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Pompe Disease and its current standard of care

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I. Introduction

Pompe disease, also known as glycogenosis type 2 or acid maltase deficiency is a rare autosomal recessive disease that disables the heart and skeletal muscles. It is caused by more than 450 mutations in the GAA gene that makes acid alpha-glucosidase. [1] The enzymatic deficiency of alpha-glucosidase leads to the accumulation of glycogen within the lysosome, which leads to deterioration in cardiac and skeletal muscle, and fatality by cardiorespiratory failure.Pompe disease encompasses a spectrum of clinical manifestations which vary by age of onset, organ involvement and degree of myopathy[2].

In general, Pompe disease is classified either as infantile onset (IOPD), often defined as onset of disease at age ≤ 12 months with cardiomyopathy or late onset (LOPD), with presentation after > 12 months of age or presentation at ≤12 months without cardiomyopathy. However, a variety of definitions are used and patients with onset of disease at ≤12 months without cardiomyopathy can also be categorized as atypical IOPD [3]. IOPD is usually characterized by a complete loss of GAA activity; most common symptoms include hypotonia, progressive weakness, macroglossia, hepatomegaly and hypertrophic cardiomyopathy. Life expectancy for IOPD is around 1 year, and death is usually due to cardio–respiratory failure [4]. In contrast, LOPD is generally associated with a wider range of age of onset and clinical symptoms, and the level of reduction of GAA enzyme activity shows inter-patient heterogeneity [5]. Common symptoms of LOPD include progressive limb girdle weakness and respiratory insufficiency, without cardiomyopathy[6].

Epidemiology

Around 1 in every 40,000 births inherit Pompe disease and experts estimate that 5,000 to 10,000 people have Pompe disease worldwide.[6] It is most common in African Americans and some Asian groups. The highest genetic prevalence for GAA deficiency is observed in the East Asian population at 1 in 12,125. In Taiwan, the incidence rate is lower and is estimated to be 1 in 34,348.[7]

One study estimated the carrier frequency (CF) and predictive genetic prevalence (pGP) of GAA deficiency by region. The authors analyzed variants of the *GAA* gene using the GnomAD (v2.1.1) database in unrelated Africans/African Americans (12,487), Latino/admixed Americans (17,720), Ashkenazi Jews (5185), East Asians (9977), Finnish (12,562), non-Finnish Europeans (64,603), South Asians (15,308), and others (3614). A total of 3270 genetic variations of *GAA* were identified, of which 154 were classified as pathogenic or likely pathogenic variants (PLPVs) (Table A).[7]

[1] "Pompe Disease | National Institute of Neurological Disorders and Stroke." *Nih.gov*, 2022, www.ninds.nih.gov/health-information/disorders/pompe-disease Accessed 13 June 2022.

[2] Manganelli F, Ruggiero L. Clinical features of Pompe disease. Acta Myol. 2013;32:82–4.

[3] Pascual SI. Phenotype variations in early onset Pompe disease: diagnosis and treatment results with Myozyme. Adv Exp Med Biol. 2009;652:39–46.

[4] Dasouki M, Jawdat O, Almadhoun O, Pasnoor M, McVey AL, Abuzinadah A, Herbelin L, Barohn RJ, Dimachkie MM. Pompe disease: literature review and case series. Neurol Clin. 2014;32:751–76 ix.

[5] van den Hout HM, Hop W, van Diggelen OP, Smeitink JA, Smit GP, Poll-The BT, Bakker HD, Loonen MC, de Klerk JB, Reuser AJ, van der Ploeg AT. The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. Pediatrics. 2003;112:332–40.

[6] Winkel LP, Hagemans ML, van Doorn PA, Loonen MC, Hop WJ, Reuser AJ, van der Ploeg AT. The natural course of non-classic Pompe's disease; a review of 225 published cases. J Neurol. 2005;252:875–84.

[7] Park KS. Carrier frequency and predicted genetic prevalence of Pompe disease based on a general population database. *Mol Genet Metab Rep*. 2021;27:100734. doi:10.1016/j.ymgmr.2021.100734

Population	Most Frequently Identified PLPVs to *GAA* (allele frequency)	Group†
African/African American	c.2560C >T (0.00189)	A, B, C
Latino/admixed American	c.-32-13T>G (0.00269)	B, C
Ashkenazi Jewish	c.-32-13T>G (0.00554)	B, C
East Asian	[c.752C >T; c.761C >T] (0.00276)	B
Finnish	c.1725C >A (0.00020)	Unknown
Non-Finnish European*	c.-32-13 T >G (0.00529)	B, C
South Asia	c.-32-13 T >G (0.00190)	B, C
Global	c.-32-13 T >G (0.00340)	B, C

Table A

Current standard of care and cure for Pompe disease

Until recently, there has been no specific treatment for Pompe disease, other than supportive care. Alanine, high-protein diets, branched chain amino acids and β-agonists such as albuterol[8] have been reported to offer limited benefits in some individuals. Epinephrine and glucagon[9], which enhance cytosolic glycogen breakdown, have also been attempted with no therapeutic effect.[10] Bone marrow transplantation has not been shown to be useful, though experience is very limited.[11] Similarly, heart transplant for which there is even less experience has not been shown to be useful.

