REVIEW

Profile of alglucosidase alfa in the treatment of Pompe disease: safety, efficacy, and patient acceptability

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Abstract: Pompe disease, also referred to as glycogenosis type II, is a rare, autosomal recessive disorder that results from the deficiency of the glycogen-degrading enzyme acid α-glucosidase. The classical form presents shortly after birth with muscle hypotonia, cardiac, and respiratory failure resulting in a fatal outcome. The late onset of Pompe disease has a very variable onset and disease presentation that often causes a delayed diagnosis. Until now enzyme replacement therapy with alglucosidase alfa is the only causative therapy option for Pompe patients that can slow down disease progression. However, uncertainty remains about the efficacy regarding survival and quality of life in Pompe patients under this very cost-intensive treatment. This paper provides a systematic review of the literature stressing different aspects of enzyme replacement therapy in infantile and late onset Pompe patients.

Keywords: lysosomal storage disease, glycogenosis type II, acid maltase deficiency, IOPD, LOPD, enzyme replacement therapy

Introduction

Pompe disease was first described in 1932 by the Dutch pathologist JC Pompe. It is also known as glycogen storage disease type II or acid α-glucosidase deficiency. This orphan disease (OMIM 232300) has an overall incidence which ranges from 1 in 33,000 persons to 1 in 300,000 persons, depending on the geographic region and ethnicity.[1–3] Approximately 5,000–10,000 people worldwide are affected. Pathogenetically, the disease is caused by mutations in the *GAA* gene on the cytogenetic location *17q25.3* (OMIM 606800), resulting in a deficient activity of the enzyme α-1,4-glucosidase that is located in cellular lysosomes involved in the degradation of glycogen. Deposition of lysosomal glycogen takes place in cardiac, skeletal, and respiratory muscle tissue, but also in smooth muscle of the bladder, intestine, esophagus,[4] and also the arrector pili muscles of the skin.[5] Pompe disease is classified into two clinical forms: The classic infantile onset Pompe disease (IOPD) is related to complete α-glucosidase deficiency that results in a severe disease with onset within the first 6 months after birth. The non-classic form is usually related to partial enzyme deficiency and progresses more slowly with disease onset at any age. It can be sub-categorized as non-classic childhood, juvenile, and adult form (late onset Pompe disease, LOPD).[6] Because of the systemic character, clinical features are multiform (Table 1). Cardiomyopathy with heart failure and respiratory insufficiency are the reason for a median age of death between 6 and 9 months in untreated infants[7] and a survival rate of 25.7% for the first 12 months.[8] In the non-classic form, a progressive limb girdle muscular weakness is the hallmark of the disease, but the broad spectrum of clinical presentations often delays the correct
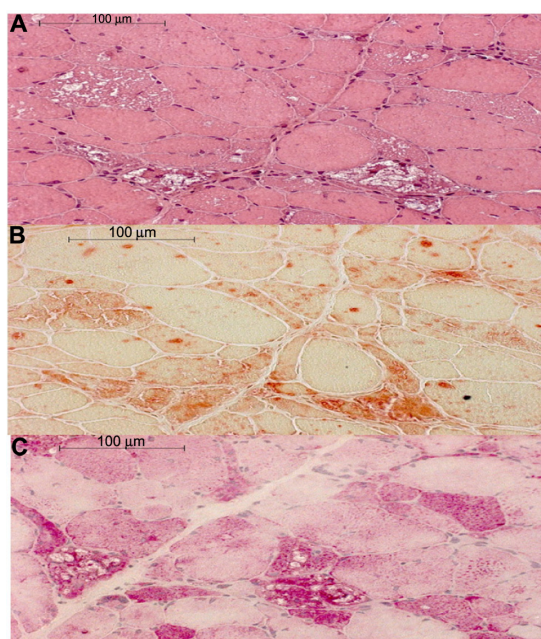
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Table 1 Clinical features of classic and non-classic Pompe patients

