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Review Article

Pompe disease: genetics and management

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Abstract

Pompe disease (PD) is an autosomal recessive disease caused by partial or complete deficiency of the lysosomal hydrolase acid alpha-glucosidase, resulting in accumulation of glycogen in various tissues. It affects primarily the skeletal, smooth muscle and cardiac system. Pompe disease clinically presents as a continuum in its age of onset and multisystem involvement and is often fatal. Diagnosis can be difficult due to nonspecific phenotype of the disease. Enzyme replacement therapy (ERT) is the standard treatment for the disease since 2006. Although of considerable clinical benefit to some patients, there are significant limitations to ERT. Studies in novel therapeutic approaches show positive outcomes. In the context of therapeutic options, the earliest diagnosis and initiation of treatment can make a difference. Early identification through newborn screening and more effective therapies will hopefully lead to improved outcomes for patients with Pompe Disease.

Keywords: Pompe disease, glycogenosis type II, acid maltase deficiency, acid α-glucosidase, enzyme replacement therapy, immune tolerance induction

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Abbreviations:

CRIM: cross-reactive immunological material

CN: CRIM negative

CP: CRIM positive

DBS: dried blood spot

PD: Pompe Disease

ERT: Enzyme Replacement Therapy

FVC: Forced Vital Capacity

GAA: acid α-glucosidase

HSAT: high sustained antibody titer

HTCP: high-titer CRIM positive

IOPD: infantile-onset Pompe Disease

ITI: Immune Tolerance Induction

LOPD: late-onset Pompe Disease

NBS: Newborn Screening

rh-GAA: recombinant human acid a-glucosidase

Introduction

Pompe disease (PD) (OMIM:232300), also termed glycogen storage disease type II or acid maltase deficiency, is a rare genetic deficiency of lysosomal acid α-glucosidase (GAA). PD is an autosomal recessive disease and hundreds of mutations have been identified in the GAA gene. Certain mutations correlate with different phenotypes of PD (Nascimbeni et al., 2008) and are potentially specific to families, geographic regions or ethnicities (Hirschhorn and Reuser, 2001; Leslie and Bailey, 2007). PD has an estimated frequency of approximately 1/40.000. The incidence of Pompe disease may vary, depending on geographic region, ranging from 1:14.000 in African Americans to 1:100.000 in individuals of European descent (Leslie and Bailey, 2007).

The growing literature on PD reveals significant clinical variability regarding age of onset, organ involvement, degree of myopathy and rate of progression (Dasouki et al., 2014). The two broad subtypes encountered in clinical experience are based on the age and the primary symptoms: the infantile-onset and the late-onset Pompe disease. The infantile-onset form of PD (IOPD) usually appears by age 1. In IOPD, the most common symptoms are hypotonia, generalized muscle weakness, developmental delay, cardiac defects and respiratory insufficiency (Chan et al., 2017). IOPD associated with cardiomyopathy is referred to as classic Pompe disease and in the absence of cardiomyopathy as non-classic Pompe disease. Classic IOPD is rapidly progressive and has a fatal outcome within the first two years of life if left untreated. The late-onset type of PD (LOPD) begins in childhood, adolescence, or adulthood. The most prominent manifestations in LOPD are progressive muscle weakness, gait abnormalities, exercise intolerance, lower back pain, feeding problems, respiratory insufficiency, orthopnea, sleep apnea and hepatomegaly (Chan et al., 2017). LOPD is usually milder than the infantile-onset forms of the disease.

Interest in Pompe disease has grown significantly since the approval of the first specific enzyme replacement therapy (ERT) for this deficiency with recombinant human acid α-glucosidase (alglucosidase alfa) in 2006. ERT dosage is being studied especially in patients that lack clinical improvement (van der Ploeg et al., 2010; van Gelder et al., 2016). Since the advent of ERT, early diagnosis is vital as disease's natural course may be altered. The gold-standard test for diagnosis is DBS (Llerena Junior et al., 2015). Definitive diagnosis of Pompe disease is being based on the molecular analysis of the GAA gene for the presence of two pathogenic allelic mutations. Newborn screening studies raise interest in incorporating dried blot spot GAA testing into newborn screening protocols (Bodamer et al., 2017; Chien et al., 2008).

ERT and, currently studied, gene therapy are two therapeutic strategies for Pompe disease, yet, immune responses against GAA are a substantial drawback. With the advent of immunomodulation therapies, identification of patients at risk for developing immune response should be considered before commencing ERT (Banugaria et al., 2011). Detection of CN (Cross-reactive immunologic material-negative) patients can be achieved through Western Blot analysis and genetic analysis (Burton et al., 2017). Some additional therapeutic approaches currently investigated are chemical chaperones, enzyme modification and substrate reduction therapy (Byrne et al., 2017; Han et al., 2016; Kishnani et

al., 2017; Smith et al., 2013). Nevertheless, treatment remains challenging, particularly in patients who have profound deficiency of GAA activity.