Moreover, the treatment of Pompe disease is disease-specific, symptomatic and supportive. The input of pediatricians, internists, neurologists, orthopedists, cardiologists, dieticians, physical therapists and other healthcare professionals may be needed to develop the treatment plan.

The assessment of cardiac function by echocardiography is an essential part of the ongoing management of Pompe patients. Initial findings of increased wall thickness and left ventricular (LV) mass need to be evaluated on a regular basis by a standardized approach since establishing the stage of the cardiomyopathy is useful in determining treatment. This also can help with following disease progression and response to intervention. Functional measures including 2-D ejection fraction (EF) and the myocardial performance index are helpful in longitudinal follow-up.[12]In the presence of LV outflow tract obstruction, the use of digoxin, other inotropes, diuretics, and afterload reducing agents such as ACE-inhibitors may exacerbate the left ventricular outflow tract obstruction.

There is a liberal use of bronchodilators, steroids and selective beta agonists like levalbuterol for Cardiomyopathy. Supplemental O2 (either nocturnal or continuous) can be used to treat hypoxia, provided that hypoventilation is not present, and this has proven to work on infants as well[13]

If hypoventilation is present while both awake and asleep, consideration is given to using continuous noninvasive positive pressure ventilation or tracheostomy tube placement with mechanical ventilation.

[8] Angelini C, Pegorora E, Marsala SZ, Vergani L, et al. Adult acid maltase deficiency: an open trial with albuterol and branched chain amino acids. *Basic Appl Myol.* 2004;14:71–78.

[9] Bodamer OA, Leonard JV, Halliday D. Dietary treatment in late-onset acid maltase deficiency. *Eur J Pediatr*. 1997;156:S39–S42.

[10] Hug G, Schubert WK, Soukup S. Treatment related observations in solid tissues, fibroblast cultured and amniotic fluid cells of type II glycogenosis, Hurler disease and metachromatic leukodystrophy. *Birth Defects Orig Art Ser.* 1973;9:160–183.

[11] Watson JG, Gardner-Medwin D, Goldfinch ME, Pearson AD. Bone marrow transplantation for glycogen storage disease type II (Pompe's disease) *N Engl J Med.* 1986;314:385.

[12] Cooke A. Ambulatory electrocardiogram analysis in infants treated with recombinant human acid alpha glucosidase enzyme replacement therapy for Pompe disease. *Genet Med.* In press.

[13] Kravitz RM, Mackey J, DeArmey S, Kishnani PS. Polysomnogram findings in patients with infantile Pompe disease. *Proc Am Thorac Soc*. 2005;2:A459.

Additionally, people suffering from Pompe disease require physiotherapy and nasoduodenal or gastro-jejunal feeding to minimize the risk of aspiration. They also require needle electromyography (EMG) in initial evaluation to determine presence of denervation as evidence of anterior horn cell involvement.

Several open-label clinical trials involving patients with infantile-onset Pompe disease have shown that enzyme replacement therapy significantly prolongs survival,[14] decreases cardiomegaly[15], and improves cardiac and skeletal muscle function. In the vast majority of cases cardiac response appears to be good, irrespective of the stage of the disease at the start of Enzyme Replacement Therapy (ERT) . Skeletal muscle response has been more variable than cardiac muscle response. The best skeletal muscle response has been noted in patients treated early, prior to severe skeletal muscle damage. There are several patients on ERT who can walk. With the advent of ERT, the natural history of this once lethal disease has changed and additional physical and mental disabilities may be uncovered. However, there are patients who have not had a good outcome despite early treatment. Factors such as muscle fiber type, stage of disease at start of therapy, genotype and immune response to the recombinant enzyme may play a role in determining outcome and need further investigation. Additional larger-scale trials in infants to establish the extent of long-term benefit, the optimal dosing protocol, and the effect of other factors on outcome of therapy are needed and are currently underway. Trials of ERT in late onset Pompe disease are also underway. With the introduction of therapies such as ERT, long term survival is now a reality and closer attention to the natural history of treated patients is of paramount importance.