Organ system	Symptoms of Pompe disease
Skeletal muscle	Classic form:
	Floppy infant, delayed motor milestones
	Non-classic form:
	Proximal muscle weakness (limb girdle)
	Exercise intolerance
	Axial weakness, rigid spine[83]
	"Dropped head"
	Rare: IBM-like phenotype[9,84]
	Preclinical, isolated hyper-CK-emia[10]
Pulmonary function	Respiratory failure/hypoxia
	Respiratory infections
	Diaphragmatic weakness[83,85]
	Exertional dyspnea
	Hypercapnia
	Sleep apnea[86]
Heart	Classic form:
	Cardiomyopathy, cardiac insufficiency
	Short PR interval, high QRS voltage
	One infant case of Wolff–Parkinson–White syndrome
	Non-classic form:
	Rare cardiac involvement[87]
	One adult case of Wolff–Parkinson–White syndrome
Skeletal system	Scoliosis[83,88]
	Osteoporosis
	Fractures[89]
	Feet deformities, contractures[90]
Other organs	Classic form: hepatomegaly
	Non-classic form: hepatomegaly only reported in the childhood and juvenile onset Pompe disease, not in adults
	Macroglossia
	Gastrointestinal symptoms
	Hearing loss[91,92]
	Artheriopathy (aneurysms)[93]
	Rare: tongue weakness[94]
	Oropharyngeal dysphagia[95]
	Ptosis[96]
CNS/PNS	Cognitive impairment[97]
	Rare: small fibre neuropathy[98]

Abbreviations: CK, creatine kinase; CNS, central nervous system; PNS, peripheral nervous system.

Figure 1 Histological findings in Pompe disease.
Notes: Muscle biopsy sections of a patient with genetically confirmed Pompe disease presenting as vacuolar myopathy in H&E staining (**A**). Elevated lysosomal activity is marked by acid phosphatase reaction (**B**) in the numerous vacuoles that are loaded with glycogen detected by periodic acid Schiff (PAS) stain (**C**). Magnification 200×.
Abbreviation: H&E, hematoxylin and eosin.

Vacuoles have a high content of glycogen detected by periodic acid Schiff reaction and are strongly reacting for acid phosphatase, indicating that they are secondary lysosomes.[17] It is important to keep in mind that in less severely affected muscles, the vacuoles only show in 25%–75%, and clinically unaffected muscle can be spared from pathological changes, especially in the adult disease.[18] A relatively reliable tool for screening for acid α-glucosidase (GAA) deficiency is the assay in blood collected on a filter paper (dried blood spot test [DBS]).[19] High-throughput mass spectrometry methods are used for the implementation of newborn screening for lysosomal storage disorders (including Pompe disease) in pilot studies in Taiwan, North America, and Europe.[20–23] Currently, the "gold standard" diagnostic for Pompe disease is the GAA assay performed on skin fibroblasts or muscle biopsy followed by DNA analysis[24,25] with detection of homozygote or compound heterozygote mutations in the *GAA* gene. To date more than 300 different mutations have been found,[26] without strict genotype–phenotype correlation.[27]

Enzyme replacement therapy with alglucosidase alfa

The basis for the use of enzyme replacement therapy (ERT) in Pompe disease was built by positive results of intravenously injected precursor forms of recombinant human

diagnosis in the patients by an average of 5–8.6 years after the first symptoms.[9,10] A decline in the pulmonary function is the main cause of death in this form.[11–13] Besides the clinical assessment, other diagnostic clues for Pompe disease include the recognition of a myopathic pattern or myotonic discharges without clinical myotonia[14,15] in the electromyography (EMG). Muscle magnetic resonance imaging (MRI), or even better whole body MRI, is more sensitive in detecting subclinical affected muscles and in selecting an appropriate location for muscle biopsy.[16] Histologically, Pompe disease presents as vacuolar myopathy in the light microscopy (Figure 1).

