International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 6, June 2025 ijppr.humanjournals.com ISSN: 2349-7203

Pompe Disease: The Advanced Strategy

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Received: 2025-04-24 Revised: 2025-05-05 Accepted: 2025-05-10

ABSTRACT

Acid alpha-glucosidase deficiency in Pompe disease (PD), a lysosomal storage illness brought on by mutations in the GAA gene, hinders the breakdown of glycogen and results in its abnormal accumulation, especially in the skeletal and cardiac muscles. Infantile-onset (IOPD) and late-onset (LOPD) are the two main forms of the illness, and they differ in severity and clinical course. Over 250 documented GAA mutations, including frequent ethnic-specific variants and pseudodeficiency alleles, are highlighted in this article that examines the genetic underpinnings of Parkinson's disease. Defective autophagy plays a major role in disease pathophysiology, particularly in skeletal muscle failure, which limits the effectiveness of enzyme replacement therapy (ERT).The article details recent advances in treatment approach, including pharmacological chaperones, enhanced ERT formulations, and constructing gene therapies that utilize adeno-associated virus (AAV) vectors to address muscle or liver tissue. To optimize patient outcomes and overcome existing therapy limitations, the article highlights the importance of early diagnosis, personalized therapeutic regimens, and novel delivery platforms. In an effort to guide future clinical research and treatment of Pompe disease, this comprehensive review combines molecular, clinical, and pharmacologic information.

Keywords:- Pompe disease, Autophagy, Adeno-Associated Virus, Mutation

INTRODUCTION

Pompe disease, sometimes referred to as acidic substances an enzyme called malt insufficiency or disease of glycogen storage type II, is a chromosomal illness that is by intralysosomal glycogen accumulations buildup within every cell, especially in the muscles of the bones, because of anomalies of alpha 1,4 glucosidase .[1] A lack of acid alpha-glucosidase (GAA), a lysosomal enzyme that hydrolyzes glycogen to glucose, results in Pompe disease, a neuromuscular condition. Pathological glycogen accumulation, the disease's hallmark, impairs many cell types' metabolism and functioning, particularly those of muscles, which can result in respiratory, muscular, and cardiac problems. The classical infantile-onset (IOPD) and late-onset (LOPD) variants of Pompe disease comprise the two primary spectrums of symptoms.[2] GAA maintains the integrity of glycogen during the lysosomal breakdown process. When GAA levels are low, glycogen gradually accumulates and stores in the lysosome, cytoplasm, and free glycogen pools within muscle fibers, which significantly impairs normal muscle ultrastructure and function.[3-5] Pompe disorder refers to chronic muscle impairment triggered by mutations in the acid alpha-glucosidase (GAA) genetic material, which degrades glycogen in the acidic conditions of the lysosome. When glycogen has been fully converted GAA into glucose, it can leave the lysosome. parts that are catastrophically injured are the muscles of the skeleton and cardiovascular, however lysosomal buildup of glycogen occurs in numerous tissues due to an enzyme shortage. Other names for the illness include "Acid maltase deficiency" and "alongside Type II glycogen storage disease (GSDII. When examining cases of "hyper-creatine kinase-anemia" or other ineluctably raised serum enzymes, like lactate dehydrogenase, or the "liver enzymes," aspartate/alanine aminotransferase, that are released from the injured muscle tissue, an unexpected or coincidental discovery may lead to the diagnosis of Pompe disease. [6] Dr. Pompe shed light on the disease's fundamental biochemistry, which is the extensive Vacuolar glycogen is stored in nearly every type of tissue. 1932 was the same year that comparable cases were reported.[7,8] Following decades of progress in fundamental research, the glycogen metabolic pathway was identified. Comprising the lysosome, a widely distributed membrane-bound vesicle with an acidic intraluminal pH that was recently identified as a cellular organelle and hydrolytic enzymes.[9,10]. The enzyme that breakdown glycogen called acid alpha-glucosidase was identified in 1963 by Belgian researcher Henri-Gery Hers. It is typically absent from Pompe disease and present in the lysosome.. [11] deposition diseases, could be explained by the lack of other lysosomal which prompted researchers to look for the enzymes in other lysosomal storage diseases (LSDs) that are in charge of the storage compounds. Of the several lysosomal storage diseases currently known to exist, Pompe illness holds the distinction of being the first one to be scientifically documented. [12]