Genetic Basis

PD is caused by recessive mutations in the autosomal GAA gene. The α-glucosidase gene (NM 000152) is located on the long arm of chromosome 17 (chr17q25.3). GAA gene consists of 20 (19 coding) exons which encode 952 amino acids. Acid α-glucosidase has 4 isoforms, 2 catalytically active sites, 3 disulfide bonds and 7 N-linked glycosylation sites. Many normal allelic variants exist in GAA gene and are responsible for the three known alloenzymes. GAA is synthesized as a membrane bound, catalytically inactive precursor which is sequestered in the endoplasmic reticulum. It undergoes modification in the Golgi complex, followed by transport into the secretory pathway, or into lysosomes where it is trimmed in a process at both the amino- and carboxyl-termini. Phosphorylation of mannose residues ensures efficient transport of the enzyme to the lysosomes via the mannose 6-phosphate receptor. GAA catalyzes the hydrolysis of α1→4 glucosidic linkages in glycogen at acid pH. Specificity for glycogen is gained during its maturation.

More than 450 mutations in GAA gene have been identified, which are catalogued at the Pompe Center of the Erasmus University (Rotterdam). Nonsense mutations, large and small gene rearrangements, and splicing defects have been reported (http://www.pompecenter.nl/). GAA mutations result in mRNA instability and/or severely truncated protein or an enzyme with significantly decreased activity. Mutations that result in complete absence of GAA enzyme activity are commonly seen in individuals with infantile-onset disease, whereas combinations of mutations that allow partial enzyme activity usually have a later-onset presentation (Nascimbeni et al., 2008). The most common mutation in adults with LOPD (50-85%) is the pathogenic variant c.336-13T>G typically in the compound heterozygous state. An estimated 50-60% of African Americans with IOPD have the pathogenic variant p.Arg854Ter (c.2560C>T). The p.Asp645Glu (c.1935C>A) variant is common in Chinese with IOPD (40-80%). In these populations targeted analysis for pathogenic variants can be useful (Hirschhorn and Reuser, 2001; Leslie and Bailey, 2007).

Diagnosis

Diagnosis of Pompe disease can be made clinically based on a typical clinical presentation with limb weakness, difficulty walking or limb girdle dystrophy. Patients presenting with a limb-girdle syndrome or dyspnea secondary to diaphragm weakness should undergo further testing. Typically, IOPD patients present with hypotonia, upper and low limb weakness, macroglossia, hepatomegaly, progressive hypertrophic cardiomyopathy and cardio-respiratory insufficiency. LOPD patients usually present with slowly progressive limb girdle weakness, respiratory deterioration, rigid spine syndrome, scoliosis, low body mass, ptosis, bulbar palsy and urinary incontinence. The pathologic accumulation of glycogen in several tissues in PD show the following clinical correlations: diaphragm and intercostal muscles - respiratory failure, proximal skeletal muscle - progressive limb-girdle myopathy, genioglossus - tongue weakness, extraocular muscles - unilateral or

bilateral ptosis, smooth muscle – abdominal pain/nausea/vomiting/diarrhea/urinary incontinence, and cerebral vasculature - cerebral aneurysm (Dasouki et al., 2014). The nonspecific phenotype of Pompe disease leads to consideration of different conditions (Table 1) (Chan et al., 2017; Llerena Junior et al., 2015). Early involvement of respiratory muscles preceding muscle weakness may differentiate LOPD from other neuromuscular diseases, in which respiratory insufficiency occurs after loss of ambulation (Llerena Junior et al., 2015).

Concurrently, diagnosis can be based on the following (Barba-Romero et al., 2012; Bodamer et al., 2017; Burton et al., 2017; Chien et al., 2008; Llerena Junior et al., 2015):

- Physical examination
- Spirometry, FVC change
- Blood biochemistry analysis (CK, ALT, AST, LDH), urine analysis (Glc4)
- Dried blood spot testing (DBS)
- Confirmation: GAA activity in lymphocytes, genetic testing

Physical examination should focus on the muscular and respiratory systems. Clinical evaluation must include manual assessment –Medical Research Council (MRC) scale– or quantification of muscle strength combined with the performance of functional tests such as the Gowers maneuver and gait assessment (Barba-Romero et al., 2012). Patients may demonstrate a positive Gower's sign and waddling gait. A positive Trendelenburg's sign and a positive Beevor's sign may also be observed (Chan et al., 2017).

Spirometry is very useful for detecting respiratory impairment that is common in LOPD and may even occur in the presymptomatic stage. It is very helpful to measure the change of forced vital capacity (FVC) in the upright and lying supine positions. A decrease by more than 10% in FVC from the upright to the supine position suggests weakness of the diaphragm (Chan et al., 2017).