α-glucosidase (rhGAA) in the Japanese acid maltase-deficient quail that led to reversal of glycogen accumulation in muscle cells.[28] Later similar effects were observed with rhGAA in a *GAA*-knockout mouse model.[29] Subsequently, pilot Phase I/II studies of rhGAA from purified Chinese hamster ovarian cell culture[30] or transgenic rabbit milk[31] significantly prolonged the survival of patients. Since 2006 alglucosidase alfa derived from Chinese hamster ovarian cells (Myozyme®, Lumizyme®; Genzyme Corporation, a Sanofi Company, Cambridge MA, USA) is used for ERT.[17,32]

ERT in classical form

Multiple studies have demonstrated the impressive effect of ERT for improving the survival in classic-infantile Pompe patients (Table 2). An open-label, multinational, multi-center Phase II study demonstrated safety and efficacy of rhGAA in treatment of infantile onset Pompe disease. While untreated IOPD patients die at a median age of 8.7 months, under ERT the 3-year mortality risk is reduced by 95% compared to the natural course.[7,33,34] Especially, the cardiovascular system responds quickly and strikingly to ERT with a significant reversal of cardiac hypertrophy.[34–36] However, application of ERT is not a cure but has changed the face of the disease burden from mortality to morbidity. The longer lifespan of infants, who would have died untreated of progressive cardiac involvement, results in manifestation of a more protracted course of muscle weakness, motor speech deficits, sensori-neural and/or conductive hearing loss, osteopenia, gastroesophageal reflux, and dysphagia with aspiration risk and respiratory complications.[37] Early treatment before development of clinically noticeable motor weakness appears to have the best results for development of the infants. Therefore, newborn screening, as it is practiced in Taiwan, might further render the prognosis positive in IOPD in the future.[38]

Antibody formation

Long-term efficacy and safety of ERT in classic-infantile Pompe disease is strongly dependent on antibody formation against alglucosidase alfa (anti-rhGAA-IgG). Pompe patients without any synthesis of GAA protein are labeled as negative for cross-reacting immunological material (CRIM negative). Kishnani et al demonstrated that CRIM negative patients experienced an initial response to ERT, but then entered a phase of devastating clinical decline comparable to the rate observed in untreated infantile patients. After 2 years of ERT, 11/11 CRIM negative patients were deceased or on invasive ventilation support in contrast to only 4/21 CRIM positive patients.[39] CRIM negative patients had earlier, higher, and

Table 2 Efficacy of ERT in infantile Pompe disease – study summary

Year of study	Number of participants	Age at start of ERT (months)	Duration of ERT (months)	CRIM status	Survival	LVMI reduction	Achieving motor milestones	Ventilator free	Alternative ERT dose to 20 mg/kg body weight	AE	Study
2009	18	2.7–14.6	13–36	4/18 negative	13/18	17/18	11/18	9/18	10–40 mg	11/18	Kishnani et al[33,34]
	1	2	2.5	N/K	Yes	Yes	Yes	Yes	No	Yes	But et al[99]
2010	20	0.5–32	1–102	N/K	14/20	N/K	4/10[c]	7/20	N/K	N/K	Chakrapani et al[100]
	1	0.8	26	N/K	Yes	Yes	Yes	Yes	No	No	Del Rizzo et al[101]
	1	2	44	Negative	Yes	Yes	Yes	Yes	No	Yes	Rohrbach et al[102]
2012	2	6	48	1 negative	Yes	Yes	Yes	Yes	No	No	
	1	0.2	24	1 negative	Yes	Yes	Yes	Yes	No	Yes	Khallaf et al[103]
	1	4.2	36	1 negative[a]	No	Yes	No	No	After 1 year highdose	N/K	Banugaria et al[104]
	4	N/K	24	N/K	4/4	4/4	4/4	N/K	No	No	Cho et al[105]
2013	1	5	84	N/K	Yes	Yes	Yes[b]	No	After 5 years 20 mg/week	No	Amartino and Cavagnari[106]
	5	0–9	1–48	N/K	2/5	4/5	3/5	2/5	No	N/K	Fathalla and Ahmed[107]
2014	1	5	36	1 positive[a]	Yes	Yes	No	No	After 1 year 40 mg	Yes	Markic et al[44,108]
2015	10	0.25–1	28–90	10 positive	10/10	10/10	10/10	10/10	No	N/K	Chien et al[38]
	23	0–9.3	30	9 positive, 2 negative, 12 N/K	5/9, 0/2, 8/12	N/K, N/K, N/K[d]	8/9, 0/2, 8/12	5/9, 1/2, 4/12	4/9 40 mg, 1/9 80 mg, 1/2 40 mg, 4/12 40 mg, 2/12 30 mg	8/23	Hahn et al[36]
	11	0.1–8.3	48	8 positive, 3 negative	8/8, 0/3	8/8, 2/3	6/8, 2/3	5/8, 1/3	7/8 40 mg, 1/3 40 mg	8/8, 2/3	van Gelder et al[40]