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Volume 31, Issue 6, June 2025 ijppr.humanjournals.com ISSN: 2349-7203

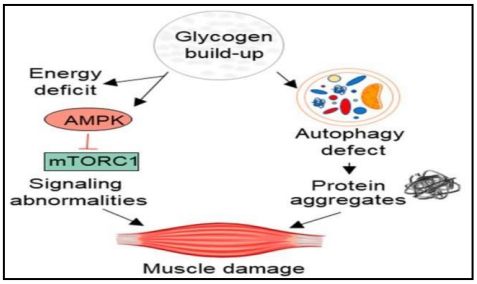

Figure 1: Pompe disease

GENE DEFECT

A GAA gene is located on chromosomal number 17q25. The gene is around 28 kb long and has 20 exons together.The first exon and the second exon are separated by an intron of about 2.7 kb., which is not translated. The gene codes for a peptide with a molecular weight of 110 kDa and 952 amino acids. The mature GAA proteins, which are 70 kDa and 76 kDa, are the product of extensive post-translational changes of proteins, including glycosylation and proteolytic processing. [13] Over 250 mutations have been found on the GAA gene. [14] and gene is affected by the mutations. various ethnic groups have various common mutations, such as the splicing variantc.-32-13T>G in patients who are Caucasian. [15] the p.D645E mutation in Chinese individuals from Taiwan, and the p.R854X mutation in African Americans1.22 A handful of the mutations have been expressed in cultured cells, and there is a correlation between the severity of the disease and the detected GAA activity.[16,17]. Chinese ethnic groupings differ significantly from Caucasians in terms of mutations, as evidenced by the among Taiwanese citizens. i.e. A mutation like p.D645E is an illustration of a founder effect., which has been discovered in up to 80% of infantile cases and is linked to a haplotype.[18]. The LOPD gene mutation p.W746C is linked to it.[19]Asian groups, especially those in Taiwan and Japan, are even more likely to have two additional sequence variations [20].Later research revealed that variation p.E689K was a neutral polymorphism nevertheless, since that patient lacked glycogen storage in his skeletal muscles, the significance of variation p.G576S remained mysterious. GAA activity for variation p.G576S was 20% lower via transient transfection in COS-7 cells than for the wild-type construct,28 which led to the variation's classification as a "pseudodeficiency.[21,22] At least two significant features of the pseudodeficiency allele p.G576S are as follows: It has two main effects(1) it makes other mutations more severe by creating a background; and (2) it increases the false-positive rate in newborn screening that uses GAA activity measures.[23] The GAA protein's residue 576 is a conserved codon, but the serine to glycine transition is not. Even though it very slightly alters conformation and exhibits typical apparent Km values Because of this, p.G576S may alter other cis mutations. For instance, an adult African-American patient 31 with the mutation p.D645E was shown to have a milder phenotype since they did not have the p.G576S variation32. In transfected fibroblasts, the p.W746C mutation yields only 8% of normal GAA activity, while the p.[W746C; G576S] mutation does not produce detectable GAA activity (0.3% of normal, p = 0.029).9. We have coexpressed a number of additional mutations with p.G576S, and because of p.G576S, all of them exhibit reduced GAA activity. [19, 23,24]Taiwanese people have an allele frequency of 14.5% (94 in 650 chromosomes)17 for the pseudodeficiency allele p.G576S, which is significantly greater than that of European as well as African/sub-Saharan populations.28 From estimates, 3.3% to 3.9% of people in Asian populations are homozygous,25, 28 which is in line with our 3.69% result.17 But none of those homozygous people have been identified as having Pompe disease, as far as we know.[20-26]