Elevations of creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and urinary glucose tetrasaccharide (Glc4) levels are sensitive but non-specific indicators for Pompe disease (Barba-Romero et al., 2012). These enzyme biomarkers can be helpful when trying to establish a diagnosis in a patient with a positive NBS result for Pompe disease. Other useful tests would be: muscle biopsy, electromyogram, muscle imaging MRI, electrocardiogram, echocardiogram, chest X-ray, polysomnography and nocturnal oximetry.

Measurement of GAA activity in dried blood spots (DBS) is the recommended method for screening patients with suspicion of PD. Factors that need to be considered when evaluating the results of GAA enzymatic activity testing include the presence of a pseudodeficiency allele that can alter the residual enzyme level in a screened infant and the possibility that the assay conditions and procedures may not be optimal, leading to false-positive results (Burton et al., 2017). If clinical suspicion of PD persists, the test should be repeated (Llerena Junior et al., 2015). The finding must be confirmed by a second enzyme assay in another tissue (lymphocytes, fibroblasts or muscle) or molecular analysis of the GAA gene (Barba-Romero et al., 2012; Llerena Junior et al., 2015).

Newborn Screening

The potential benefit of ERT and need for early intervention in PD has led to considering dried blood spot GAA testing as the basis for newborn

Table 1: Differential diagnosis of Pompe Disease

Muscular dystrophies	Duchenne, Becker, limb-girdle types of muscular dystrophies Myotonic Dystrophy type 2
Inflammatory myopathies	Polymyositis
Congenital myopathies	Danon disease
Metabolic myopathies	Glycogen Storage disease types IIIa, IV, V and VII Mitochondrial myopathies
Motor neuron disease	Spinal muscular atrophy
Neuromuscular junction disease	Myasthenia gravis

screening (NBS). Methods for NBS for PD are assays based on the analysis of enzyme activities by using artificial substrates in DBS, either by fluorometry, tandem mass spectrometry (MS/MS), or microfluidics combined with fluorometry (Bodamer et al., 2017). Other methods are based on analysis of accumulating substrate, immune quantification, and/or immune capture activity of the enzyme of interest. Molecular sequencing of the GAA gene is important for confirmatory (second tier) testing after a positive newborn screen for Pompe disease (Bodamer et al., 2017). Patients with classic IOPD identified through NBS and, therefore, commenced early on ERT presented better outcomes as demonstrated by the Taiwan NBS program (Chien et al., 2015). This supports the need for the earliest possible identification of patients with classic IOPD.

Early treatment often prevents morbidity and mortality. Thus, the diagnosis of classic IOPD cannot be delayed by waiting for the sequencing result. Patients with low enzyme activity should undergo cardiac evaluation, ideally by chest radiograph, ECG, and ECHO to detect classic IOPD immediately (Burton et al., 2017). The diagnosis of IOPD can be established after a positive NBS result when physical examination, echocardiography and elevated CPK support the diagnosis. The management of LOPD based on enzymatic and molecular analysis remains a clinical challenge, because these patients will be normal at the time of diagnosis. Patients will need to be followed closely in order that they begin ERT as soon as they present clinical pathology (Kronn et al., 2017). Analysis of GAA enzyme activity in cultured skin fibroblasts may be helpful when LOPD is suspected or when asymptomatic individuals are ascertained through screening tests.

Cross Reactive Immunological Material (CRIM)

The combination of two deleterious mutations leads to a complete lack of GAA protein and an extremely low residual GAA activity (< 1%) (Chan et al., 2017; Llerena Junior et al., 2015), such genotype is associated with the classic IOPD, which presents a clinical phenotype with a rapid progression. From an immunological standpoint, these individuals have no cross-reactive material and are classified as Cross-Reactive Immunological Material (CRIM) negative patients. Patients with at least one mild mutation, that allows partial enzyme activity present a clinical phenotype with a slower progression. From an immunological point of view, these patients are classified as CRIM positive (Leslie and Bailey, 2007; Llerena Junior et al., 2015).

The CRIM status can be predicted by Western blot analysis of cultured skin fibroblasts, a process that can take a few weeks, and by molecular genetic testing if the patient's genotype has previously been associated with CRIM status (Bali et al., 2012). A method for determining CRIM status using peripheral blood mononuclear cells has been reported (Wang et al., 2014). This method can yield results within 48 to 72 hours but there is still no clear conclusion about its validity (Bali et al., 2015).