Notes: [a]Immunomodulation treatment; [b]motor milestones achieved, but lost after third year; [c]motor milestones reported only for 10 patients >1 year of age; [d]echocardiographic data available after 6 months of ERT show reversal of cardiac hypertrophy in 14/15 patients.
Abbreviations: AE, adverse events; CRIM, cross-reacting immunological material; ERT, enzyme replacement therapy; LVMI, left ventricular mass index; N/K, not known.

more sustained antibody responses that were associated with a reduced clinical outcome. CRIM positive patients, on the opposite, have detectable amounts of GAA protein, although its function is insufficient or ineffective. These patients are less prone to immune reactions against rhGAA with usually low antibody titer and typically a better clinical outcome.[40] However, high doses of therapeutic rhGAA (20–40 mg/kg once a week to biweekly application) can also trigger an immune reaction against ERT in species with only mild mutation of *GAA*.[41] Immunomodulatory therapy is a therapeutic approach to reduce the impact of neutralizing antibodies. Combination of rituximab, methotrexate, and intravenous immunoglobulin[42–44] and also additional treatment with bortezomib, targeting plasma B-cells, successfully reduced antibody titer in infantile Pompe patients and resulted in concomitant sustained clinical improvement.[45] Importantly, success to induce immune tolerance toward ERT is more likely when immune modulation is started at the onset off ERT.[46] Therefore, the evaluation of CRIM-negative patients with subsequent immune modulation is important for optimizing benefit from ERT in these patients. In approximately 90% CRIM status can be predicted by mutation type in the corresponding *GAA* gene.[47] In uncertain cases, Western blot analysis can be applied for the final CRIM status determination.[46]

Cost effectiveness and quality of life

Besides the question of therapeutic effectiveness, there is also rising interest in the cost effectiveness of ERT in Pompe disease, especially in the face of tensed health care budgets.

In 2014, Kanters et al assessed this topic by a patient simulation model that compared costs, survival, quality of life, and quality-adjusted life years in classic-infantile Pompe disease under ERT and untreated patients. Due to the prolonged survival of treated patients, lifetime incremental quality-adjusted life years were 6.8 with incremental costs-per-life-year-gained estimated to be €0.5 million, of which 95% consisted of treatment costs.[48]

ERT in non-classic form

In contrast to the substantial effect of ERT for survival in the classic Pompe disease, the data of ERT in LOPD patients are more variable. Only one randomized placebo-controlled trial in the LOPD exists, which is the basis for approval of reimbursement in the treatment of LOPD.[49] Since then there have been numerous case reports and observation studies emphasizing the benefit of ERT in non-classic Pompe disease, even though results are not as convincing as in classic Pompe patients (Table 3). Güngor et al demonstrated the positive effect of ERT for survival in 202 ERT-treated versus 81 non-treated adults during a median follow-up of 6 years. In all, 28 (61%) of the 46 deaths occurred in the non-ERT-group at a median age of 59.[50] A review of all studies until January 2012 evaluated effectiveness of ERT in 368 patients. It was shown that at least a stabilization of motor and respiratory function was achieved in most patients. Newer studies support the hypothesis that ERT can extend the time until wheelchair or ventilator dependence. Nevertheless, no clear correlation between length of treatment and clinical improvement could be found.[51] In contrast, ERT in the British cohort of