Autophagy failure in pompe disease

Autophagy: Christian de Duve coined the word "autophagy" in the 1960s after discovering the lysosome and putting up a completely novel theory regarding the lysosome as a degradative organelle.[27] The phrase, which means "self-eating" in literal translation, was coined to draw attention to the distinction between the internal components delivered by lysosomes and the extracellular materials that are taken up through a process de Duve termed "heterophagy" (endocytic pathway). Before the identification of genes linked to autophagy and the essential molecular machinery involved in the process, the field of autophagy study lay dormant for thirty years and mostly depended on morphological investigations. [28] With an ever-growing number of publications, the topic has practically taken off since the 1990s and is now one of the most researched fields in biomedical science. Mammalian cells are known to exhibit three morphologically distinct forms of autophagy: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy. All three types of autophagy entail the delivery of cytoplasmic Substances are broken down and recycled within the lysosomal lumen. There are three types of autophagy; the most studied is macroautophagy, or autophagy. involves the de novo production of the autophagosome, a transitory double membrane vesicle. The phagophore, a cup-shaped membrane structure, first appears at the beginning of the process[29] It encloses a section of the cytoplasm, grows, and then contracts to create an autophagosome with two membranes. Amphisomes that generate early or late endosomes can combine with autophagosomes. [30] or with lysosomes generating autolysosomes, in which lysosomal hydrolases degrade the inner membrane

and the cargos that have been sequestered. As discussed in, the byproducts of lysosomal breakdown, which include amino acids, monosaccharides, free fatty acids, and other building blocks, are carried to the cytoplasm where they are recycled in a number of biosynthetic procedures.[31,32] The creation of fully developed, functional lysosomes marks the end of the autophagic process.[33] Protein unfolding and substrate translocation into the lysosome are mediated by a luminal form of Hsc70. In CMA, a subset of soluble cytosolic proteins bearing the KFERQ-like motif bind to a chaperone (the heat shock protein Hsc70). This chaperone transports the substrate protein to the protein–chaperone complex interacts with its receptor on the lysosomal surface, the lysosome-associated membrane protein type 2A (LAMP-2A). [34]

Autophagy's Contribution to Pompe Disease's Skeletal Muscle Injury

Early investigations into autophagy in Pompe disease resulted from preclinical trials evaluating Myozyme's effectiveness in a knockout mice (KO) model. [35] Heart pathology was successfully reversed, and heart glycogen levels were brought down to normal by the treatment. On the other hand, skeletal muscle absorbed the enzyme at a far lower rate than the liver and heart, and muscle glycogen clearance was minimal at best. This was especially the case for fast-twitch glycolytic type II myofibers.[36] Ironically, in untreated KO, the heart stores much more glycogen than skeletal muscle, suggesting that the amount of storage material is not the only factor in the therapeutic impact. Large areas of autophagic debris, including double-membrane autophagic vacuoles with undigested materials, multivesicular bodies, concentric multimembrane electron dense structures, etc., were seen in the KO mice's primarily type II muscle by electron microscopy in addition to the usual larger lysosomes packed with glycogen. comparable structures, sometimes known as "non-contractile inclusions," were discovered in the muscles of another Model of Pompe illness in mice.[37] There is reduction in muscle performance seemed to be attributed to the mechanical impact of these insertions.[38] Furthermore, back in 1970, Andrew G. Engel published the first report on the morphology discovery of substantial pools of autophagic detritus in muscle biopsies from adult patients with Pompe syndrome.[39] However, at that time, little was known about the function of autophagy or the autophagy apparatus, which included the proteins and the order of events needed to finish the autophagy route. The field of autophagy had advanced notably by the time of preclinical testing and clinical trials with Myozyme, and a range of techniques to monitor different phases of the process were now available. Autophagy disease in the injured muscle appeared to have significant practical implications in addition to stimulating scholarly interest: Resistance to therapy was linked to autophagic accumulation in the muscle tissue of KO mice.(but not in the cardiac muscle).[40] Preclinical evidence was supported by the outcomes of investigator-led long-term research, follow-up, and ERT clinical trials. Although the disease's infantile stage was formerly known to be an early death, treatment with alglucosidasealfa which caused newborn cardiac abnormalities to quickly and dramatically reverse and many patients now have a chance to survive considerably longer.[41,42]