Enzyme Replacement Therapy

Enzyme replacement therapy (ERT) is currently the standard-of-care treatment of Pompe disease. ERT is based on the intravenous administration of recombinant human GAA (rhGAA). Symptomatic patients should start the treatment when the diagnosis is established, whereas asymptomatic patients should start the ERT when the firsts symptoms appear or when functional tests show a decline (Barba-Romero et al., 2012). Before beginning ERT it is necessary to perform a complete clinical and laboratory evaluation. During follow-up it is important to monitor the efficacy of the ERT through manual assessment of muscle strength (MRC scale), spirometry, timed functional test and mobility scales (6-minute walk test) (Barba-Romero et al., 2012). The recommended dosage regimen of alglucosidase α is 20 mg/kg of body weight administered once every 2 weeks. In some cases, 40 mg/kg doses have been given but there is no certitude about the clinical benefit(Broomfield et al., 2015).

Treatment significantly improves motor, respiratory and cardiac function. However, residual disease persists, indicating that ERT is not completely effective in clearing glycogen and correcting all the associated underlying pathologies in the different systems(Chien et al., 2015; Prater et al., 2012). Patients still present risks of arrhythmia (Kronn et al., 2017), while progressive respiratory weakness and pulmonary decline persist (Regnery et al., 2012). The addition of recombinant enzyme into the systemic circulation cannot reverse GAA deficiency in the CNS because does not effectively cross the blood-brain barrier. Neurological problems in PD include hearing loss due to a problem in the cochlea or middle ear, hypernasal speech with a flaccid dysarthria and aspiration risk and delays or deficiencies in brain myelination (Chan et al., 2017; Mcintosh et al., 2018). Muscle weakness, including generalized weakness, decreased endurance, and persistent fatigue (Chien et al., 2013) is possibly attributed to autophagy buildup, poor accessibility of the skeletal muscle fibers to systemically delivered enzyme, low expression of mannose-6-phosphate receptors (M6PR), or epigenetic and environmental factors (Regnery et al., 2012). Also, immunological responses to therapeutic enzyme often attenuate treatment efficacy (Doerfler et al., 2016).

Studies showed that early diagnosis and timely treatment allow a better motor development and may lead to better long-term outcomes (Chien et al., 2013). Age at onset of treatment, the initial health status and condition of the patients at diagnosis are significant determinants of clinical response. The best response is seen in patients who have less muscle pathology (Thurberg et al., 2006). In patients with less-advanced disease, early initiation of ERT improves outcomes (van der Ploeg et al., 2010). In IOPD it is vital to commence ERT at the earliest time point possible due to the attendant risks associated with

the development of IOPD-relevant complications, especially cardiorespiratory failure followed by death (van Gelder et al., 2016).

In a clinical study including IOPD patients, elevation of biomarkers and impairment of motor function was noticed over time on ERT. Increase in dosage or frequency to 20mg/kg/week or 40mg/kg/2weeks when clinical decline was noticed possibly lead to better outcomes, suggesting a dosage/frequency escalation over time on treatment (Chien et al., 2015). Another study including CRIM-positive patients with classic IOPD, demonstrated that patients on ERT receiving increased doses (40 mg/kg/week) performed better than those receiving 20 mg/kg/2weeks regarding motor function and respiratory involvement (Broomfield et al., 2015). Overall, patients who experience plateau or decline in motor function over time on therapy, seem to present some clinical benefit when treated with 40 mg/kg doses (Case et al., 2015; van der Ploeg et al., 2010).

Physical therapy, such as gentle facilitation of movement with active, graded assistance in infants, and aerobic functional exercise with active assistance in adults might preserve motor and physiologic function in patients and maximize the benefits of ERT (Mellies and Lofaso, 2009).

Immune Responses

Antibody responses to the therapeutic enzyme may be without overt clinical significance or may lead to hypersensitivity reactions, decreased bioavailability, or decreased efficacy. A patient developed nephrotic syndrome from immune complex-mediated nephritis when escalating doses of rhGAA were administered as part of an experimental immune tolerance regimen (Hunley et al., 2004).

CRIM status is an important predictor of response to ERT. CRIM-negative (CN) status has been associated with a poor prognosis, attenuated response to ERT and tendency to develop high antibody titers (Banugaria et al., 2011; Kishnani et al., 2010). Patients who are identified as having CN status, have a complete deficiency of endogenous GAA. Thus, rhGAA is perceived as a foreign protein by the immune system in these patients, resulting in the development of anti-GAA B- and T-cells that render ERT ineffective (Banugaria et al., 2011). CN patients tend to do poorly on ERT with death or need for invasive ventilation (Mellies and Lofaso, 2009). It is recommended to determine the CRIM status of each patient using GAA mutation analysis and Western-blot analysis on skin fibroblast cell extracts (Burton et al., 2017). This step should be done before the first infusion of recombinant enzyme as it is essential to optimize the treatment by increasing doses and/or combining ERT with induction of immune tolerance in patients CN or having a poor response (Burton et al., 2017; Kishnani et al., 2010).

