme Replacement Therapy (ERT) is the primary treatment for patients with MPS I, particularly for those with attenuated forms of the disease, such as MPS I-Hurler-Scheie and MPS I-Scheie. This therapy aims to provide a sufficient supply of the IDUA enzyme to help break down the accumulated GAGs, thereby alleviating some of the symptoms associated with the disorder [63, 64].

The mechanism of action of ERT involves the administration of a recombinant form of the IDUA enzyme, which is designed to mimic the natural enzyme. This enzyme is delivered intravenously, allowing it to enter the bloodstream and reach the tissues where GAG accumulation occurs. Once inside the cells, the enzyme helps to degrade the GAGs, reducing their levels and mitigating associated symptoms [63, 64].

The clinical benefits of ERT have been documented in clinical studies, showing significant improvements in various aspects of health for patients with MPS I. These benefits include reduction in organ size (e.g., liver and spleen), improvement in joint mobility and function, enhanced respiratory function, and an overall better quality of life for patients [63, 64].

The treatment regimen of ERT is typically administered on a regular schedule, often every two weeks. The frequency and dosage may vary based on the patient's age, weight, and specific health needs. Continuous monitoring is essential to assess the treatment's effectiveness and make any necessary adjustments [63, 64].

However, ERT has limitations. Although it has proven effective for many patients, it does not address all symptoms of MPS I, particularly those related to neurological involvement. Patients with the severe form of MPS I (Hurler syndrome) may experience cognitive decline and other neurological issues despite receiving ERT. Therefore, ERT is often combined with other treatment modalities, such as hematopoietic stem cell transplantation (HSCT), especially in younger patients diagnosed early [65].

Regarding long-term outcomes, studies indicate that patients receiving ERT have improved health outcomes and a better quality of life compared to those who do not receive treatment. However, the long-term efficacy and safety of ERT continue to be evaluated in ongoing clinical trials [64, 65].

4. Mucopolysaccharidosis type II (MPS II) – 300823

Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is a rare lysosomal storage disorder that is inherited in a recessive manner and is linked to the X chromosome. The disease is caused by a deficiency of the lysosomal enzyme iduronate-2-sulfatase (I2S), which catalyzes the hydrolysis of 2-sulfate groups in dermatan sulfate and heparan sulfate [66].

The deficiency of this enzyme leads to the abnormal accumulation of these two glycosaminoglycans (GAGs), resulting in the dysfunction of multiple organ systems, including the brain in most patients, thus presenting a severe clinical phenotype [67].

Since the disease is inherited in an X-linked recessive manner, it almost always occurs in males. Female carriers of the mutated IDS gene are asymptomatic, though cases of affected female patients have been reported [66].

MPS II is clinically heterogeneous and has traditionally been described as either a severe or attenuated form, based on survival duration and the presence or absence of neurological disease. It is becoming increasingly clear that the disease exists on a continuum between the two forms, and that its severity is related to the relative levels of the IDS enzyme [68].

Presents in two clinical forms: neuropathic, which affects the central nervous system (CNS), and non-neuropathic, which does not. In the non-neuropathic variant, the accumulation of dermatan sulfate occurs without involving the CNS. It is estimated that about two-thirds of patients have the neuropathic form, which can manifest earlier in life. Newborns

with MPS II typically have a higher birth weight compared to healthy infants; however, the non-neuropathic form, also known as attenuated, is characterized by a slow progression of peripheral symptoms and a reduction or absence of cognitive issues. Patients with this latter form generally survive into late adulthood [66].

5. Enzyme therapy

Currently, the main treatment consists of enzyme replacement therapy (ERT) using recombinant human iduronate-2-sulfatase administered intravenously. ERT helps to lower GAG levels in the urine, reduce liver and spleen size, improve physical endurance, and stabilize bone and cardiac abnormalities [69].