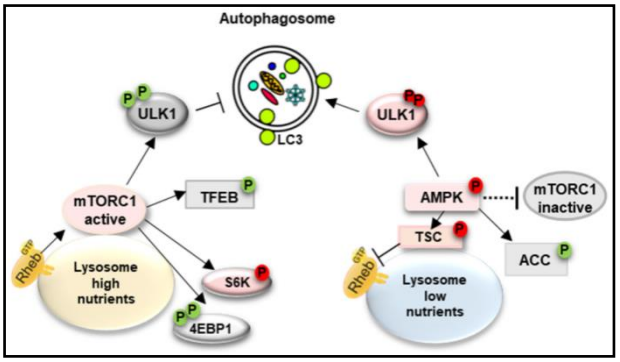

Figure 2: Failure of autophagy in pompe disease

Advanced therapies for the treatment of PD

Enzyme replacement therapy: Given that the symptoms of IOPD and LOPD are progressive and frequently irreversible, it was hypothesised—based on data from clinical trials—that patients with these conditions would benefit most from early ERT initiation. Implementing treatment early in the disease course and simplifying diagnosis were made possible by the establishment of an NBS program. The use of the DBS test in NBS methods was evaluated for the first time in the pilot NBS program, which Genzyme sponsored and supported. When Enzyme Replacement Therapy (ERT) was first developed, patients with Pompe Disease (PD) had a much better prognosis, and it became the standard of care. Initial clinical studies with patients diagnosed with infantile-onset Pompe disease (IOPD) demonstrated unequivocally that ERT improves cardiovascular and skeletal muscle mass. [43-45] Due to these findings, the initial medication for IOPD was approved in 2006, and ERT for LOPD (alglucosidase alfa, Sanofi Genzyme; Lumizyme in the USA and Myozyme outside of the USA) was approved in 2010. On alternate weeks, recombinant acid alpha-glucosidase (rhGAA) is injected intravenously at a suggested dosage of 20 mg per kilogram; however, patients with IOPD may

alternatively get larger dose regimens, up to 40 mg/kg. These doses are significantly more than those needed for other lysosomal storage diseases, which may be due to the skeletal muscle of Pompe patients having a greater tolerance for correcting GAA deficit. Furthermore, the liver absorbs the majority of rhGAA—up to 85%—as well as severely restricts its ability to activate specific muscles. ERT with recombinant human GAA has greatly increased the survival percentage of Infantile-onset Pompe disease patients and amply exhibited improvements in cardiovascular and airway function.[46]Nonetheless, rhGAA delivery in IOPD is often linked to diminished therapeutic efficaciousness and survival as well as the emergence of neutralizing humoral immune responses against the enzyme. This is especially important for individuals who are cross-reactive immune-material negative (CRIM–) and have no remaining GAA antigen, meaning they have zero central sensitivity to the polypeptide.[47]The insufficient effectiveness of ERT is another significant drawback. For instance, respiratory function is only partially restored by the treatment, and about 30% of patients receiving treatment of rhGAA eventually require supported airflow, whether it be intrusive or otherwise.[48]Enhancement of skeletal muscle function is another benefit of ERT; however, the results are very inconsistent, with some patients retaining their ability to walk independently and others experiencing only slight adjustments before becoming incapacitated by.[49,50]According to the majority of analyses available, ERT improves the activity of muscles in the majority of patients as determined by the 6-minute exercise examination, but ongoing research indicate that respiratory function is only stabilized in patients with light-on-progressive dyspnea (LOPD).[51]