CN patients and some CRIM-positive (CP) patients develop high sustained antibody titer (HSAT) after exposure to ERT, which is considered to be a key factor in the poor response to ERT. Patients with HSAT have an attenuated therapeutic response to enzyme replacement therapy (Berrier et al., 2015). In a retrospective study, it was found that high-titer CP (HTCP) patients showed a period of improvement in the first 6 months of enzyme replacement, after which they declined across all outcome measures, similar to CN patients (Banugaria et al., 2011). The CN and HTCP groups presented no statistically significant differences for any outcome measures and both patient groups responded poorly. The persistence of high titer

Table 2: Clinical trials on therapeutic approaches for Pompe Disease

INTERVENTION/ TREATMENT	**PHASE**	**ClinicalTrials.gov Identifier**
Drug: GZ402666 Drug: alglucosidase alfa (GZ419829)	Phase 3	NCT02782741
Drug: ATB200 Drug: AT2221	Phase 1/2	NCT02675465
Drug: Duvoglustat	Phase 2	NCT00688597
Drug: rAAV1-CMV-GAA (study agent) Administration Other: RMST	Phase 1/2	NCT00976352
BMN 701	Phase 3	NCT01924845
Drug: Clenbuterol Drug: Placebo	Phase 1/2	NCT01942590
Drug: Albuterol Drug: Placebo	Phase 1/2	NCT01885936
Drug: Salbutamol	Phase 4	NCT02405598

GZ402666: rhGAA conjugated to a synthetic branched hexasaccharide containing two terminal mannose-6-phosphate (M6P) residues, ATB200: rhGAA with an optimized carbohydrate structure, AT2221 (Miglustat): pharmacological chaperone, Duvoglustat (AT2220): pharmacological chaperone, RMST: Respiratory Muscle Strength Training BMN 701: fusion protein between GAA and insulin-like growth factor 2 (IGF2-GAA) Clenbuterol, Albuterol, Salbutamol: b2-agonists

antibody correlated with the observed clinical decline in HTCP patients. Low-titer CP patients, in whom antibody titer was either persistently low or declining by 26 weeks, had a more favorable clinical outcome. The antibody response observed in CN and HTCP patients and the favorable outcome in low-titer CP patients further supports the correlation of poor clinical response to ERT with the increased and persistent antibody response.

Immune Tolerance Induction

While early diagnosis and treatment is significant in improving overall clinical outcomes in IPD, early diagnosis and initiation of treatment by itself does not prevent the development of antibodies against rhGAA. Immune tolerance induction (ITI) in the naïve setting has proven to be successful in preventing the development of antibody titers, which substantiates the use of ITI therapies in the ERT-naïve setting. Patients who present high-titer antibody response to ERT tend to respond more poorly and ultimately require invasive ventilation or die prematurely if not treated with ITI (Banugaria et al., 2011; Berrier et al., 2015). Therefore, implementation of ITI in the naïve setting is of vital importance for CN patients with antibodies to rhGAA and CP patients at risk for a high-titer sustained immune response (Banugaria et al., 2013; Berrier et al., 2015; Doerfler et al., 2016; Messinger et al., 2012).

Successful ITI has been achieved, and results are encouraging with regimens of rituximab, methotrexate, and/ or immunoglobulin (intravenous immunoglobulin [IVIG]), which may prevent the deleterious immune response against alglucosidase alfa (Banugaria et al., 2013; Messinger et al., 2012). Studies using this ITI regimen concurrent with ERT support it is safely tolerated (Case et al., 2015; van Gelder et al., 2016). It seems to

improve clinical response and decrease antibody titers. Other ITI regimens, including inhibition of B cell activating factor using anti-BAFF monoclonal antibody and an inhibitor of the mammalian target of the rapamycin (mTOR) pathway (sirolimus), are being investigated (Doerfler et al., 2016; Elder et al., 2013).

Studies on Therapeutic Options

Further modifications of the treatment that can address the limitations of ERT, such as a better uptake formulation and gene therapy are being explored (Table 2) (Byrne et al., 2017; Han et al., 2016; Kishnani et al., 2017; Smith et al., 2013).