The most common adverse reaction to this therapy is a hypersensitivity response related to the infusion, which primarily appears as a skin rash, fever, and headache. This reaction can be managed by slowing the infusion rate and administering antihistamines [70].

Another causal treatment approach is hematopoietic stem cell transplantation (HSCT). Peripheral blood monocytes can cross the blood-brain barrier and settle in the central nervous system as microglial cells. This ability, along with the advantage of a single transplant procedure, is a compelling argument in favor of using HSCT. However, complications arising from immunosuppressive therapy and graft-versus-host disease (GVHD) require careful consideration of this method [69].

Substrate reduction therapy (SRT) is designed to inhibit GAG production, thereby reducing intracellular substrate accumulation. Since the substrates in MPS are the same across different types, SRT is suitable for all types and can cross the blood-brain barrier. Genistein can suppress GAG synthesis and improve the cell cycle in MPS II by inhibiting epidermal growth factor receptor phosphorylation, subsequently impacting the expression of specific genes regulated by EGF-dependent signaling pathways [70].

6. Gaucher disease - 230800, 230900, 231000

Gaucher disease (GD) is the most prevalent inherited lysosomal storage disorder, resulting from mutations in the acid β-glucosidase (GBA) gene [71].

This enzyme deficiency causes glucocerebroside lipids to build up in one or more organs, leading to various symptoms. Additionally, complex mechanisms like inflammation, localized cell interactions, and GCase substrate preferences have been suggested to explain the disease's impact on specific organs and the possible effectiveness of treatments [72].

Gaucher disease has traditionally been categorized into three clinical types based on symptom severity.

Type 1 (GD1) is the most common and presents with varying levels of anemia, thrombocytopenia, hepatosplenomegaly, and bone issues. Type 2 (GD2) is a rare, severe form that leads to neurodegeneration and early death. Type 3 (GD3) is a chronic, progressive neurodegenerative variant that typically appears between infancy and adolescence, though it can occasionally develop in adulthood [73].

In severe cases, enzymatic deficiency leads to inflammation, organomegaly, bone disease, and neurodegeneration. Neuronopathic Gaucher disease (nGD) presents in two forms, characterized by chronic or acute damage to the central nervous system (CNS). Cellular and molecular studies investigating the pathological mechanisms of nGD primarily focus on lysosomal dysfunction, as the lysosome is the key organelle affected in Gaucher disease. However, recent research reveals alterations in other organelles that also contribute to nGD pathology. For instance, the abnormal accumulation of GluCer in lysosomes due to the loss of β-GC activity results in excessive calcium release from the endoplasmic reticulum (ER), activating the ER-associated degradation pathway and the unfolded protein response [74].

6.1. Diagnosis of Gaucher Disease Types 2 and 3

Type 2 Gaucher disease (GD2) may present before birth, in the neonatal period, or during the first year of life, so obstetricians, neonatologists, and pediatricians should include it in the differential diagnosis when encountering suspicious symptoms. In contrast, type 3 Gaucher disease (GD3) is more heterogeneous and is usually diagnosed based on neurological manifestations, particularly abnormal horizontal saccadic eye movements, though it includes multiple phenotypes and can be identified from childhood to later stages in life [75].

6.2. Targeted therapy

Options include enzyme replacement therapy (ERT) or substrate reduction therapy (SRT; for example, miglustat, eliglustat). Hematopoietic stem cell transplantation may be considered for individuals with severe GD, particularly those with chronic neurological involvement (type 3 GD) [76].

Gene therapy has emerged as a promising approach for treating inherited diseases, such as lysosomal storage disorders (LSDs). It aims to alter gene expression to replace defective genes, deactivate malfunctioning ones, or introduce new genes for therapeutic effects. This therapy uses vectors—either viral or non-viral—to deliver therapeutic genes to targeted cells. Non-viral methods offer low immune responses but are less efficient in delivering genetic material, making viral vectors more effective for clinical use. Common viral vectors include retroviruses, adenoviruses, lentiviruses, and adeno-associated viruses (AAVs). AAVs, due to their low immunogenic risk and ability to target specific tissues, have become particularly attractive in gene therapy [77].