Studies currently accessible additionally indicate that in patients with later stages of the disease, ERT may stabilize or perhaps marginally enhance breathing capacity and strength of the muscles.[52,53]Apart from effectiveness constraints, (I) the necessity of receiving significant dosages of rhGAA intravenously on a regular basis, (II) the potential for both CRIM− and CRIM+ patients to experience significant and harmful immune responses [54-56]and (III) the modified enzyme's failure to pass the blood-brain barrier and fix the neural system.[57]make the need for novel PD medicines to be developed urgent.
Since ERT for Pompe disease was developed, attempts have been made to address aspects of this treatment's drawbacks. Currently, two primary approaches that seek to increase the bioavailability of enzymes in various tissues are in the latter stages of clinical trials. The primary strategy involves changing the recombinant enzyme to include more M6P residues [58]Utilizing pharmaceutical supplements to increase ERT performance is a second approach.[59,60]A greater affinity rhGAA-containing subsequent-generation ERT targeting M6P receptors[61]is presently being assessed as part of a phase III clinical trial (NCT02782741; Sanofi Genzyme; avalglucosidase alfa, Neo-GAA). Neo-GAA delivered biweekly at doses ranging from 5 to 20 mg/kg will be tested in this study, with the option to change doses as needed. Patients with LOPD are being recruited for this phase III clinical research, which compares the safety and effectiveness of biweekly infusions of avalglucosidase alfa with alglucosidase alfa. ATB200 (Amicus Therapeutics) is a further experimental rhGAA that has been produced and is undergoing clinical trial testing in conjunction with pharmacological chaperones. Its increased content of M6P and bis-M6P glycan residues (see infra). GAA enzymes designed with artificial M6P residues enhanced Pompe mice's muscle function in preclinical experiments, either by itself.[62]

Alternatively, in addition to chaperones.[63]and demonstrated enhanced targeting in ocytes from Pompe patientsin contrast to rhGAA of the initial phase. Using absorption regions is a different approach that has been tried to increase the GAA enzyme's availability in cells and, as a result, its capacity to remove glycogen more effectively. Animal preliminary models of Pompe disease were used to test a number of chimeric GAA peptides with absorption regions. [64-67]The glycosylation-independent lysosomal targeting (GILT) domain-carrying engineered version of rhGAA for intestinal absorption is one.[68]completed late-stage clinical research after being evaluated on individuals with LOPD (NCT01924845, BMN 701, BioMarin Pharmaceutical). Regrettably, the process was stopped due to worries that low glucose levels was possible after enzyme injection. [69]The murine 3E10 antibody has recently given rise to a chimeric version of rhGAA that has a humanized Fab segment.[70]started phase II/II clinical trials (Validon Therapeutics, LLC; NCT02898753, VAL1221). Pharmaceutical compounds are being considered as a possible means of enhancing ERT's effectiveness in Pompe disease. Once the enzyme is provided by ERT, the combination of rhGAA with β2 agonists, such as clenbuterol or albuterol, caused enhanced M6P receptor expression, better muscular performance, and decreased glycogen buildup in tissue and mind.[71,72]alternatively through liver-mediated gene modification (see infra).[73]A stage I/II clinical trial evaluating the efficacy of albuterol plus rhGAA demonstrated improved motor performance and elevated M6P receptor expression in muscle samples.[74]Enhanced motor performance and the adjustment of disease-related biological markers in tissue were observed in a second clinical trial examining the impact of clenbuterol on the effectiveness of ERT.These two early-phase trials, conducted on individuals with LOPD, demonstrated evidence of enhanced efficacy when combined with ERT and only minimal adverse reactions. More extensive experiments will be need to distinctly illustrate the benefit of the methodology in contrast to ERT alone.Pharmacological chaperone therapy (PCT) is the foundation of another combined method to treating Pompe disease (PD). Tiny chemicals called chaperones are known to encourage packing or increase the reliability of peptides and enzymes. [75,76]

Gene therapy:PD is a prime candidate for the development of gene replacement therapies due to its monoclonal origin. Several in vivo and ex vivo methods have been tested in animal models since 1998, the year of the first in vivo gene therapy strategy for Pompe disease (PD). The goal of these approaches is to rectify the PD phenotypic. [77,80]