References

Bali, D.S., Goldstein, J.L., Banugaria, S., Dai, J., Mackey, J., Rehder, C., Kishnani, P., 2012. Predicting cross-reactive immunological material (CRIM) status in Pompe disease using GAA mutations: Lessons learned from 10 years of clinical laboratory testing experience. Am. J. Med. Genet. Part C Semin. Med. Genet. 160C, 40–49. https://doi.org/10.1002/ajmg.c.31319

Bali, D.S., Goldstein, J.L., Rehder, C., Kazi, Z.B., Berrier, K.L., Dai, J., Kishnani, P.S., 2015. Clinical laboratory experience of blood CRIM testing in infantile Pompe disease. Mol. Genet. Metab. 5, 76–79. https://doi.org/10.1016/j.ymgmr.2015.10.012

Banugaria, S.G., Prater, S.N., Ng, Y., Kobori, J.A., Finkel, R.S., Ladda, R.L., Chen, Y., Amy, S., Kishnani, P.S., 2011. The impact of antibodies on clinical outcomes in diseases treated with therapeutic protein: Lessons learned from infantile Pompe disease. Genet. Med. 13, 729–736. https://doi.org/10.1097/GIM.0b013e3182174703

Banugaria, S.G., Prater, S.N., Patel, T.T., Dearmey, S.M., Milleson, C., Sheets, K.B., Bali, D.S., Rehder, C.W., Raiman, J.A.J., Wang, R.A., Labarthe, F., Charrow, J., Harmatz, P., Chakraborty, P., Rosenberg, A.S., Kishnani, P.S., 2013. Algorithm for the Early Diagnosis and Treatment of Patients with Cross Reactive Immunologic Material- Negative Classic Infantile Pompe Disease : A Step towards Improving the Efficacy of ERT. PLoS One 8, e67052. https://doi.org/10.1371/journal.pone.0067052

Barba-Romero, M.A., Barrot, E., Bautista-lorite, J., Gutiérrez-rivas, E., Illa, I., Jiménez, L.M., Ley-martos, M., Munain, A.L. De, Pardo, J., Pascual-pascual, S.I., Pérez-lópez, J., Solera, J., Vílchez-padilla, J.J., 2012. Clinical guidelines for late-onset Pompe disease. Rev. Neurol. 54, 497–507. https://doi.org/10.33588/rn.5408.2012088

Berrier, K.L., Kazi, Z.B., Prater, S.N., Bali, D.S., Goldstein, J., Stefanescu, M.C., Rehder, C.W., Botha, E.G., Ellaway, C., Bhattacharya, K., Tylki-Szymanska, A., Karabul, N., Roseburg, A.S., Kishnani, P.S., 2015. CRIM-negative infantile Pompe disease: characterization of immune responses in patients treated with ERT monotherapy. Genet. Med. 17, 912–918.https://doi.org/10.1038/gim.2015.6

Bodamer, O.A., Scott, C.R., Giugliani, R., 2017. Newborn Screening for Pompe Disease. Pediatrics 140, S4–S13. https://doi.org/10.1542/peds.2016-0280c

Broomfield, A., Fletcher, J., Davison, J., Finnegan, N., Fenton, M., Chikermane, A., Beesley, C., Harvey, K., Cullen, E., Stewart, C., Santra, S.,

Vijay, S., Champion, M., Abulhoul, L., 2015. Response of 33 UK patients with infantile-onset Pompe disease to enzyme replacement therapy. J. Inherit. Metab. Dis. 39, 261–271. https://doi.org/10.1007/s10545-015-9898-5

Burton, B.K., Kronn, D.F., Hwu, W., Kishnani, P.S., 2017. The Initial Evaluation of Patients After Positive Newborn Screening : Recommended Algorithms Leading to a Confirmed Diagnosis of Pompe Disease. Pediatrics 140, S14–S23. https://doi.org/10.1542/peds.2016-0280d

Byrne, B.J., Geberhiwot, T., Barshop, B.A., Barohn, R., Hughes, D., Bratkovic, D., Desnuelle, C., Laforet, P., Mengel, E., Roberts, M., Haroldsen, P., Reilley, K., Jayaram, K., Yang, K., Walsh, L., 2017. A study on the safety and efficacy of reveglucosidase alfa in patients with late- onset Pompe disease. Orphanet J. Rare Dis. 12, 144. https://doi.org/10.1186/s13023-017-0693-2

Case, L.E., Bjartmar, C., Morgan, C., Casey, R., Charrow, J., Clancy, J.P., Dasouki, M., Dearmey, S., Nedd, K., Nevins, M., Peters, H., Phillips, D., Spigelman, Z., Tifft, C., Kishnani, P.S., 2015. Safety and efficacy of alternative alglucosidase alfa regimens in Pompe disease. Neuromuscul. Disord. 25, 321–332. https://doi.org/10.1016/j.nmd.2014.12.004

Chan, J., Desai, A.K., Kazi, Z.B., Corey, K., Austin, S., Hobson-Webb, L.D., Case, L.E., Jones, H.N., Kishnani, P.S., 2017. The emerging phenotype of late-onset Pompe disease: A systematic literature review. Mol. Genet. Metab. 120, 163–172. https://doi.org/10.1016/j.ymgme.2016.12.004