6.3. Enzyme Replacement Therapy (ERT)

ERT is the most common treatment for Gaucher disease and involves administering glucocerebrosidase to replace the deficient enzyme. Approved treatments include:

- Imiglucerase (Cerezyme): Approved for individuals over 2 years old.
- Velaglucerase alfa (VPRIV) and Taliglucerase alfa (Elelyso): Approved for individuals over 4 years old [78].

6.4. Substrate Reduction Therapy (SRT)

SRT, primarily used in adults, reduces the production of glucocerebroside, allowing the residual enzyme to function properly. Approved medications include:

- Eliglustat (Cerdelga) and Miglustat (Zavesca): Both approved for adults [78].

7. Pompe disease - 232300

Pompe disease is a rare and deadly muscle disorder. The disease is a glycogen storage disorder, a lysosomal disorder, and an autophagic myopathy [79].

Pompe disease (PD) is a rare autosomal recessive disorder caused by mutations in the GAA gene, located on chromosome 17, which encodes the enzyme acid alpha-1,4-glucosidase (GAA). To date, over 560 mutations have been identified in this gene. The GAA enzyme is responsible for breaking down α-1,4 and α-1,6-glucosidic bonds in glycogen. A deficiency in GAA activity results in the accumulation of glycogen within lysosomes, particularly affecting muscle tissue. PD is a chronic, progressive condition commonly marked by limb-girdle muscle weakness and respiratory complications. It is classified into two forms based on the age of onset: infantile and childhood/adult. Patients with PD present with a range of systemic symptoms influenced by the timing of disease onset. Early diagnosis is critical to mitigate or prevent irreversible organ damage caused by disease progression [80].

Gene therapy represents a promising strategy for Pompe disease due to its multisystemic nature and the need to target central nervous system manifestations. This approach is feasible and provides an opportunity to comprehensively address the underlying pathology of cellular glycogen accumulation [81].

The diagnosis of Pompe disease has advanced with the use of dried blood spot (DBS) testing to assess AAG enzyme activity and the availability of next-generation sequencing (NGS) in hospitals, particularly in developed nations. When clinical suspicion arises, DBS testing is conducted to measure enzyme activity, and if levels are low, genetic testing is used to confirm the diagnosis. Furthermore, patients with muscle weakness are frequently diagnosed through genetic panels that include the GAA gene [82].

Other tests, such as electromyography, reveal myopathic patterns with myotonic discharges in specific muscles, while muscle MRI detects fat infiltration in certain muscles. In muscle biopsies, glycogen buildup is readily observed in infantile-onset Pompe disease (IOPD), whereas in late-onset Pompe disease (LOPD), it may appear normal or show only mild alterations. The definitive diagnosis is confirmed by identifying two pathogenic variants in the GAA gene. In more complex cases, advanced DNA or RNA sequencing and enzyme activity testing in various tissues are required for confirmation. Some variants cause pseudodeficiency, which is characterized by low enzyme activity without muscle damage [82].

8. Enzyme therapy

Enzyme replacement therapy can help enhance muscle tone and reduce glycogen accumulation in individuals with Pompe disease. The following drugs have been approved for treatment: Alglucosidase alfa (Myozyme) for infantile-onset Pompe disease, Lumizyme for individuals of all ages with Pompe disease, and Avalglucosidase alfa-ngpt (Nexviazyme) for individuals aged 1 and older with late-onset Pompe disease [83].