Methods of gene therapy. The process of directly administering a genetic transport vector—viral or non-viral—to the receiver of the gene transfer is known as in vivo gene therapy. For Pompe disease, AAV vector-mediated gene transfer has accounted for the majority of experience to date. In vivo gene therapy, autologous CD34+ hematopoietic progenitors transduced with integrative vectors (e.g., lentiviral vectors) and re-infused in the recipient after myeloablative bone marrow conditioning, is one method of delivering AAV vectors to target the muscle. There is evidence that this gene therapy approach may effectively transfer GAA to the central nervous system. AAV vectors are adeno-associated viruses; GAA stands for acid alpha-glucosidase. [81-84]

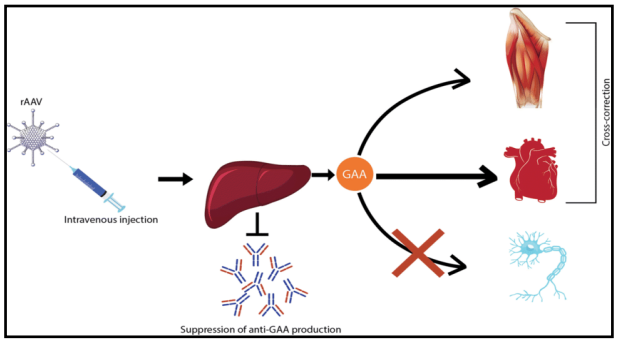

Figure:3 Gene therapy

AAV Vector: The creation of gene therapy techniques could be a viable option for treating Pompe disease (PD) in place of ERT. Numerous clinical investigations have shown that adeno-associated virus (AAV) vectors are a safe and promising platform for human in vivo gene transfer. One documented trial using PD involved injecting an AAV1 encoding the human GAA transgene intradiaphragmatically into pediatric participants.There was proof that the operation was safe and that respiratory function had improved. [85]·Numerous preclinical investigations on gene therapy have been documented, utilizing a reputable Gaa knockout mice model (referred to as Gaa−/− from now on). Among these investigations, we recently demonstrated complete PD rectification in symptomatic 4-month-old Gaa−/− mice using liver gene transfer of a modified secretable GAA (secGAA) transgene via an AAV vector. [86]The external DNA of choice—which is flanked by the ITRs and is known as the transgene expression cassette—replaces the sequences encoding rep and cap in the genome of recombinant AAV vectors, leaving only the two ITRs (cis packaging signals) intact. Recombinant AAV vectors differ from the wild type virus in that their genomes mostly keep episomal in the transduced cells' nuclei, without undergoing site-specific integration in the host DNA. Random integration events are also observed, albeit they occur infrequently—between 0.1% and 1% of transduction events. [87,89]

Liver gene therapy for PD: Many factors make the liver an appealing target for the development of gene-based therapeutic strategies for Pompe disease(PD) and other genetic diseases, including: (I) the liver is one of the body's primary organs for biosynthesis, is highly permeable, and has an efficient system for secreting protein molecules into the circulation; (II) Research employing intravenous AAV vectors has shown that liver can be targeted highly efficiently in both human beings and large and small models of mammals.[90-95](III) Long-term translation following gene transfer to the hepatic was observed in human beings and large animals, spite of the primarily non-integrative characteristics of AAV carriers; and (IV) transgenic vocalization in hepatocytes induces antigen-specific tolerance mediated by regulatory T cells.[96] Given that AAV vectors are primarily non-integrative, liver-directed gene therapy may be appropriate for adult patients; however, as hepatocyte replication takes place in younger patients, this approach may not be the best choice for IOPD patients.[97]

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International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 31, Issue 6, June 2025 **ijppr.humanjournals.com** ISSN: 2349-7203

How to cite this article:
Sagar Singh et al. Ijppr.Human, 2025; Vol. 31 (6): 87-96.

Conflict of Interest Statement: All authors have nothing else to disclose.