Table 3 Efficacy of ERT in non-classic Pompe disease – study summary

Year of study	Total number of participants	Motor performance (6MWT) (n) increase/unchanged/decline	Respiration, FVC, FEV_1 (n) increase/unchanged/decline	Ventilation (n)	AE (n)	Study
Up to 2012	368	(122) 77.9%/8.2%/13.9%	(124) 51.5%/13.7%/34.7%	N/K	(303) 30	Toscano and Schoser[51]
2012	69	N/K	(62) Stable	(25) 8 NIV reduced 1 NIV stopped 14 NIV stable 2 NIV intensified 2 NIV started	(69) 12	de Vries et al[61]
2013	6	N/K	(6) 50%/0%/50%	(6) 3 NIV stable 1 NIV started	N/K	Schneider et al[86]
2014	1	Stable	Improved	Stable	None	Isayama et al[109]
	4	(4) 50%/50%/0%	(4) 50%/0%/50%	N/K	N/K	Andreassen et al[54]
	8	(8) 87%/12.5%/0%	(8) Stable	2 NIV reduced	(8) 1	Deroma et al[56]
	59	(20) Improved	(N/K) Stable	N/K	(59) 3	Anderson et al[52]
2015	14	(12) 58.3%/8.3%/33.3%	(12) 16.6%/25%/58.3%	N/K	None	Montagnese et al[9]
	5	(5) 20%/60%/20%	(5) 20%/60%/20%	4 NIV stable	(5) 2	Park et al[110]

Abbreviations: AE, adverse events; ERT, enzyme replacement therapy; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; 6MWT, 6-Minute Walk Test; NIV, non-invasive ventilation; N/K, not known; n, number of participants for which results were available.

59 non-classic Pompe patients suggested a stabilization of pulmonary function, but a motoric decline in the 6-Minute Walk Test after 2 years of treatment.[52] Furthermore, it has been found that approximately one-third of patients do not respond to therapy.[51,53] The reasons why ERT is less effective in LOPD than in the classic form are various. Firstly, a long-time span until diagnosis is related to advanced muscle degeneration. This might explain why the effect on both motor and pulmonary functions is larger when therapy is started early and baseline muscular function is still high.[49] A recent MRI study confirms that mildly affected leg muscles respond better to ERT than severely affected muscles in a 5-year follow-up. However, also severely affected muscle groups can still benefit from ERT and improve in strength.[54] Interestingly, in some presymptomatic patients MRI demonstrated already lipomatous muscle alterations despite the absence of clinical symptoms.[10,55] Therefore, it may be possible to start ERT at this early time to prevent further worsening with manifestation of muscle weakness. In fact, ERT initiation in five asymptomatic juvenile patients was shown to prevent the development of muscle and respiratory symptoms after 6 years in an Italian cohort.[56] However, others have raised ethical concerns regarding this procedure and treatment guidelines recommend beginning of ERT only in patients with objective signs of the disease.[57,58] Secondly, effectiveness of ERT is dependent on the rhGAA uptake in the skeletal muscles that is limited by a low expression of the cation-independent mannose-6-phosphate receptor (CI-MPR).[59,60] Women seem to benefit more from ERT than males[61] in respect to muscle strength because of a higher dose uptake of alglucosidase per gram of muscle fiber due to their smaller fibers with a higher surface-to-volume ratio.

Antibody formation in non-classic Pompe disease
As in infants, the late onset Pompe patients usually develop IgG anti-rhGAA within the first 3 months under ERT.[53,62] Data from our own cohort, as well as the data from Patel et al, attest that peaks of anti-rhGAA IgG antibody titers can occur even after several years of ERT.[63] However, a clear correlation between anti-rhGAA IgG titer and clinical outcome under ERT cannot be found. Interestingly, 3/10 patients had undetectable or borderline anti-rhGAA-IgG titers and remained stable under ERT after 4 years compared to deterioration in some patients with antibodies.[64]

Quality of life
A sufficient tool for assessment of Quality of Life (QoL) is the Medical Outcomes Survey Short Form-36 Health Survey (SF-36), which can be divided further into a mental and a physical component score. The international Pompe survey revealed that in 210 untreated adult Pompe patients, the QoL was lower in almost all SF-36 domains relative to the general population. Interestingly, a longer disease duration was associated with a better score in the "role functioning physical" and "mental health" domains, most likely due to coping mechanisms. The 10-year international follow-up data suggest a positive effect of ERT on QoL and on participation in daily life activities in adults, by prolonging the natural course of the disease decline.[65] However, only 8.3% of 156 patients under ERT reported an overall improvement in the QoL-scores in contrast to the objective physical improvement of motor and respiratory performance.[51]