Alternative treatments to enzyme replacement therapy (ERT), which involves repeated intravenous infusions of recombinant human GAA (rhGAA), represent the only available option for Pompe disease (PD). Over a decade since its introduction, it has become clear that ERT can extend the lifespan of those with infantile-onset Pompe disease (IOPD) and stabilize disease progression in late-onset Pompe disease (LOPD); however, it does not cure PD. Challenges such as the limited uptake of the enzyme in key tissues and the high immunogenicity of rhGAA hinder the full effectiveness of ERT. Gene transfer of the GAA gene using adeno-associated virus (AAV) vectors has shown promise in reducing glycogen buildup and improving the PD phenotype in preclinical studies [84].

9. Fabry disease-30064

Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the GLA gene (300644), a reduced to null activity of the enzyme α-galactosidase A resulting in a progressive accumulation of glycolipids in plasma and cells throughout the body, tissues such as kidneys, heart, vessels and the CNS/P are affected and show a progressive functional deterioration of varying degrees among individuals [85].

The gene is located on the long arm of the X chromosome (band q22), is 12 kb long and consists of seven exons and six introns so an affected father transmits the mutation to all daughters while his sons are unaffected. An affected mother transmits the mutation to 50% of all children [86]. Due to the random inactivation of one of the two X chromosomes in each cell in early embryogenesis, the variability of the clinical picture is greater in females [87].

Fabry disease is a progressive, potentially life-threatening condition that impacts multiple systems in the body. It affects both men and women across all ethnicities, with an estimated incidence ranging from 1 in 40,000 to 1 in 117,000 individuals [88].

It can be divided into a classic phenotype which is more frequent in men causing almost no activity less than 5% of the normal mean and are usually severe phenotypes with characteristic signs, and the non-classic also called late-onset which is usually phenotypically milder and usually have residual enzyme activity and are less affected with manifestations that may be limited to one organ [89,90].

The treatment is directed at specific signs and symptoms, as well as preventing secondary complications.

10. Enzyme Replacement Therapy (ERT)

Enzyme replacement therapy (ERT) is utilized to alleviate symptoms associated with Fabry disease and stabilize organ function. Other researchers recommend initiating ERT after the diagnosis of the disease, prior to the onset of irreversible complications, and suggest that ERT should be avoided after irreversible organ damage. Moreover, its use should be discontinued if there is no improvement in the function of the affected organ. [91].

ERT has become the primary therapy for Fabry disease since 2001. It has effects on cardiac structure, including progressive decreases in interventricular septum (IVS) thickening and left ventricular (LV) mass. However, there are not many systematic reviews focusing on the improvement of left ventricular hypertrophy (LVH) after ERT [92].

ERT involves the exogenous supplementation of the alpha-galactosidase A (GLA) enzyme and has been successfully administered in the treatment of Fabry disease. The effect of ERT is also influenced by the age at which treatment is initiated. According to current recommendations, enzyme replacement therapy (ERT) should be initiated in males at the age of 16, regardless of their symptomatic status, although it should be considered individually from the age of 8–10 years [93]. Starting ERT at an early age (<25 years) can effectively reduce the deposition of Gb3 and attenuate the progressive clinical manifestations of Fabry disease; however, it cannot reverse clinical manifestations [94].

Agalsidase alfa and beta are generally safe. The most common adverse events are infusion associated reactions (IAR), which are mild or moderate and tolerable in most cases [93].

Enzyme replacement therapy (ERT) faces several challenges, including significant clinical variability among patients, high treatment costs, and a common occurrence of mild to moderate infusion-related reactions. These reactions are often linked to the development of antibodies against the infused enzyme. Additionally, ERT requires lifelong biweekly intravenous infusions, imposing a substantial logistical and emotional burden on patients [95].

11. Conclusion

Lysosomal diseases underscore the critical role of lysosomes in cellular health and highlight the severe consequences of their dysfunction. Enzyme replacement therapy has emerged as a transformative solution, offering improved outcomes and renewed hope for affected individuals. This progress demonstrates the profound impact of advancing biomedical research, not only in addressing the challenges of rare genetic disorders but also in fostering innovation that benefits broader healthcare systems and society as a whole.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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