Chien, Y., Chiang, S., Zhang, X.K., Keutzer, J., Lee, N., Huang, A., Chen, C., Wu, M., Huang, P., Tsai, F., Chen, Y., Hwu, W., 2008. Early Detection of Pompe Disease by Newborn Screening Is Feasible : Results From the Taiwan. Pediatrics 122, e39–e45. https://doi.org/10.1542/peds.2007-2222

Chien, Y., Hwu, W., Lee, N., 2013. Pompe Disease : Early Diagnosis and Early Treatment Make a Difference. Pediatr. Neonatol. 54, 219–227. https://doi.org/10.1016/j.pedneo.2013.03.009

Chien, Y., Lee, N., Chen, C., Tsai, F., Tsai, W., Shieh, J., Ms, H.H., Hsu, W., Tsai, T., Hwu, W., 2015. Long-Term Prognosis of Patients with Infantile-Onset Pompe Disease Diagnosed by Newborn Screening and Treated since Birth. J. Pediatr. 166, 985-991.e2. https://doi.org/10.1016/j.jpeds.2014.10.068

Dasouki, M., Jawdat, O., Almadhoun, O., Pasnoor, M., McVey, A.L., Abuzinadah, A., Herbelin, L., Barohn, R.J., Dimachkie, M.M., 2014. Pompe Disease: Literature Review and Case Series Majed. Neurol. Clin. 32, 751–ix. https://doi.org/10.1016/j.ncl.2014.04.010

Doerfler, P.A., Nayak, S., Corti, M., Morel, L., Herzog, R.W., Byrne, B.J., 2016. Targeted approaches to induce immune tolerance for Pompe disease therapy. Mol. Ther. - Methods Clin. Dev. 3, 15053. https://doi.org/10.1038/mtm.2015.53

Elder, M.E., Nayak, S., Collins, S.W., Ann, L., Kelley, J.S., Herzog, R.W., Modica, R.F., Lawrence, R.M., Byrne,

B.J., 2013. B-cell Depletion and Immunomodulation Prior to Initiation of Enzyme Replacement Therapy Blocks the Immune Response to Acid Alpha Glucosidase in Infantile Onset Pompe Disease. J. Pediatr. 163, 847-854.e1.https://doi.org/10.1016/j.jpeds.2013.03.002

Han, S., Li, S., Koeberl, D.D., 2016. Salmeterol enhances the cardiac response to gene therapy in Pompe disease. Mol. Genet. Metab. 118, 35–40.https://doi.org/10.1016/j.ymgme.2016.03.006

Hirschhorn, R., Reuser, A.J., 2001. Glycogen storage disease type II: acid alpha-glucosidase (acid maltase) deficiency, in: Scriver CR, Beaudet A, Sly WS, Valle D, Eds. The Metabolic and Molecular Bases of Inherited Disease. pp. 3389–420.

Hunley, T.E., Corzo, D., Dudek, M., Kishnani, P., Amalfitano, A., Chen, Y., Richards, S.M., Iii, J.A.P., Fogo, A.B., Tiller, G.E., 2004. Nephrotic Syndrome Complicating -Glucosidase Replacement Therapy for Pompe Disease. Pediatrics 114, e532–e535. https://doi.org/10.1542/peds.2003-0988-L

Kishnani, P., Tarnopolsky, M., Roberts, M., Sivakumar, K., Dasouki, M., Dimachkie, M.M., Finanger, E., Goker-alpan, O., Guter, K.A., Mozaffar, T., Pervaiz, M.A., Laforet, P., Levine, T., Adera, M., Lazauskas, R., Sitaraman, S., Khanna, R., Benjamin, E., Feng, J., Flanagan, J.J., Barth, J., Barlow, C., Lockhart, D.J., Valenzano, K.J., Boudes, P., Johnson, F.K., Byrne, B., 2017. Duvoglustat HCl Increases Systemic and Tissue Exposure of Active Acid α-Glucosidase in Pompe Patients Co-administered with Alglucosidase α. Mol. Ther. 25, 1199–1208. https://doi.org/10.1016/j.ymthe.2017.02.017

Kishnani, P.S., Goldenberg, P.C., DeArmey, S.L., Heller, J., Benjamin, D., Young, S., Bali, D., Smith, S.A., Li, J.S., Mandel, H., Koeberl, D., Rosenberg, A., Chen, Y.-T., 2010. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. Mol. Genet. Metab. 99, 26–33. https://doi.org/10.1016/j.ymgme.2009.08.003

Kronn, D.F., Day-salvatore, D., Hwu, W., Jones, S.A., 2017. Management of Confirmed Newborn- Screened Patients With Pompe Disease Across the Disease Spectrum. Pediatrics 140, S24–S45. https://doi.org/10.1542/peds.2016-0280e