Safety of ERT
ERT is unusually well tolerated by the patients and estimated as a safe therapy. Infusion-associated reactions can occur, such as sweating, headaches, elevated temperature, or hypotension, during infusion of rhGAA. Adverse events, involving at least two of three body systems, are reported in 14% of all patients with ERT. Anaphylactic shock and/or cardiac arrest requiring life-support measures have been registered in 1% of patients (Table 4). Steroids or anti-histaminic treatment can be administered to prevent the occurrence of adverse events during the infusions.[32]

Other therapeutic strategies
A lot of effort has been undertaken to further improve the efficacy of ERT. Insufficient rhGAA muscle uptake is likely due to sub-optimal levels of mannose-6-phosphate (M6P), a carbohydrate that binds CI-MPR at the cell surface, resulting in enzyme internalization and lysosomal targeting. Therefore, the design of novel, so-called next-generation forms of

Table 4 Adverse events (AE) and severe adverse events (SAE) reported under ERT

AE	SAE
Infusion-associated reactions:	Anaphylactic reaction[52]
Erythema, exanthema, itch,	Cardiac arrest
pruritus	Bronchospasm[111]
Flushing	Severe emphysema and pneumothorax[112]
Tachycardia	Severe tracheal hemorrhage[113]
Chest discomfort	Serious pneumothorax[114]
Hypertension	Severe tongue edema[49]
Reduced oxygen saturation	Acute hearing loss[115]
Globus pharyngis	
Vomiting	
Flu-like symptoms	
Pyrexia, chills	
Hyperhidrosis	
Muscle cramps	

Abbreviation: ERT, enzyme replacement therapy.

rhGAA with optimized muscle uptake is in progress. Results are awaited for a completed Phase I study known as NEO1 and an ongoing extension study (NEO-ext), evaluating the safety and efficacy of neoGAA with improvement of the CI-MPR-dependent muscle uptake[66] in adults with LOPD.[67] In 2010, BioMarin (BioMarin Pharmaceutical, San Rafael, CA, USA; ClinicalTrials.gov identifier: NCT01230801) started clinical studies with GAA ligated with insulin-like growth factor 2 (BMN 701), which allows the enzyme to attach to the surface of the muscle cell more tightly than the normal acid α-glucosidase. Others aim to design ERT with a significantly higher M6P content compared to the alglucosidase alfa (ATB200).[68] Enzyme enhancers might also increase the CI-MPR expression and thereby improved rhGAA uptake as it was successfully achieved by the selective β_2 agonists Albuterol in $GAA^{-/-}$ mice, as well as in humans.[69] Notably, Albuterol-reduced muscular glycogen even independently from receptor-mediated GAA uptake in the murine model.[70] Another strategy is the use of small molecules known as pharmacological chaperones, which bind to the mutant enzyme and recover its lysosomal activity by correcting the protein folding.[71,72] However, the presence of a misfolded enzyme with recoverable function is essential for an effect of this class of drug. A potential candidate for pharmacological chaperone therapy is the imino sugar N-butyldeoxynojirimycin, which was shown to increase more than 1.85-fold in α-glucosidase activities in 11 of 13 patients treated with ERT in combination with this chaperone.[73] Promising future therapies also involve injection of recombinant adeno-associated virus vectors, as this therapy has been demonstrated to augment cardiac, respiratory, and motorneuron function in $GAA^{-/-}$ knockout mice.[74–78] Importantly, the degree of restoration once again seems to depend on the severity of disease. Therefore, an early therapy appears to be the most effective.[79] First clinical trials of gene transfer treatment in five ventilator-dependent Pompe patients demonstrated acceptable safety outcomes and longer periods of unassisted breathing.[80,81] Genome editing via CRISPR/Cas9[82] is another revolutionary approach that might tremendously change the therapeutic options for Pompe patients by modulating disease-causing alleles. However, this approach is yet far away from clinical trials.

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Disclosure

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