The use of small molecules to treat lysosomal storage disorders is also emerging as a therapeutic option either as a single agent or in combination with other therapies. Work on a second generation recombinant enzyme for Pompe disease for more efficient targeting to muscle is currently in the preclinical stages. Pharmacologic chaperones that bind to the affected proteins and restore their shape, proper trafficking, and biological activity may also become available for those who can make protein. Several challenges remain before clinical testing of these therapeutic strategies can be considered. In the case of gene therapy, work still remains, especially in terms of safety.

Moreover, treatment with the two-part investigational therapy AT-GAA improved walking ability and lung function for up to three years among adults with Pompe disease in a Phase 1/2 clinical trial. AT-GAA is an investigational two-component therapy that consists of cipaglucosidase alfa (ATB200), a recombinant human acid alpha-glucosidase (rhGAA) enzyme with optimized carbohydrate structures, particularly bis-phosphorylated mannose-6 phosphate (bis-M6P) glycans, to enhance uptake into cells, administered in conjunction with miglustat (AT2221), a stabilizer of cipaglucosidase alfa. In preclinical studies, AT-GAA was associated with increased levels of the mature lysosomal form of GAA and reduced glycogen levels in muscle, alleviation of the autophagic defect and improvements in muscle strength.

The ongoing study enrolled three cohorts of ambulatory patients: 2–6 years (n=11; aged 18–65 years) or ≥7 years (n=6; aged 18–75 years) prior enzyme replacement therapy (ERT) with 20 mg/kg alglucosidase alfa biweekly, ERT-naïve (n=6; aged 18–65 years). Doses were 20 mg/kg cipa glucosidase alfa by intravenous infusion/260 mg miglustat orally biweekly in the long-term extension. Changes from baseline (CFBL) in multiple endpoints were assessed at intervals. Results from ATB200-02 showed that most ERT-experienced patients either improved or stabilized in their efficacy and biomarker outcomes. ERT-naïve patients demonstrated clinical benefit with cipa glucosidase alfa/miglustat. Overall, there were sustained and durable improvements in clinical response up to 36 months' follow-up.

Companies working in Enzyme Replacement Therapy and AT-GAA

1. Sanofi Genzyme

The FDA cleared Sanofi's Nexviazyme, also known as avalglucosidase alfa-ngpt, to treat patients ages one and older with LOPD. It marks the FDA's second approved drug for the rare genetic disease, the first of which also belongs to Sanofi.[16]

The company's earlier ERT, alglucosidase alfa, was first approved in 2006 as Myozyme for IOPD. In 2010, the same ERT was approved as Lumizyme to treat LOPD in patients ages eight and older, and, in 2014, the FDA expanded its label to treat IOPD as well.

[14] Van den Hout H, Reuser AJ, Vulto AG, Loonen MC, et al. Recombinant human alpha-glucosidase from rabbit milk in Pompe patients. *Lancet.* 2000;356:397–398.

[15] Kishnani PS, Nicolino M, Voit T, Rogers RC, et al. Results from a phase II trial of Chinesse hamster ovary cell–derived recombinant human acid alpha–glucosidase in Infantile–onset Pompe disease. *J Pediatr.* 2006 in press.

[16] "Sanofi's Investigational Enzyme Replacement Therapy Shows Clinically Meaningful Improvement in Critical Manifestations of Late-Onset Pompe Disease - Sanofi." *Sanofi.com*, 2020, www.sanofi.com/en/media-room/press-releases/2020/2020-06-16-12-00-00-2048709. Accessed 15 June 2022.

2. Amicus Therapeutics

The US FDA has accepted filings for Amicus' AT-GAA for the treatment of Pompe disease.[17] The FDA has set a Prescription Drug User Fee Act (PDUFA) action date of May 29, 2022 for the NDA and July 29, 2022 for the BLA. The BLA and NDA are based on the evaluation of the effects of AT-GAA in Pompe disease patients and its safety profile, which include data from the Phase 1/2 and Phase 3 PROPEL studies as well as data from the open-label extension study.[18]

[17] "MDA Clinical & Scientific Conference 2022." *MDA Clinical & Scientific Conference 2022*, 2022, mdaconference.org/index.php/node/1752. Accessed 15 June 2022.

[18] "Pompe Disease Program | Amicus Therapeutics." *Amicus Therapeutics*, 2022, www.amicusrx.com/programs-pipeline/pompe-disease/#:~:text=Pompe%20disease%20is%20an%20inherited,of%20muscles%20and%20other%20tissues.. Accessed 15 June 2022.