Leslie, N., Bailey, L., 2007. Pompe Disease. Adam MPR, Ardinger HH, Pagon RA, al., Ed. GeneReviews 1–26. Llerena Junior, J.C., Nascimento, O.J.M., Oliveira, A.S.B., Emilio, M., Junior, T.D., Marrone, C.D., Siqueira, H.H., Sobreira, C.F.R., Dias-tosta, E., Werneck, L.C., 2015. Guidelines for the diagnosis , treatment and clinical monitoring of patients with juvenile and adult Pompe disease. Arq. Neuropsiquiatr. 166–177. https://doi.org/10.1590/0004-282X20150194

Mcintosh, P.T., Hobson-webb, L.D., Kazi, Z.B., Prater, S.N., Banugaria, S.G., Austin, S., Enterline, D.S., Frush, D.P., Kishnani, P.S., 2018. Neuroimaging findings in infantile Pompe patients treated with enzyme replacement therapy. Mol. Genet. Metab. 123, 85–91. https://doi.org/10.1016/j.ymgme.2017.10.005

Mellies, U., Lofaso, F., 2009. Pompe disease : A neuromuscular disease with respiratory muscle involvement. Respir. Med. 103, 477–484. https://doi.org/10.1016/j.rmed.2008.12.009

Messinger, Y.H., Mendelsohn, N.J., Rhead, W., Hershkovitz, E., Champion, M., Jones, S.A., Olson, R., White, A., Wells, C., Bali, D., Kishnani, P.S., 2012. Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease. Genet. Med. 14, 135–142. https://doi.org/10.1038/gim.2011.4

Nascimbeni, A.C., Fanin, M., Tasca, E., Angelini, C., 2008. Molecular pathology and enzyme processing in various phenotypes of acid maltase deficiency. Neurology 70, 617–626. https://doi.org/10.1212/01.wnl.0000299892.81127.8e

Prater, S.N., Banugaria, S.G., Dearmey, S.M., Botha, E.G., Stege, E.M., Case, L.E., Jones, H.N., Phornphutkul, C., Wang, R.Y., Young, S.P., Kishnani, P.S., 2012. The emerging phenotype of long-term survivors with infantile Pompe disease. Genet. Med. 14, 800–810. https://doi.org/10.1038/gim.2012.44

Regnery, C., Kornblum, C., Hanisch, F., Vielhaber, S., Strigl-Pill, N., Grunet, B., Muller-Felber, W., Glocker, F.X., Spranger, M., 2012. 36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy. J. Inherit. Metab. Dis. 35, 837–845. https://doi.org/10.1007/s10545-012-9451-8

Smith, B.K., Collins, S.W., Conlon, T.J., Mah, C.S., Lawson, L.A., Martin, A.D., Fuller, D.D., Cleaver, B.D., Cle, N., Phillips, D., Islam, S., Dobjia, N., Byrne, B.J., 2013. Phase I / II Trial of Adeno-Associated Virus – Mediated Alpha-Glucosidase Gene Therapy to the Diaphragm for Chronic Respiratory Failure in Pompe Disease : Initial Safety and Ventilatory Outcomes. Hum. Gene Ther. 24, 630–640. https://doi.org/10.1089/hum.2012.250

Thurberg, B.L., Maloney, C.L., Vaccaro, C., Afonso, K., Tsai, A.C., Bossen, E.H., Kishnani, P.S., Callaghan, M.O., 2006. Characterization of pre- and post-treatment pathology after enzyme replacement therapy for pompe disease 86, 1208–1220. https://doi.org/10.1038/labinvest.3700484

van der Ploeg, A.T., Clemens, P.R., Corzo, D., Escolar, D.M., Florence, J., Groeneveld, G.J., Ph, D., Herson, S., Kishnani, P.S., Laforet, P., Lake, S.L., Sc, D., Lange, D.J., Leshner, R.T., Mayhew, J.E., Morgan, C., Nozaki, K., Ph, D., Park, D.J., Pestronk, A., Rosenbloom, B., Skrinar, A., Capelle, C.I. Van, Beek, N.A. Van Der, Wasserstein, M., Zivkovic, S.A., Ph, D., 2010. A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe's Disease. N. Engl. J. Med. 362, 1396–1406. https://doi.org/10.1056/nejmoa0909859

van Gelder, C.M., Poelman, E., Plug, I., 2016. Effects of a higher dose of alglucosidase alfa on ventilator-free survival and motor outcome in classic infantile Pompe disease: an open-label single-center study. J. Inherit. Metab. Dis. 39, 383–390. https://doi.org/10.1007/s10545-015-9912-y

Wang, Z., Okamoto, P., Keutzer, J., 2014. A new assay for fast , reliable CRIM status determination in infantile-onset Pompe disease. Mol. Genet. Metab. 111, 92–100. https://doi.org/10.1016/j.ymgme.2013.08.010